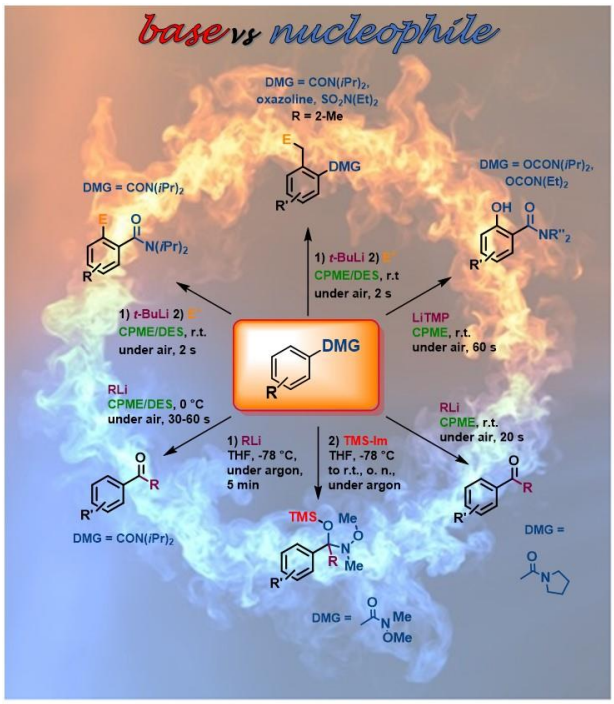
Università degli Studi di Torino
Doctoral School of the University of Torino
PhD Programme in Chemical and Materials Sciences XXXIV Cycle

Ultrafast Chemo- and Regioselective Transformations of Amides and Carbamates Mediated by Organolithium Reagents in Unconventional Sustainable Media



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Foreword

My PhD grant was totally supported by the company Huvepharma Italy s.r.l. in the framework of an ongoing collaboration with the Organic Synthesis research group of the Department of Chemistry. The aim of my PhD project was to revise common synthetic procedures applied in the portfolio of Huvepharma products in terms of Green Chemistry perspective and, in the long term of the Sustainable Developments Goals.

The *file rouge* of my PHD scientific project consisted in addressing the environmental impact of the use of solvents in organic synthesis and in evaluating their substitution with more sustainable options. Solvents are of great environmental concern in a chemical process mainly because they are used in vast quantities; it has been estimated that they represent more than 70% of the waste associated with API production. Common volatile organic compounds (VOCs), which are the conventional solvents used in most industrial processes, as well as in academic research, possess many drawbacks from an environmental point of view, as they show accumulation in the atmosphere, flammability, high toxicity, and non-biodegradability.

However, a change in the solvent of the synthetic procedure may completely change the way in which functional groups react. The use of new unconventional solvents implies that at basic research level, there is a need to investigate not only a new and so far unpredictable reactivity, but also chemo, regio and stereoselectivities.

Given these premises, my research activity during my PhD can be resumed at two main levels

- Study of the reactivity of organolithium compounds in protic reaction media. Investigation of the nucleophilic versus basic reactivity of organolithium reagents in non anhydrous conditions and at room temperature,
- Application of new greener conditions to the production of APIs in the Huvepharma portfolio, with focus on strategies to overcome the use of VOCs. In agreement with Huvepharma R&D coordinator, I have studied the synthesis of Febrifugina derivative Halofuginone, a coccidiostat used in the veterinary medicine, and I have tried to analyse some modifications of the synthetic steps according to the green chemistry principles, in particular using a convergent approach, cascade or multi-steps reaction, biobased solvents (CPME, 2-MeTHF, DESs, water) and catalytic reagents.

List of abbreviations and acronyms

Ac	acetyl
A*o*F	anionic *ortho*-Fries
API	active pharmaceutical ingredient
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Ch	choline
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DBE	di-*n*-butyl ether
DCM	dichloromethane
DEE	diethyl ether
DES	deep eutectic solvent
DFT	density functional theory
DMG	direct metalation group
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMU	1,3-dimethylurea
DMPU	*N,N'*-dimethylpropylidenurea
D*o*M	directed *orto*-metalation
DPP	diphenyl phosphoryl
EDG	electron donating group
EWG	electron withdrawing group
Fru	fructose
Gly	glycerol
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HMPA	*N,N,N',N',N'',N''*-hexamethylphosphoramide
HOMO	highest occupied molecular orbital
IL	ionic liquid
Im	imidazole
LA	lactic acid
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LL	lateral lithiation
LUMO	lowest unoccupied molecular orbital
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MTBE	*tert*-butyl methyl ether
NaDES	natural deep eutectic solvent

PCM	polarizable continuum model
PE	petroleum ether
PG	protecting group
PMDTA	*N,N,N′,N″,N″*-pentamethyldiethylenetriamine
PO	peroxide
SI	internal standard
SM	Suzuki-Miyaura
S_NAc	nucleophilic acyl substitution
TBA	tetrabutylammonium
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMCDA	*N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	*p*-toluenesulfonyl
VOC	volatile organic compound
Xyl	xylitol
ZPE	zero point energy

CHAPTER 1. Properties and applications of organolithium reagents

Lithium organic compounds have always been of great importance in organic synthesis since their discovery by Schlenk and Holz in 1917.[1] Major improvements in the synthesis and use of these reagents have been achieved by Ziegler,[2] Wittig[3] and Gillman[4, 5] by properly developing correct handling procedures for the preparation and use of these reagents in several synthetic methodologies such as polymerization, lithium halogen exchange and other metalation reactions. Nowadays organolithiums are indispensable reagents in organic as well as inorganic synthesis; as an example, more than 95% of the total syntheses of natural products rely upon lithium-based reagents in one form or another. However, the popularity of these reagents among the synthetic community arises not only from their high reactivity. Their availability as fairly cheap and stable commercial solutions mainly in hydrocarbons, together with the formation of relatively non-toxic byproducts (alkanes and lithium salts), make them a never-ending resource for the synthetic community.

1.1 Aggregate structure and reactivity relationship in organolithium compounds

Organolithiums (with the exception of methyllithium and phenyllithium) are soluble in hydrocarbons,[6-8] as a consequence most of organolithium-based starting materials are available as stable hydrocarbon solutions. On the other hand, methyllithium and phenyllithium require the presence of coordinating solvent (such as DEE or THF) to be stable at room temperature. Hydrocarbon solution of *n*-, *s*-, *t*-BuLi, and ethereal solution of MeLi and PhLi are the most common reagents and are generally employed as base to generate new organolithiums starting from a more acidic substrate.

The electron-deficient lithium atom of an organolithium compound requires high stabilization, since from the first pioneering studies by Dietrich and Hakansson *et al.*[9] it was demonstrated that organolithium reagents do not exist as monomers in solution, but provide stable aggregates as hexamers, tetramers and dimers.[10] The structures of these aggregates in solution were determined by X-ray diffraction[10] and deeply investigated by theoretical calculations.[11, 12] The basic building principle of solid state aggregation, driven by electrostatic interactions, is the arrangement of the lithium cations in a Li_3 triangle capped by a carbanionic α-C atom. This is the base unit of this polyhedral core in which the lithium has its preferred coordination

number of four. In simple alkyllithium reagents, these triangles aggregate to form tetrahedral or octahedral structures, as shown in Figure 1.1.[10]

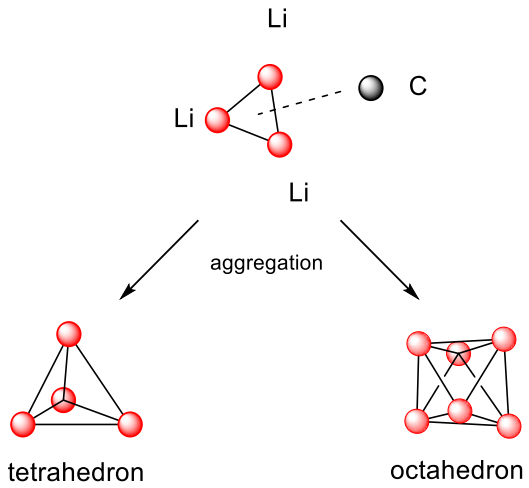


Figure 1.1. Tetrahedron and octahedron metal cores formed by aggregation of the Li_3 triangle coordination complex.

The aggregation state of simple organolithiums in solution can be easily rationalized on the basis of the steric hindrance. As shown in Table 1.1, primary organolithiums are hexamers in non-coordinating hydrocarbon solution, while secondary and tertiary organolithiums are tetramers. Finally, only very bulky organolithium reagents (such as benzyllithium and menthyllithium) are dimers.[8, 13]

Table 1.1. Typical aggregation state in hydrocarbon solution.

Hexameric	Tetrameric	Dimeric	Monomeric
EtLi	*i*PrLi	$PhCH_2Li$	-
n-BuLi	*t*-BuLi		

Coordinating ligands have a crucial effect on the stabilization of the electron-deficient lithium atoms being a powerful source of electron density. These ligands stabilize the aggregates by coordinating the lithium atoms at their vertices, promoting an entropically favoured lower degree of aggregation. The first class of these disaggregating agents are common ethereal solvents such as THF, DEE, DBE, MTBE and DME. As shown in Table 1.2, the presence of coordinating solvents promotes a shift down of the aggregation state, for example *n*-BuLi and EtLi remain tetramers in DEE, THF and DME, while *t*-BuLi becomes dimeric in DEE and monomeric in THF at low temperatures.[6]

Table 1.2. Typical aggregation state in the presence of DEE or THF.

Hexameric	Tetrameric	Dimeric	Monomeric
-	MeLi	*i*PrLi	*t*-BuLi[a]
	EtLi	*t*-BuLi	ArLi[a]
	n-BuLi	*s*-BuLi	
		ArLi	

[a] in THF at < -100 °C

The aggregation state dramatically influences the reactivity of the organolithium reagents; from a practical point-of-view, basic coordinating solvents and additives are commonly employed in combination with organolithium reagents to lower the aggregation degree of the organolithiums and increase their reactivity. Some of the most common solvents and additives are shown in Figure 1.2.

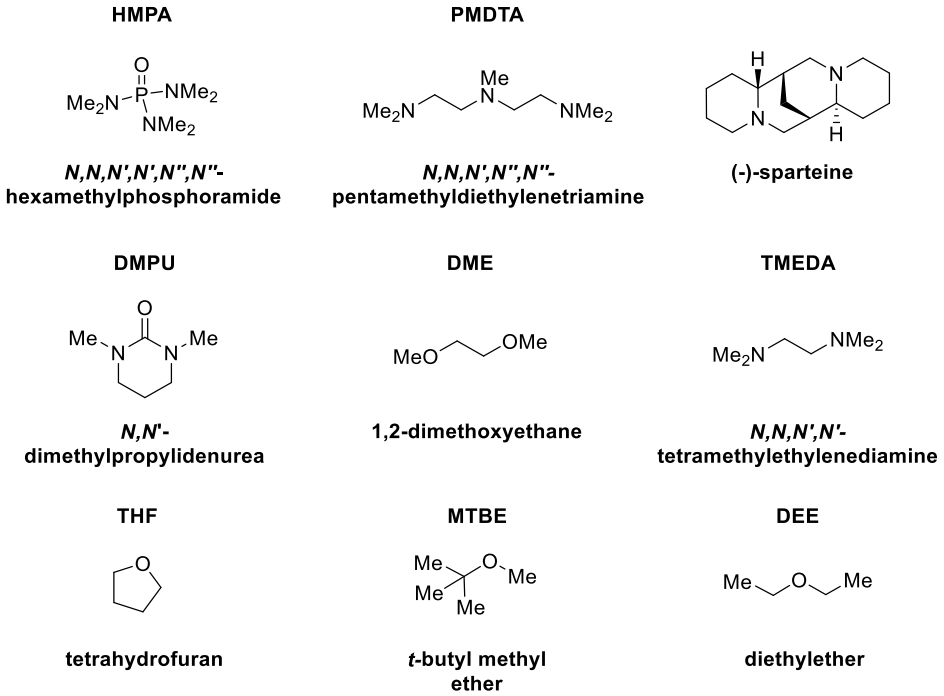


Figure 1.2. The most important coordinating solvents and additives used in organolithium chemistry in decreasing order of ability to deaggregate.

All the solvents suffer to some extent from a tendency to react with organolithiums, precluding their use at temperatures above ambient, and in some cases limiting them to 0 °C or below. It is well-known that DEE is stable over a period of days in presence of *n*-BuLi at room temperature,[14] while THF is easily decomposed at this temperature by a reverse cycloaddition mechanism.[15] *s*-BuLi

and *t*-BuLi decompose ethereal solvents much more rapidly than *n*-BuLi, therefore their use is limited to temperatures below 0 °C.[16] The stability of an organolithium in the presence of a specific additive is commonly evaluated on the basis of its half-life time (time required to reduce the initial concentration of 50%), as shown in Table 1.3.

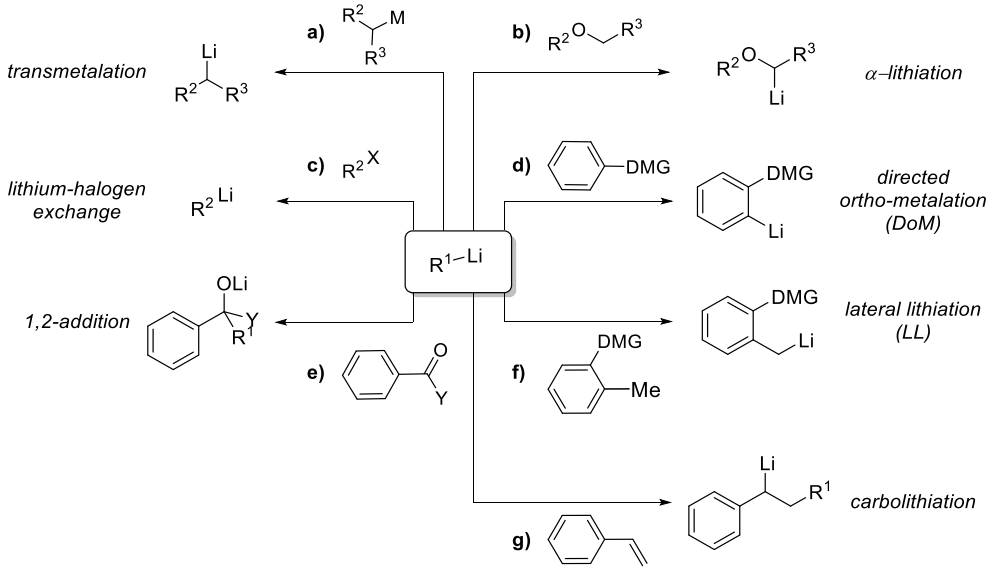
Table 1.3. Stability of organolithiums in commonly used solvents.

RLi	Solvent	Temperature (°C)	Half-life
MeLi	DEE	25	3 months
PhLi	DEE	35	12 days
n-BuLi	DME	0	5 minutes
	DEE	25	153 hours
	DEE/TMEDA	25	10 hours
	THF	35	10 minutes
	THF/TMEDA	25	30 minutes
	THF/TMEDA	-20	50 hours
t-BuLi	DEE	0	1 hours
	DEE	-20	8 hours
	THF	-20	45 minutes

As previously mentioned, solutions of alkyllithiums are the ultimate source of most organolithiums, but a number of other bases are widely used to generate organolithiums starting from more acidic substrates. Among them, hindered lithium amide bases (*e.g.* lithium diisopropylamide, LDA, and lithium 2,2,6,6-tetramethylpiperidine, LiTMP) are extensively employed in organic synthesis by virtue of the combination of their features, such as strong Brønsted basicity and low nucleophilicity, especially with respect to electrophilic carbon centres. LDA and LiTMP are not soluble in hydrocarbons and are generally freshly prepared in ethereal solvents because of their relatively low stability and difficult storage. Advanced ^{6}Li, ^{13}C and ^{15}N NMR experiments reported by Collum *et al.*[17] combined with crystallographic studies[18] have clearly demonstrated that these species exist in solution as solvated dimer-monomer, and the nature of these aggregates is strongly influenced by the presence of coordinating additives (such as the same dialkylamino-precursor when used in slight excess) and by the concentration.[19, 20]

1.2 Basic reactivity of organolithium compounds: C-H functionalization

Organolithium reagents are used in a plethora of different organic transformations in which they act either as strong bases or nucleophiles. The most common applications of organolithiums in organic synthesis are shown in Scheme 1.1.



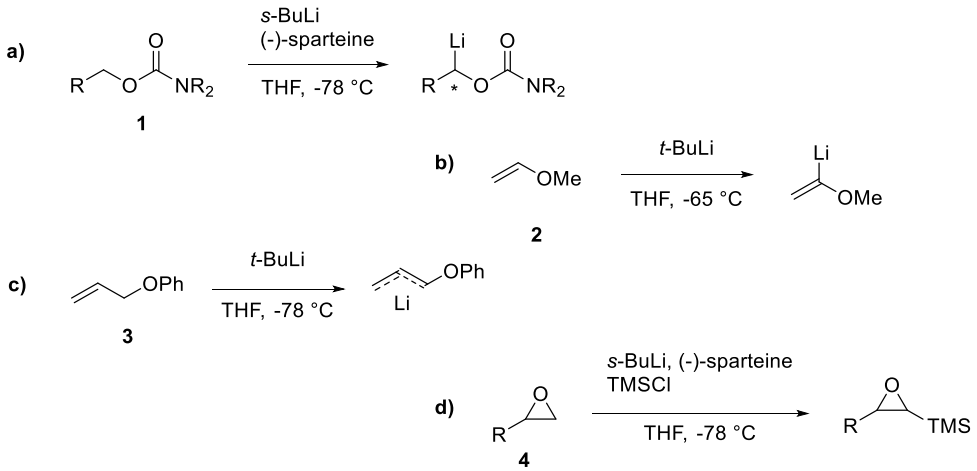
Scheme 1.1. Examples of organolithium reactivity with different electrophilic starting materials: **a)** transmetalation; **b)** α-lithiation to heteroatoms; **c)** lithium-halogen exchange; **d)** directed *ortho*-metalation; **g)** 1,2-addition to carboxylic acid derivatives; **e)** lateral lithiation of arenes; **f)** carbolithiation of olefines.

The capacity to activate a specific C-H bond and transform it into a more versatile functional group represents an important and long-standing goal in chemistry.[6, 21] The strong basicity of the organolithiums makes these reagents elected for C-H deprotonation-functionalization strategies of weakly acidic substrates. In general, lithiation by deprotonation of a C-H bond occurs only if the resulting organolithium displays two features: a) intramolecular coordination of the electron-deficient lithium atom to a heteroatom-containing functional group (for this reason hydrocarbons are extremely difficult to lithiate) and b) stabilization of the electron-rich C-Li by a nearby empty orbital or electron-withdrawing functionalities. In the next section, three of the most common syntheses of organolithiums by C-H deprotonation will be discussed: deprotonation α to heteroatoms, directed *ortho*-metalation and lateral lithiation of arenes.

1.2.1 Lithiation α to heteroatoms

Lithiation adjacent to a heteroatom is favoured by strongly acidifying groups, able to enhance the acidity of the α proton by inductive effect, but it can also take place in positions adjacent to oxygen or nitrogen-containing functional groups which apparently decrease the acidity of the adjacent proton. In general, this lithiation proceeds easily if the proton to be removed is in a benzylic or allyl-stabilized position.[22]

Deprotonation α to oxygen is unfavorable because of an antibonding interaction between the oxygen lone pairs and C-Li bond.[6] This repulsive effect is dampened in the presence of carbonyl groups (*e.g.* in carbamate functional group) due to the delocalization of oxygen lone pair; for this reason one of the most versatile α lithiation is the deprotonation of bulky benzylic or allylic carbamates **1** promoted by *s*-BuLi, which can be remarkably carried out in an enantioselective fashion in the presence of (-)-sparteine as chiral ligand (Scheme 1.2 a). This strategy was applied to the asymmetric synthesis of highly nucleophilic organolithium species, which could be reacted with a plethora of electrophiles with excellent stereo-fidelity.[23, 24] Despite their intrinsic low stabilities, other vinylic, allylic and benzylic oxygen-containing functional groups such as vinyl **2**[25] and allyl ethers **3**,[26] furans[27] and epoxides **4**[28] were used as platforms to generate the corresponding lithiated species at low temperature in the presence of *t*-BuLi or *s*-BuLi (Scheme 1.2 b-d).



Scheme 1.2. Examples of metalation α to oxygen-containing functional groups.

Compared to oxygen, the lone pair of a nitrogen atom destabilizes any adjacent C-Li bond as consequence of a major antibonding interaction. For this reason, the direct deprotonation α to nitrogen is usually impossible with commercial

organolithiums unless the nitrogen lone pair is involved in conjugation with a carbonyl group or delocalized around an aromatic ring. The conjugation with a carbonyl group not only makes the nitrogen-containing functional group more electron-withdrawing, but also provides a new electron-rich oxygen atom that is able to stabilize the lithium atom by coordination (Figure 1.3).[6, 29] For this reason, the amide functionality is one of the most important directing group in metalation chemistry, and its use as starting material is mostly exploited in the directed *ortho*-metalation of aromatic rings (see the next section).

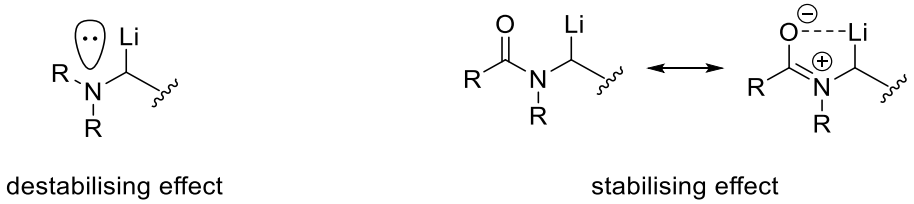
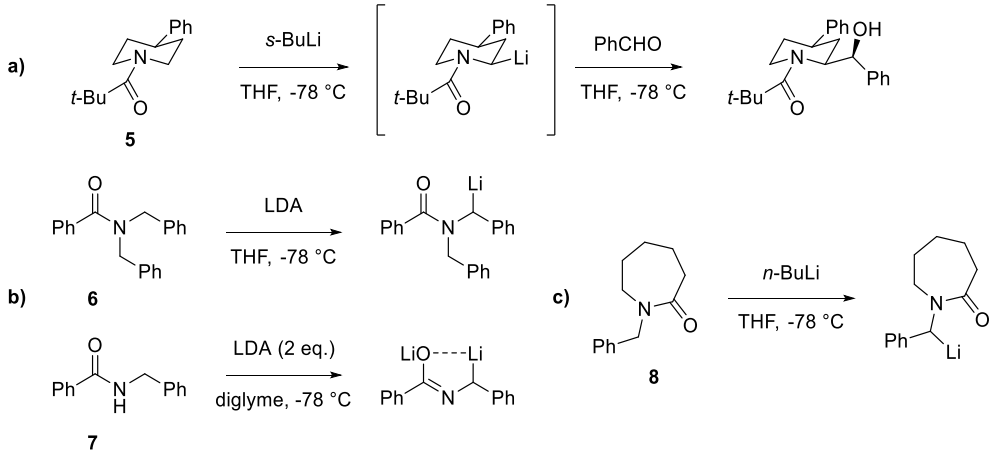


Figure 1.3. Destabilizing C-Li - N antibonding interaction and stabilizing coordination effect in the α-lithiation of carboxamides.

Example of α-lithiation of carboxamides are less common and required hindered and enolisable carboxamides (especially cyclic amides) in addition to a careful control of the reaction conditions to overcome all the possible side reactions. The synthetic impact of this strategy has been clearly illustrated in the metalation of hindered piperidines **5**, in which the selectivity is driven by the repulsion between C-Li and the π-system of the amide (Scheme 1.3, a),[29] in the metalation of benzylic amides **6**, **7** with lithium amides to prevent nucleophilic substitution mechanisms (Scheme 1.3, b)[30] and in the metalation of *N*-protected lactams **8** (Scheme 1.3, c).[31]



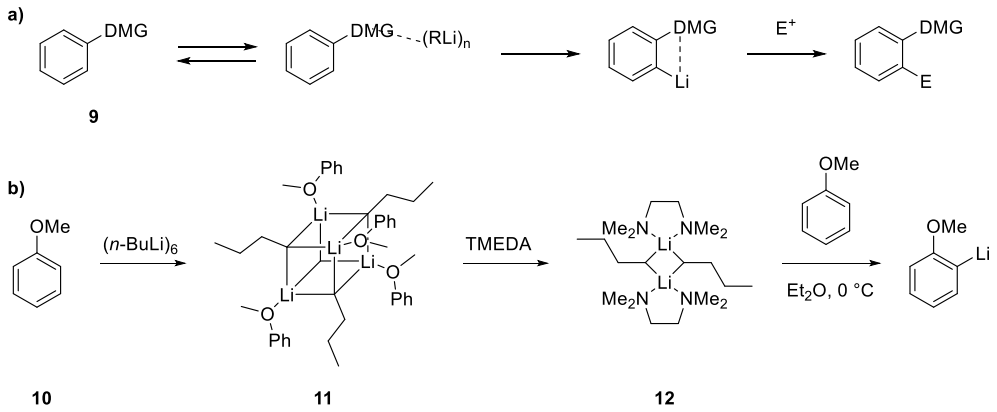
Scheme 1.3. Examples of α lithiation of amides: **a)** metalation of hindered piperidines **5**; **b)** metalation of benzylic amides **6**, **7** with LDA; **c)** metalation of *N*-benzylic lactam **8**.

α-Metalation of sulfoxides, sulfones and organic phosphates is one of most used technique to generate the corresponding ylides, very important carbon nucleophiles used in the well-known Corey-Chaykowsky and Wittig synthesis.[32] On the other hand, the metalation of thioanisole requires *n*-BuLi and DABCO in THF at 0 °C to be effective.[6, 33] In fact, the sulphur atom can increase the acidity of the α proton only by 5-10 pK_a units by an hyperconjugation effect due to the high polarizability of this atom. This strategy is used in presence of other stabilization factors such as other sulphur atoms in dithiane compounds,[34] allyl, pyridyl and imidazolyl sulfides.[22]

1.2.2 Directed ortho-metalation

The directed *ortho*-metalation (D*o*M) is the metalation of an aromatic ring in the *ortho* position of a heteroatom-containing functional group (direct metalation group, DMG) through the formation of an intermediate aryllithium species able to react with different electrophiles. Nowadays the D*o*M strategy represents the principal means of making regiospecifically substituted aromatic rings.[35]

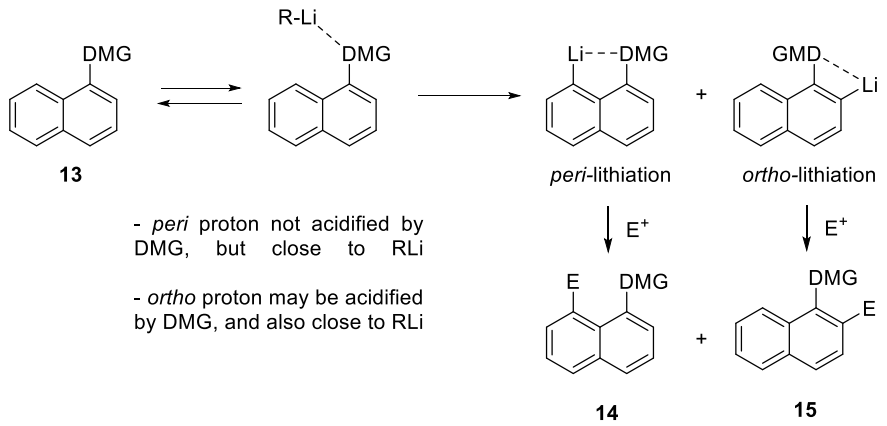
D*o*M involves the deprotonation of a substituted aromatic ring by an alkyllithium (LDA is effective only for more electron-deficient aromatic ring).[6, 35] Given that benzene is some of ten orders of magnitude more acidic than butane, thermodynamics pose no barrier to the removal of any protons by *n*-BuLi. However, the kinetic of the metalation is very slow and hampers its wide usefulness.[36] This problem can be easily overcome by the employment of disaggregating agents, such as THF and TMEDA, that lower the aggregation rate of *n*-BuLi hexamers thus allowing the reaction to proceed faster. For this reason, mechanistically, the first step of D*o*M is the pre-complexation of the alkyllithium by a coordinating site (typically a heteroatom) of the substrate **9**, whose effect is an increase of both reactivity and regioselectivity (Scheme 1.4 a).[35] For example, metalation of a benzylic amine is faster than benzene, under the same reaction conditions, owing to the capacity of amino group to activate organolithium by coordination.[37] Complexes between *n*-BuLi and anisole,[38, 39] 1,2-dimethoxybenzene and *N,N*-dimethylaniline[40] were detected by NMR and predicted by theoretical calculations. The metalation of anisole **10**, shown in Scheme 1.4 b, is considered a prototype of D*o*M: anisole **10** deaggregates the *n*-BuLi hexamers to form a tetrameric *n*-BuLi-anisole complex **11**, andh subsequent addition of TMEDA displaces the anisole from the tetramer giving a $(n\text{-BuLi})_2(\text{TMEDA})_2$ dimer **12** which represent the real metalating agent.



Scheme 1.4. D*o*M mechanism. **a)** General metalation sequence of arenes containing a directing group **9**: complexation, deprotonation, electrophilic quenching; **b)** D*o*M of anisole **10** and relative intermediate species **11**, **12**.

When the coordination with the heteroatom is hampered by electronic or geometric factors (*e.g.* in the metalation of fluorobenzene) the acidity of the *ortho*-proton is the only factor that influences the regioselectivity of the transformation. In all other cases, the regioselectivity is ruled both by electronic and geometric factors. This behaviour can be rationalized with the analysis of the metalation of 1-substituted naphthalene **13**, which could occur either in the *peri* position (favoured only by coordination) or in the *ortho* position (favoured both by coordination and acidity). The results of this comparative study, summarized in Table 1.4, showed that inductive effect becomes predominant with strong electron-withdrawing groups such as carbamates, carboxamides and MOM-protected phenols; on the other hand, in the presence of weak directors such as amino-contain functionalities the lithiation is driven by the coordination.[6]

Table 1.4. *Ortho vs peri* lithiation of 1-substituted naphthalene **13**.



DMG	Conditions	E^+	**14**, yield %	**15**, yield %
CH_2NMe_2	*n*-BuLi, Et_2O, *n*-hexane 20 °C	PhCO	58	0
NH_2	*n*-BuLi (3 eq.), Et_2O, reflux	CO_2	20	0
NMe_2	*n*-BuLi, Et_2O, 20 °C	DMF	76	0
OMOM	*n*-BuLi, TMEDA, THF -78 °C	RCHO	0	73
$OCONR_2$	*s*-BuLi, TMEDA, THF -78 °C	MeI	0	90
$CONR_2$	*s*-BuLi, TMEDA, THF -78 °C	MeI	0	85

To summarise, D*o*M is a two steps reaction (complex-formation and deprotonation) in which two features (rate and regioselectivity of the lithiation) are controlled by two factors (coordination between the organolithium and a heteroatom and acidity of the proton to be removed). The impact of these factors could be different and strictly correlated with the reaction conditions. For these reasons the choice of the directing group (DMG) is often crucial. The best performing DMGs have an "amphoteric" nature: they contain a basic heteroatom, that is able to coordinate the organolithium reagent, and at the same time, they are strongly electron-withdrawing groups capable to increase the acidity of the adjacent proton by inductive effect.[32] Chart 1 shows the most important DMGs conventionally used in organic synthesis and the general condition for their *ortho*-lithiation.

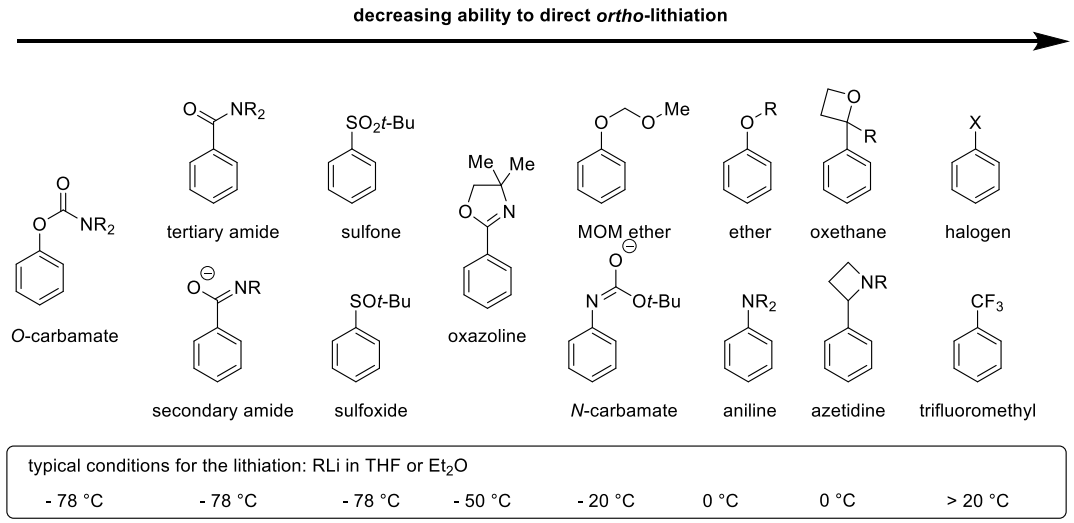
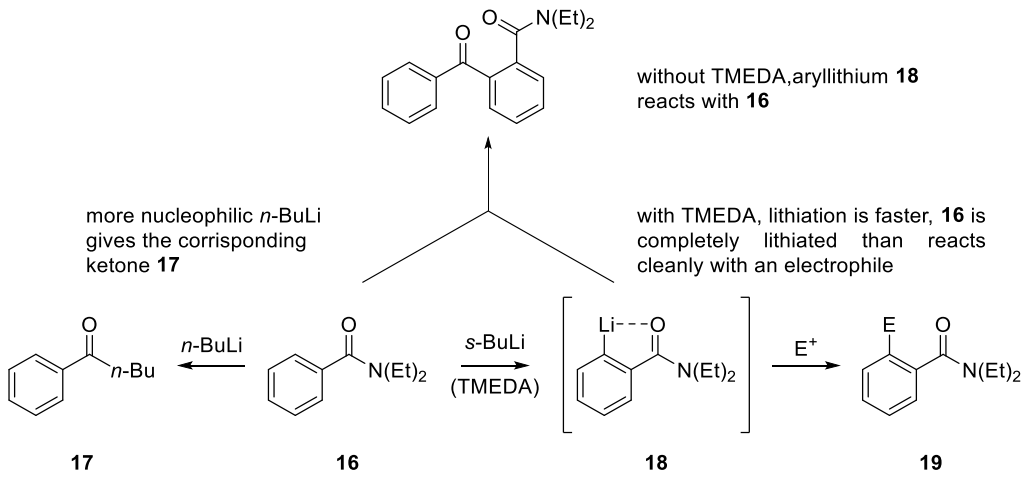


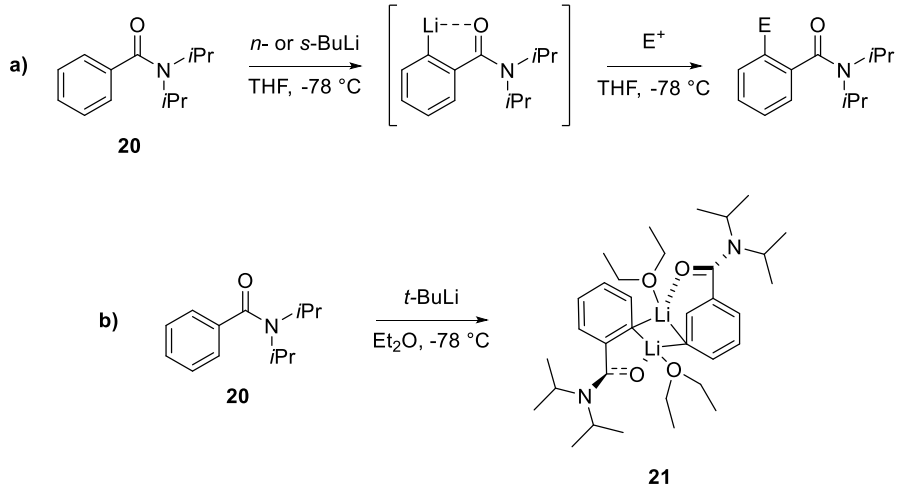
Chart 1. Most important DMGs and typical condition required for their lithiations.

The most powerful class of DMGs includes *O*-carbamates, tertiary amides and oxazolines (the so called "N+O" class). One of the major drawbacks of *O*-carbamates and tertiary amides is related to the competitive nucleophilic addition (see next section) that can be avoided by using bulkier substituent on the nitrogen atom. An example of this competition was observed in the metalation of *N,N*-diethylbenzamide **16** reported by Hauser in 1973.[41] The use of more nucleophilic *n*-BuLi lead to the formation of the corresponding ketone **17**, that could be suppressed employing *s*-BuLi. In absence of TMEDA the lithiation is slow and when the *ortho*-lithiated species **18** is formed it reacts immediately with a second molecule of starting material. On the contrary, in the presence of TMEDA the lithiation proceeds faster, the starting material is immediately lithiated and could be trapped by an electrophile leading the formation of desired *ortho*-functionalized amide **19** (Scheme 1.5).



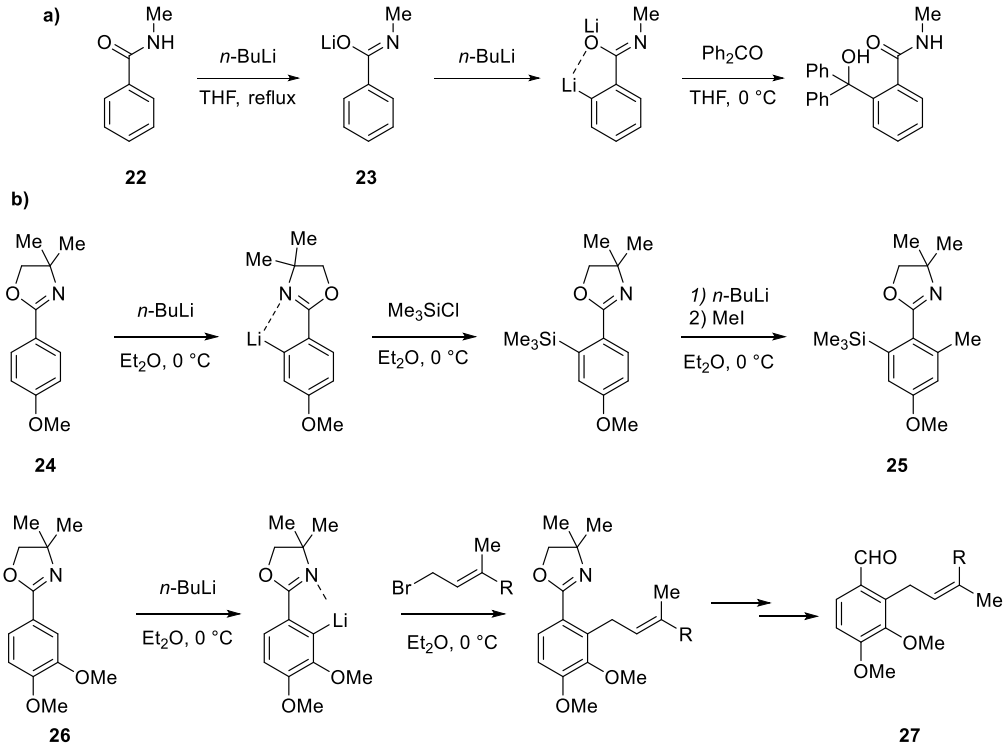
Scheme 1.5. Directed *ortho*-metalation of *N,N*-diethylbenzamide **16**: base and additives direct the reaction outcome.

On the other hand, nucleophile-resistant *N,N*-diisopropylbenzamides **20** are elected substrate for this chemistry, and they are easily lithiated at low temperature (-78 °C) using alkyllithiums in THF without TMEDA (Scheme 1.6 a).[35, 42-44] Their strong resistance to hydrolysis limits, however, their derivatization into other useful functionalities, and represent the most important drawbacks of this class of strong DMG. However, a crucial role in the clarification both of the nature of O-Li coordination and in the geometrical factor ruling the *ortho*-lithiation was also demonstrated by Clayden *et al.* who isolated and characterized the *ortho*-lithiated dimer **21**, in which one lithium atom is more or less in the plane of the amide and the other one in the plane of the aromatic ring. (Scheme 1.6 b).[45]



Scheme 1.6. a) D*o*M of *N,N*-diisopropybenzamide **20** and **b)** X-Ray crystal structure of *ortho*-lithiated *N,N*-diisopropybenzamide **21**.

N,N-dimethyl amides are, on the contrary, too much sensitive to nucleophilic attack, as a consequence they are rarely used and always at temperature below -100 °C to limit competitive pathways.[46] Another strategy used to overcome nucleophilic addition involves the use of secondary amides **22**. These are easily *ortho*-lithiated with two equivalents of base and entails the formation of the intermediate anion **23** that increases the acidity of the *ortho*-site, and prevents the 1,2 nucleophilic addition to the carbonyl by the second equivalent of the organolithium (Scheme 1.7 a).[47] Aryl oxazolines **24**, **26** show the same resistance to the nucleophilic attack and can be easily lithiated with *n*-BuLi. Example of the synthetic usefulness of these building blocks are reported in the preparations of steroid precursors **25**[48] (Scheme 1.7 b) and of lipoxygenase inhibitor AC-5-1 **27** (Scheme 1.7 c).[49]



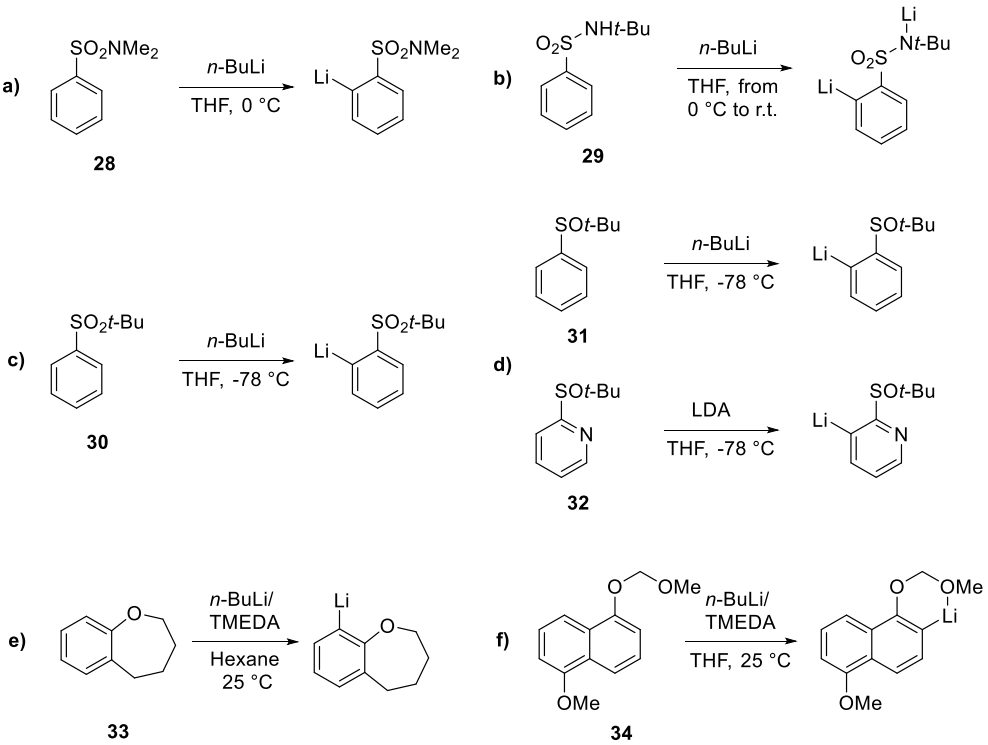
Scheme 1.7. Application of **a)** secondary amides **22** and **b)** oxazolines **24**, **26** as directing group in the D*o*M.

Strictly related to the chemistry of tertiary amides, tertiary *O*-arylcarbamates are considered one of the strongest DMGs. Their application in D*o*M was reported by Snieckus *et al.* in their pioneering study.[35] *O*-arylcarbamates are easily metalated at low temperature using alkyllithiums, however, because of the intrinsic instability of the corresponding *ortho*-lithiated species that undergo a thermal Fries rearrangement under thermodynamic conditions,[50] the control of the temperature is crucial to obtain the desired *ortho*-functionalized products. The detailed analysis of *O*-arylcarbamate both in D*o*M and in the synthesis of salicylamide derivatives *via* anionic *ortho*-Fries rearrangement will be discussed in the next section.

Within "S+O" groups, tertiary **28**[51] and secondary **29**[52] sulfonamides (Scheme 1.8 a) are among the most powerful *ortho*-directing groups known. This class does not suffer of nucleophilic attack at sulphur, and *N*-*t*-butyl sulfonamides **29** have proven to be synthetically useful since they can be easily hydrolyzed by polyphosphoric acid (Scheme 1.8 b).[52] Sulfones **30**[53, 54] and sulfoxides **31**, **32**[55] are also powerful *ortho*-directors by strong oxygen coordinative effect, but they are less useful due to the SO nucleophilic sensitivity (in sulfoxides) and competitive of α-lithiation (for these reasons *tert*-butyl derivatives are preferably used, see Scheme

1.8 c,d). On the contrary sulfides are weak *ortho*-directors and suffer of some side reaction such as the previous mentioned α-sulfur lithiation[33] and isomerization.

Among the class of the weaker *ortho*-directing groups, aryl ethers such as benzoxepine **33** have a long history in this field, and detailed studies of the mechanism of their lithiation were reported and previously discussed (see Scheme 1.4 b).[38, 39] They are often used in combination with other directors or alone[56, 57] in the presence of strong disaggregating agents (*e.g.* TMEDA) (Scheme 1.8 e). MOM-protected phenols **34** are the most used compounds of this class, where the coordination of the C-Li is the crucial component of their directing effect (Scheme 1.8 f).



Scheme 1.8. Application of further DMGs: **a)** tertiary sulfonamides **28**; **b)** secondary *N-t*-butyl sulfonamides **29**; **c)** sulfones **30**; **d)** *t*-butyl sulfoxides **31**, **32**; **e)** benzoxepines **33**; **f)** MOM-protected phenols **34**.

1.2.3 Lateral-lithiation

In strong relationship with the D*o*M strategy, the lateral lithiation (LL) of benzylic alkyl groups promoted by DMGs represents a valuable tool for the regioselective functionalization of substituted toluenes. Both the ability to coordinate and to acidify are important in a lateral directing group, and most of the classes of

functional groups which promote D*o*M are also able to promote LL. However, it is important to underline that in D*o*M processes the DMGs must operate by inductive effect since the C-Li bond lies in the same plane of the aromatic ring. On the contrary for LL, the benzylic C-Li bond means that acidifying group work best by conjugation. For this reason, lateral lithiated species have greater thermodynamic stabilization than their *ortho*-lithiated analogues (Figure 1.4).[6]

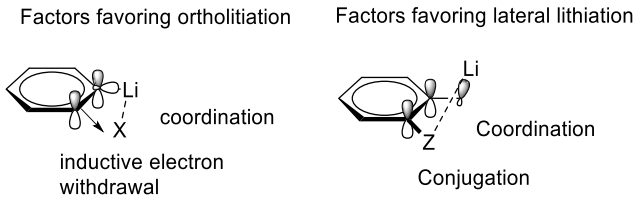
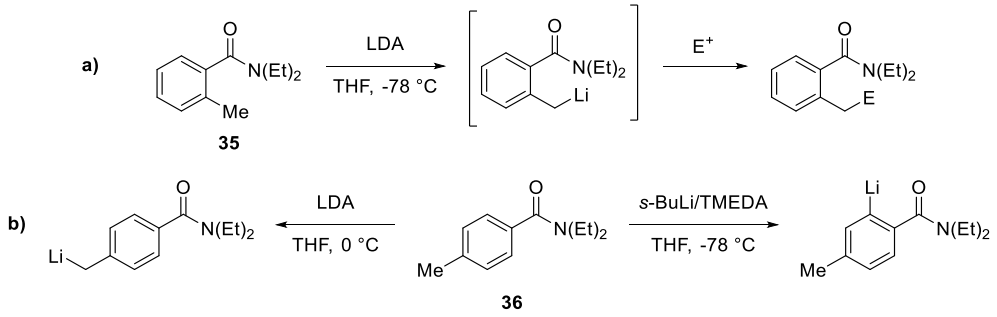


Figure 1.4. Chemical factors for C-Li stabilization in D*o*M and LL.

Due to the obvious competition with the *ortho*-deprotonation process resulting from the presence of similar DMGs, LL often suffers of cumbersome regioselectivity issues. Hence, of particular interest is the development of synthetic methods for the selective benzylic metalation of alkyl substituted aromatic compounds minimizing the competitive D*o*M pathway.[58-62] For examples, *N,N*-diethyl-2-methylbenzamides **35** are easily LL using LDA, that is basic enough to promote the benzylic lithiation, or alkyllithiums in THF at -78 °C (Scheme 1.9 a) without competition of less favored D*o*M. Using LDA, the benzylic functionalization of the less hindered *para* position in **36** is achievable suggesting that conjugation is the most important factor in the benzylic stabilization, while the coordination effect is less important (Scheme 1.9 b).[41]



Scheme 1.9. a) LL of *N,N*-diethyl-2-methylbezamide **35**; **b)** lithiation of *N,N*-diethyl-4-methylbenzamide **36** in which the base and temperature dictate the regioselectivity.

The same behavior was observed for the metalation of *N,N*-diethyl-4-methylbenzenesulfonamide **37** reported by Snieckus *et al.*[63] Under kinetic conditions at -78 °C, only the *ortho*-deuterated species was observed using *n*-BuLi in THF and

CD_3OD as electrophile; when the reaction was carried out under thermodynamic conditions (0 °C), only the lateral-deuterated product was regioselectively formed. Quenching the reaction under thermodynamic conditions, an *ortho*-lateral deuterated mixture enriched of the lateral deuterated species was formed during time, as a consequence of a dynamic equilibrium between the two lithiated species. The same benzylic product was also obtained using LDA under kinetics conditions. The same behavior was observed for tertiary toluamide **38**[43] and sulfonate **39**.[64] On other hand, the analogue secondary *N*-ethyl-4-methylbenzenesulfonamide **40** was *ortho*-lithiated using *n*-butyllithium under both kinetic and thermodynamic conditions, while the lateral lithiation was only feasible using the less basic and more hindered LDA under kinetics conditions. These experiments clearly showed that different parameters (such as base, temperature, DMGs) can influence the regioselectivity of this transformation (Figure 1.5).

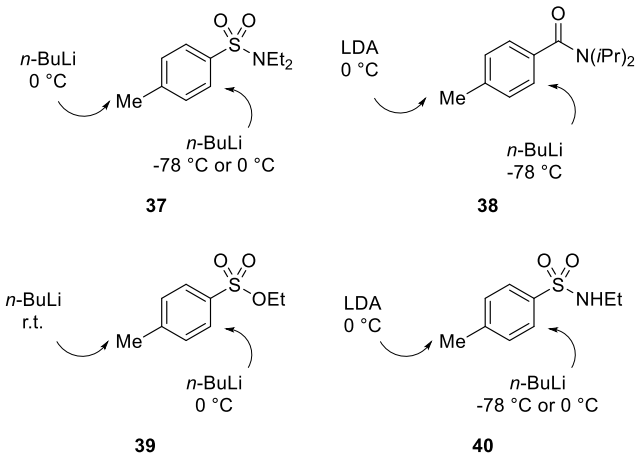


Figure 1.5. Regioselective *para* vs *ortho* functionalization.

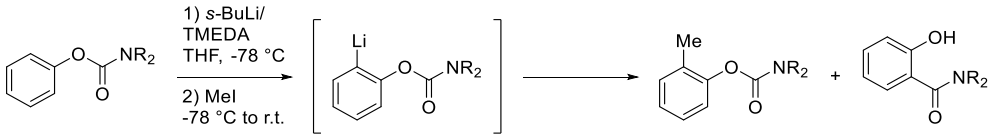
In general, *ortho* and lateral lithiation strategies have been developed in parallel since the starting materials for a D*o*M can be also employed for lateral metalations. For this reason, the specific analysis of each single DMGs will not be discussed in detail.

1.2.3 Anionic 1,3- and 1,4-Fries rearrangement

Among the wide number of functional groups which have been extensively exploited as DMGs, the *O*-aryl carbamate moiety represents one of the strongest D*o*M directors as shown in Chart 1. Aromatic carbamates are cleanly metalated at their *ortho*-position at low temperatures, allowing synthetically useful functionalizations upon electrophilic quench. In the preliminary studies reported by

Snieckus *et al.*,[65] different *N*-alkyl carbamates were tested under classical kinetic conditions in order to evaluate the effect of the *N*-substituent size on the reaction rates. The results of this study are reported in Table 1.5.

Table 1.5. Comparative study of *N*-alkyl substituents for the D*o*M of *O*-arylcarbamates **41a-c**.

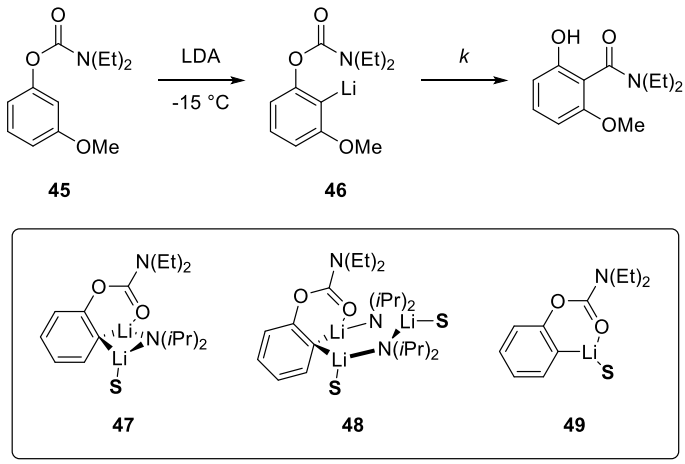


Entry	**41**, R_2	Temp. (°C)	Time (min)	*o*-Functionalized **43** yield %	Salicylamide **44** yield %
1	**a**, *i*Pr	-78	60	85	-
2	**b**, Et	-78	60	80	-
3	**c**, Me	-78	45	-	75
4	**c**, Me	-78	10	60	20
5	**c**, Me	-90	10	90	-

In the presence of bulky groups in **41a** and **41b**, the corresponding *ortho*-lithiated anions **42a** and **42b** are stable at low temperature and can be easily trapped with different electrophiles in agreement with the synthetic importance of the D*o*M process (Table 1.5 entry 1-2). On the contrary, *N,N*-dimethyl analogue **41c** affords only the corresponding salicylamide **44c** resulting from an internal carbamoyl transfer (Table 1.5, entry 3). To maximise the recovery of the *ortho*-functionalized product **43c**, lower temperature and shorter reaction times are required (Table 1.5, entry 4-5).

Independently to the nature of *N*-substituents, in the absence of an external electrophile the aryl anion generated from a *O*-arylcarbamate undergoes a rapid intramolecular carbamoyl transfer upon slow warming to room temperature, leading to the formation of functionalized salicylamides which can be further subjected to D*o*M chemistry manipulations. This process, widely known as anionic *ortho*-Fries or Snieckus-Fries rearrangement (A*o*F), has been extensively investigated by Snieckus *et al.*[66] and it is considered the anionic version of the well-known Lewis acid ($AlCl_3$) promoted cationic/radical 1,3-O shift of aryl esters at high temperature discovered by Fries in 1908.[67] Nevertheless, the high yields, the increased regioselectivity and smoother reaction conditions compared to the metal-catalysed version has made the A*o*F the first choice for the synthesis of salicylamides derivatives.

The kinetics of the Fries rearrangement can be controlled by the donor proprieties of solvent and additives, which both affect the formation of different aggregates of the lithiated species. As previously mentioned, in the absence of other functionalities on the aromatic ring, *N,N*-dimethylcarbamates undergo a rapid intramolecular acyl transfer, affording insight only into the slow (rate-limiting) *ortho* lithiation step. On the opposite, aryl carbamates such as **45** bearing activating *meta*-substituents (-OCH_3 or -F) and bulky carbamoyl groups rapidly form a relatively stable intermediate aryllithium **46**, allowing a deep kinetic and spectroscopic (NMR) investigation of the rearrangement step (Scheme 1.10).

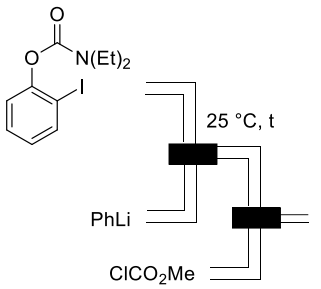


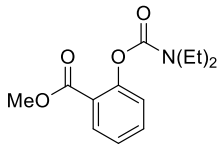
Solvent	*k*
THF	5
THF/HMPA	7700
BuOMe	90
DME	90
TMCDA	12
TMEDA	12
Me_2NEt	2

Scheme 1.10. Structures detected by NMR studies in the LDA-mediated A*o*F rearrangement of **45**.

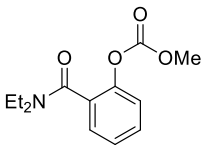
The aggregation rate depends on the concentration and the coordinating ability of the additives used. At low concentrations or in the presence of weak solvating additives, di-lithiated **47** or tri-lithiated **48** aggregates are predominant, with consequent lower reaction rates. On the contrary, the employment of strong coordinating agents, such as HMPA, leads to the formation of the mono-lithiated **49** and faster reaction rate. At high concentrations more complicated oligomers could also form.[68]

A further confirm that the A*o*F migration involves the fast formation of an *ortho*-lithiated species was given by Yoshida *et al.* with room temperature flow-experiments exploiting the high control of the residence time.[69] The recovery of the non-rearranged product **50** was possible only at very short residence time, while the increase of the residence time under these reaction conditions led to the formation of a phenate anion through an A*o*F mechanism, which was easily trapped with electrophiles leading the recovery of **51** (Scheme 1.11).





50 *non-rearranged*

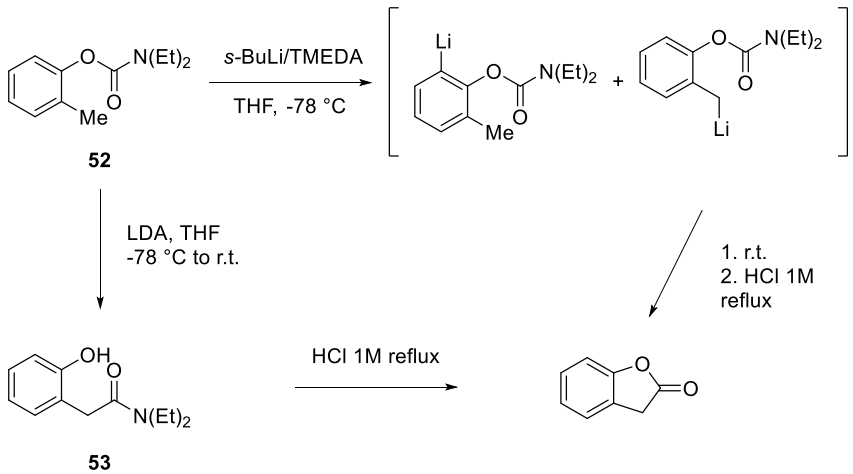


51 *rearranged*

t (ms)	**50**	**51**
628	-	91
377	20	74
220	45	51
55	73	21
14	79	15
4	87	4
0.4	91	-

Scheme 1.11. A*o*F experiments under flow conditions.

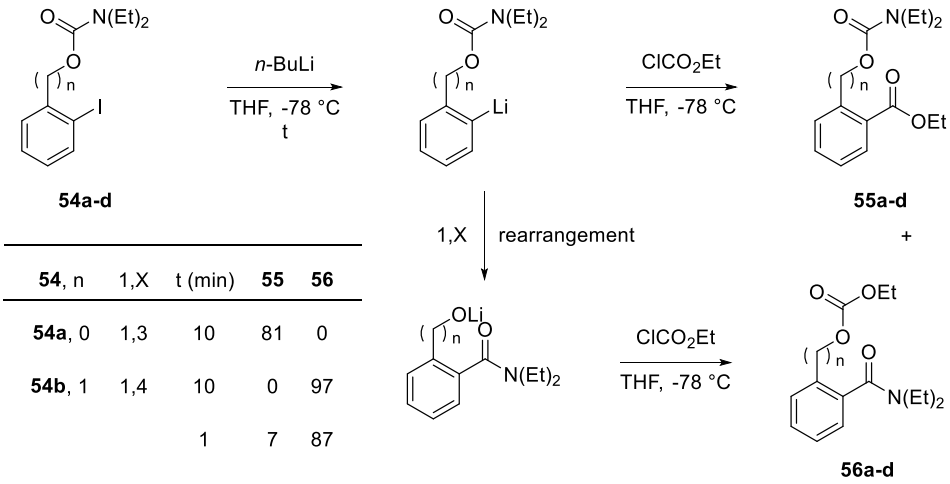
The homologous version of the A*o*F was also developed by Snieckus *et al.* based on the previously discussed lateral lithiation of substituted toluenes.[70] LDA was able to promote the lateral lithiation of *o*-tolyl carbamate **52** at low temperature, and warming the reaction at room temperature an intramolecular 1,4-carbamoyl migration lead to the corresponding benzyl amide **53**. When *s*-BuLi was used in the presence of TMEDA, a 2:1 mixture of 1,3- and 1,4- migration products was isolated, confirming the full regioselectivity of LDA as metalating agent for the lateral lithiation reaction (Scheme 1.12).[65]



Scheme 1.12. Homologous Fries rearrangement of *o*-tolyl carbamate **52**.

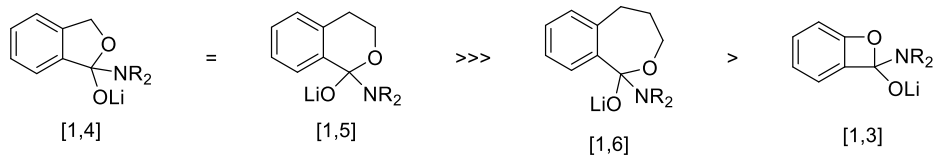
Further mechanistic insights for the remote Fries rearrangement were given by Yoshida *et al.* (Scheme 1.13),[71] using carbamate derivatives **54a-d** with an enhanced *O*-arene distance due to the presence of additional methylene units on the *O*-benzylic position. It is important to underline that in this case the metalation

step was promoted by halogen-metal exchange, at low temperatures, to direct the metalation only at the *ortho* position. In the absence of the iodine atom on the aromatic ring, the lithiation occurs selectively at the position α- to the carbamate oxygen (see Scheme 1.2 a).



54a-d **55a-d** **56a-d**

54, n	1,X	t (min)	**55**	**56**
54a, 0	1,3	10	81	0
54b, 1	1,4	10	0	97
		1	7	87
54c, 2	1,5	10	3	92
		1	5	89
54d, 3	1,6	10	82	8

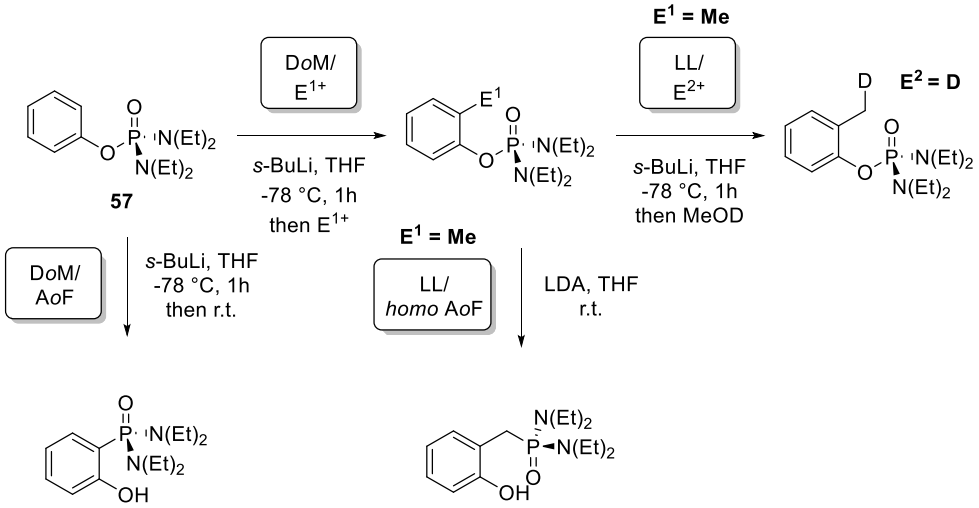


[1,4] [1,5] [1,6] [1,3]

Scheme 1.13. Chain-length dependent 1,X Fries rearrangement and ring-size dependent intermediate stability.

These results were rationalized considering the different size of the intermediate ring formed during the course of the reaction. For **54b** and **54c** (n = 1, 2), stable 5- and 6-membered cyclic intermediates are involved, which result in a rapid migration process and hence gave virtually quantitative yields of the Fries products **56b** and **56c** after 1 minute. However, for **54d** (n = 3) the 7-membered intermediate is less favoured, giving a mixture of products after 10 min. The 1,3-shift, that occurs using *O*-phenyl carbamate **54a** (n = 0), is even slower and gave exclusively the *ortho*-factionalized **55a** at low temperature.[71] This experiment further confirmed that the A*o*F involves the formation of a cyclic intermediate by the internal attack of the C-Li to the electrophilic C=O of the carbamate moiety.

The A*o*F was also extended to other acyl-containing functional groups such as carbonates, esters, carbazoles and tetrazoles, anyway the lithiation must be performed by lithium-halogen exchange as a consequence of the lower directing ability of these functional groups.[72] Finally, the scope of the A*o*F reaction has been also extended to the anionic sila-, thia- and phospho-Fries rearrangements according to the nature of the new carbon-heteroatom bond formed.[50] A recent advance in the research of new DMGs and an example of the recent application of this chemistry for the synthesis of different aromatic structures was outlined by Snieckus *et al.* using the tetraethylphosphorodiamidate **57** directing group.[62, 73] Starting from the same substate, using the previously discussed methodologies under various reaction conditions, a wide variety of products are obtainable using this peculiar P-containing directing group (Scheme 1.14).



Scheme 1.14. D*o*M, LL, phospho-A*o*F and *homo*-phospho-Fries of tetraethylphosphorodiamidate **57** directing group.

1.3 Nucleophilic reactivity of organolithiums: synthesis of ketones from amides

Organolithiums are involved in a wide number of nucleophilic reactions in organic synthesis such as addition, substitution and carbolithiation reactions in the presence of a wide array of electrophilic platforms.[32] Among these synthetically useful transformations, the nucleophilic reactivity of organolithiums with carboxylic acid amides still constitute an extremely important synthetic tool for the preparation of carbonyl-containing compounds, and will be deeply covered in this paragraph. In particular, the analysis of the nucleophilic reactivity of organolithiums will be

delimited to the same substrates discussed in the previous paragraph, with the aim of emphasize the control of the chemoselectivity.[74] The reactivity of organolithium reagents with other electrophiles will be discussed in the next chapter.

The leaving problem of the reactivity of amides with nucleophiles is the amidic resonance involving N, C and O atoms. This effect could be interpreted as a result of the delocalization of two *n* electron pairs, one from the oxygen atom and one from the nitrogen (sp^2 hybridization, Figure 1.6). As chemical evidence of this resonance, the frequencies of the amide CO stretching are lower than other carbonyl compounds, and the corresponding ^{13}C NMR spectra signals are moved upfield. Chemical consequences are displayed by the planarity of their structures, the high rotational barrier for *E/Z* isomerization, the low coordination capability of the nitrogen atom and, most important for this discussion, the high stability and the consequent limited reactivity towards nucleophiles, including organolithiums, compared to other carboxylic compounds. Furthermore, their chemical inertness could be also enhanced by the steric hindrance of the *N*- substituents.[74]

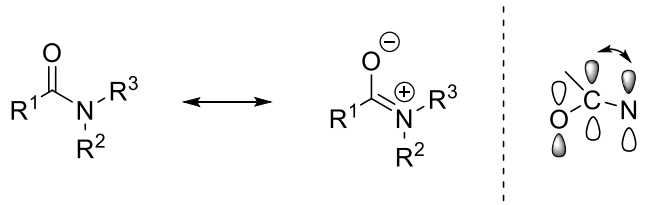
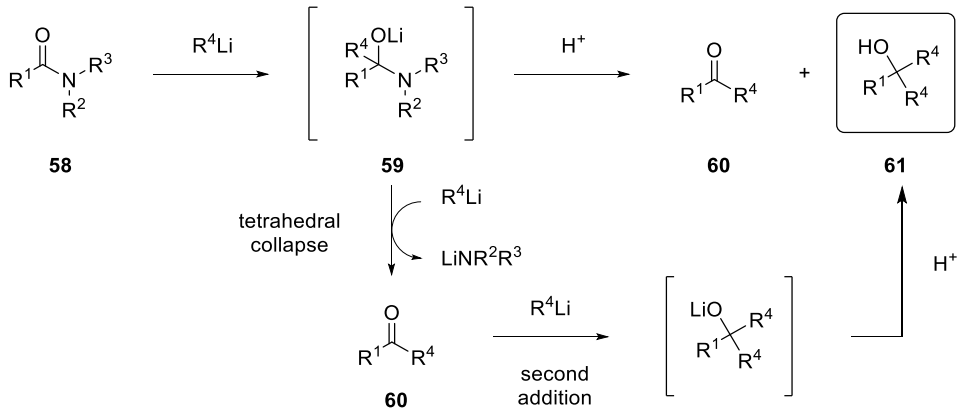


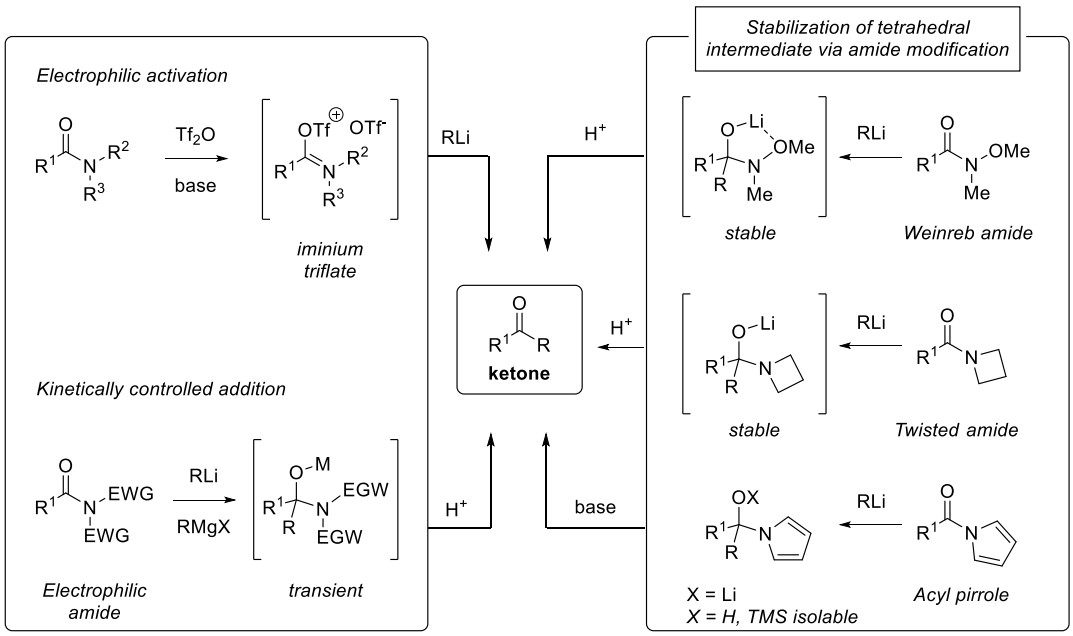
Figure 1.6. Amidic resonance.

The running problem of this chemistry consists in a mechanistic issue. It is now well known, as firstly proposed by Claisen *et al.* in 1887,[75] that the addition of a nucleophile to a carboxylic acid derivative mechanistically proceeds through the formation of a tetrahedral intermediate, in the so called addition-elimination pathway.[76] In this transformation the HOMO of the nucleophile interacts with the π* LUMO of the carbonyl leading to the formation of a new σ bond in the tetrahedral intermediate; in the second step, the interaction of an oxygen lone pair n with the σ* orbital of the C-X leads to a weakening of this bond and, finally, to the elimination of the leaving group to give the new carbonyl compound. The latter has an intrinsic reactivity toward nucleophiles and could undergo a further nucleophilic addition step leading the formation of an overaddition byproduct (alcohol). This effect is prevalent when amides **58** are used as electrophiles, since the initially formed ketone **60** is more electrophilic of the starting amide and, as a consequence, more susceptible to the nucleophilic addition of another molecule of nucleophile thus leading the formation of a tertiary alcohol **61** (Scheme 1.15).



Scheme 1.15. Mechanism of ketones **60** synthesis starting from amides **58** and the problem of the formation of overaddition byproducts.

The strategies developed for the chemoselective synthesis of ketones by direct 1,2-addition of organolithiums to amides mainly imply the increase of amide electrophilicity and/or the formation of a stable tetrahedral intermediate. These strategies can be rationalized according to: a) chemical modification of amide functionality leading to stable tetrahedral intermediates; b) kinetic controlled conditions using high electrophilic amides; c) electrophilic activation of amide via iminium triflate intermediates (Scheme 1.16).



Scheme 1.16. General strategies for the synthesis of ketones starting from amides and organolithiums.

1.3.1 Nucleophilic addition to simple amides

Despite the limitations discussed above, there are some examples of direct 1,2 addition of organolithium to simple amides, however generally associated with limited applicability and scope, specific reaction conditions and low chemoselectivity in the presence of other electrophilic functionalities.

The first example of organolithiums direct addition to *N,N*-dimethyl aliphatic amides was reported by Evans *et al.* in 1956.[77] The extension of this methodology to benzamides was reported by Olah *et al.* in 1984[78] using alkyllithiums in THF at reflux. The synthetic importance of this reaction was elated by Boche *et al.* almost fifty years later after Evans' preliminary studies with the X-ray characterization of the tetrahedral intermediate arising from the reaction between PhLi and *N,N*-dimethylbenzamide, giving the definitive demonstration that the mechanism of the acyl nucleophilic substitution reaction involves the formation of a tetrahedral intermediate.[79] Subsequently, a generalization of this methodology was reported by Scilly *et al.* with the chemoselective synthesis of ketones starting from different *N,N*-dialkylamides in moderate to good yields depending of the nature of the amides.[80] The addition of both Grignard and organolithiums to different β-aminotoluamides was reported by Brown *et al.*: the employment of benzene at room temperature is considered the key factors to suppress the competitive basic pathways.[81] Pyrrolidine amide derivatives were employed by Martin[82] and Seky *et al.*[83] for the preparation of β-hydroxyalkyl ketones and β-aminoalkyl ketones using EtLi and PhLi respectively, at low temperatures. Finally, a recent advance of this chemistry has been reported by Feringa *et al.* with the synthesis of 4-aminoaryl ketones *via* a tandem 1,2-nucleophilic addition of organolithium reagents to *N,N*-dialkylbenzamide derivatives, followed by a Buchwald-Hartwig amination reaction in THF exploiting the *in situ* released lithium amide.[84]

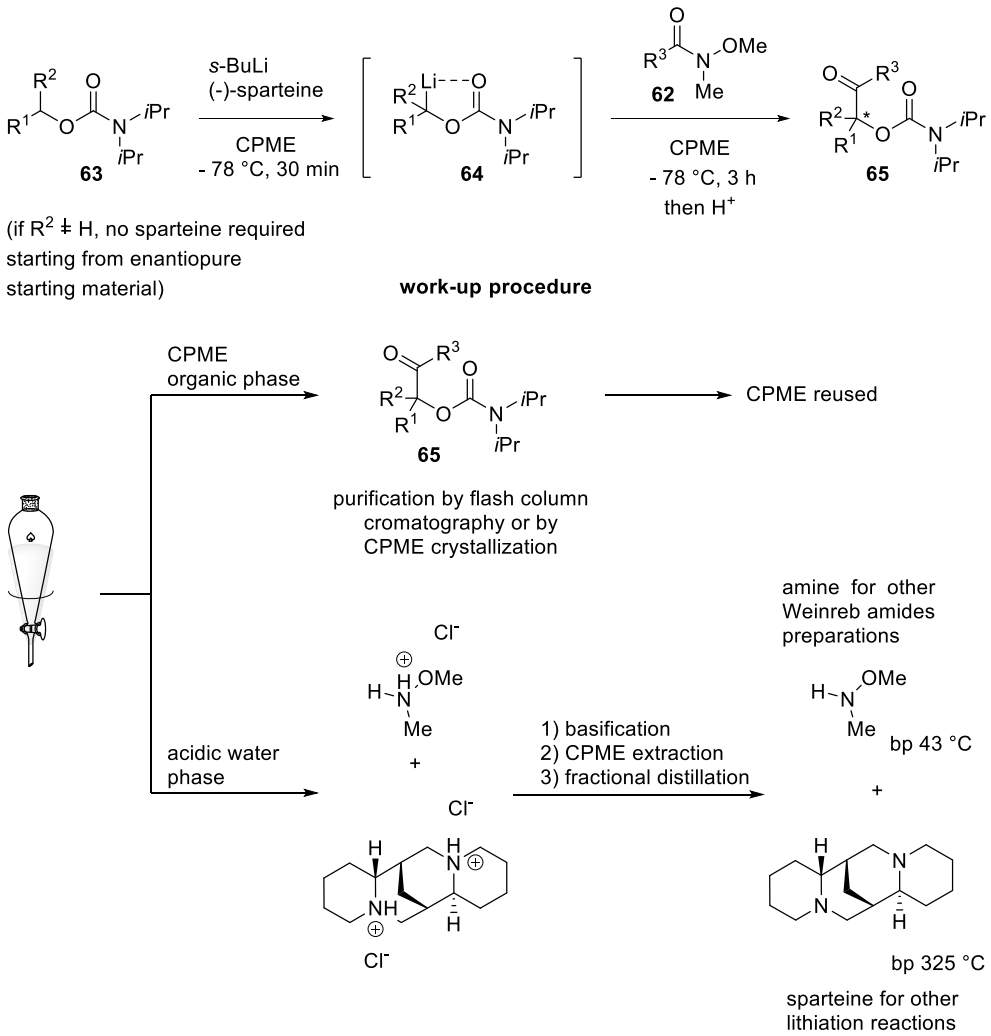
1.3.2 Nucleophilic addition to Weinreb amides and N-acylpyrroles

Before the development of robust methodologies for the activation of the amide bond, the structural modification of the amide functionality to enhance the reactivity towards nucleophiles was the predominant strategy.

Starting from the preliminary report by Weinreb and Nahm in 1981,[85] *N*-methyl-*N*-methoxy amides (the so called Weinreb amides) represented for several years the breakthrough for the chemoselective synthesis of ketones starting from acyl derivatives with total suppression of the undesired tertiary alcohol. The chemical factors for the success of this modified amides are: a) the constitutive presence of the methoxy group which highly stabilizes the tetrahedral intermediate formed upon the addition of the organolithium to the carbonyl carbon; b) the

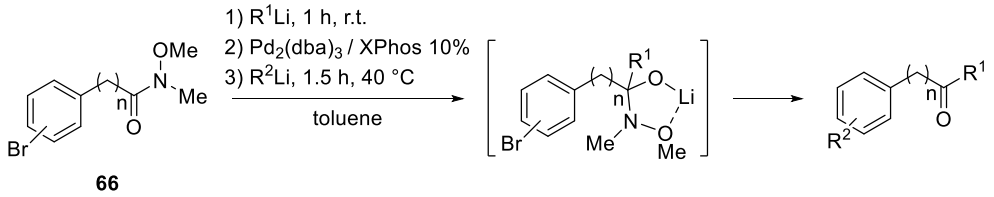
formation of a five membered chelate by coordination of the alkoxide metal cation and the methoxy group which provides excellent stability to the intermediate during the whole process, thus resulting in its collapse to deliver the ketone only at the end of the reaction upon acidic quenching (Scheme 1.16, top right); c) the methoxy group increases the electrophilicity of the carbonyl carbon, thus making it more prone to nucleophilic attack. The so obtained stabilized tetrahedral intermediate accounts for the excellent levels of chemoselectivity for the selective formation of ketones, thus suppressing overaddition phenomena also in the presence of excess of nucleophiles, as observed with different acylating agents.[86]

Comprehensive literature reviews described the application of Weinreb amides in organic synthesis, recently published by Aidhen *et al.*,[87, 88] while the development of new *N*-alkoxy amides as building blocks for different synthetic transformation has been mainly investigated by Chida and Sato.[89, 90] Pace *et al.* recently described the use of Weinreb amides as privileged acylating agents for accessing α-substituted ketones by α-functionalized organolithiums homologation reactions.[86] Expressly fascinating application reported the use of Weinreb amide **62** as acylating agents of enantiopure organolithiums **64** generated by enantioselective α-lithiation of Hoppe carbamates **63**[24] with *s*-BuLi in combination with the chiral ligand (-)-sparteine. The elected solvent for this transformation was CPME that preserved the optical purity of the generated organolithium, and, since its high hydrophobicity, allowed an extremely easy workup procedure, often limited to simple recrystallization. Furthermore, the expensive chiral ligand (-)-sparteine can be recovered by easy acid-base workup combined by fractional distillation (Scheme 1.17).[91]



Scheme 1.17. Weinreb amides as acylating agent of lithiated Hoppe carbamates **64**: synthesis of optically pure α-oxy ketones **65** and recycling procedure.

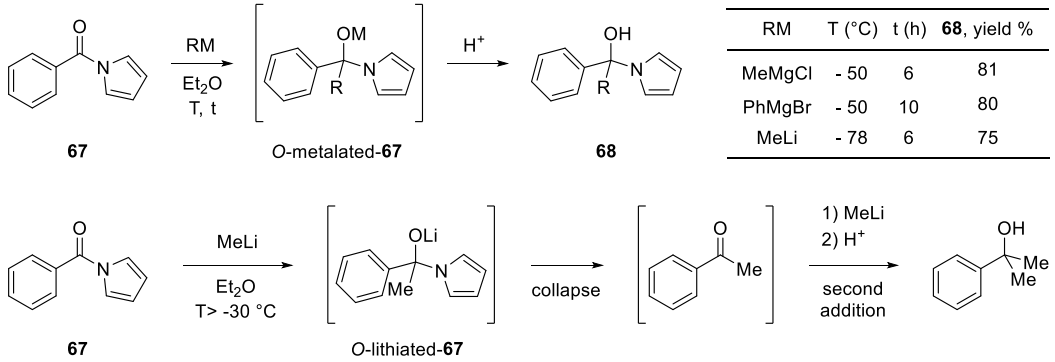
Recently, a tandem 1,2 addition/cross-coupling sequence using two different organolithiums and Weinreb amides **66** was elegantly described by Feringa *et al.* (Scheme 1.18).[92] The possibility to developed cascade reactions, exploiting in this case the modular organolithiums reactivity, is one of the most important goal in organic chemistry limiting the purification steps and the production of waste.



66

Scheme 1.18. Feringa one-pot 1,2 addition/Pd-catalysed cross-coupling with Weinreb amides.

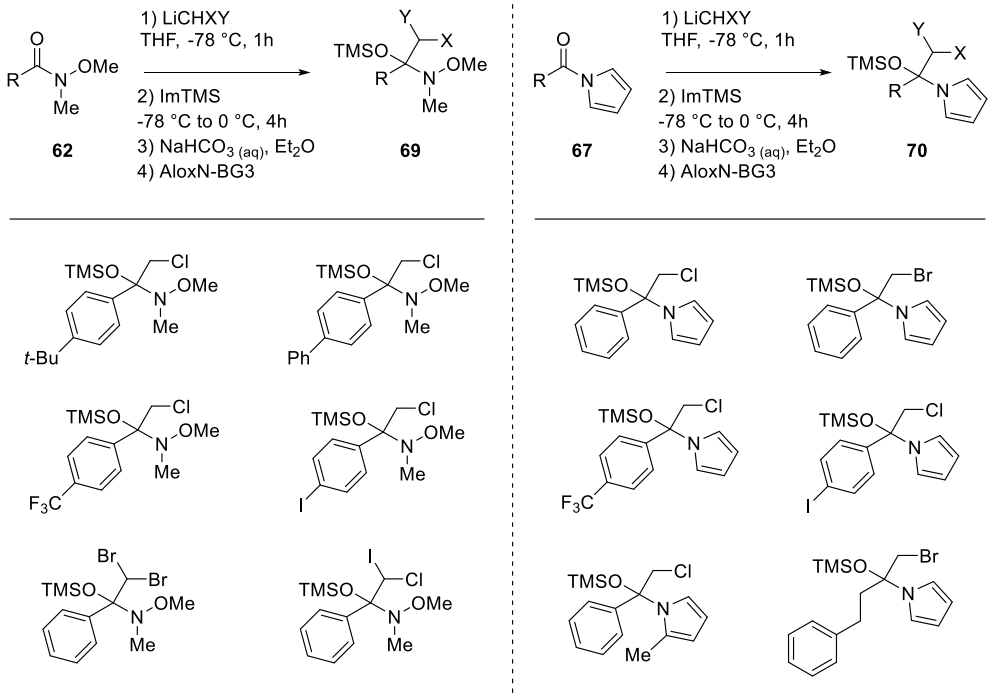
Another important class of modified amides are represented by *N*-acylpirroles **67**, described for the first time by pioneering studies by Evans *et al.* in 2002.[93] These peculiar structures were defined as ketone-like compounds as a consequence of the nitrogen lone pair delocalization in the aromatic ring. The aromatization of the nitrogen lone pair decreases the conjugation with the carbonyl fragment thus increasing its electrophilic behaviour, and at the same time deactivates the azotated moiety as leaving group. For these reasons, the nucleophilic addition of an organometallic species leads to the formation of a stable and isolable carbinol **68**. Even the stability of this adduct can be attributed to the pyrrole aromaticity, as the lack of an accessible lone pair prevents protonation of the nitrogen atom and the decomposition to the carbonyl derivative. This can be considered the first example of a stable and isolable tetrahedral intermediate. The conversion of the carbinol **68** to the corresponding ketone was finally achieved by basic treatment (Scheme 1.19). However, the choice of temperature and the organometallic reagent is crucial to define the stability of *O*-metalated-**67**. By *in situ* IR spectroscopy investigations the authors observed that if organolithiums are used for this protocol, the corresponding *O*-lithiated-**67** is stable only below -30 °C.



RM	T (°C)	t (h)	**68**, yield %
MeMgCl	- 50	6	81
PhMgBr	- 50	10	80
MeLi	- 78	6	75

Scheme 1.19. Addition of organometallics to *N*-acylpyrroles **67**: synthesis of carbinols **68** and stability towards organolithiums.

Beyond the Evans carbinol, the inherent transient nature of the tetrahedral intermediates implies severe difficulties in their isolation and spectroscopic investigations. To this purpose, Pace *et al.* recently proposed an elegant derivatization of these species exploiting the highly oxophilic TMS-imidazole (ImTMS) trapping agent (Scheme 1.20).[94]



Scheme 1.20. *O*-TMS protected hemiaminals **69**, **70** from Weinreb amides **62** and *N*-acylpyrroles **67** and lithium carbenoids as nucleophilic agents.

Pivotal for the successful isolation and characterization of the *O*-TMS hemiaminals **69**, **70** were a) the choice of a trapping agent with a remarkable oxophilicity and at same time providing the sufficient stability to avoid the undesired elimination of the nitrogen moiety; b) chromatographic purification on deactivated alumina; c) the use of C_6D_6 as deuterated solvent for NMR characterization. The potential and the preserved chemical integrity of **69**, **70** were tested in a Feringa organolithium cross-coupling[95] and on the one step formation of an α,β-epoxyketone. Nevertheless, the scope of this transformation was limited to only mono- and dihalo lithium carbenoids as nucleophilic partner.

The discovery of stable tetrahedral intermediates by amide modification boosted the research toward the development of new synthons for the preparation

of unsymmetrical ketones by controlled double addition of organolithiums (Figure 1.7).[96, 97, 98, 99]

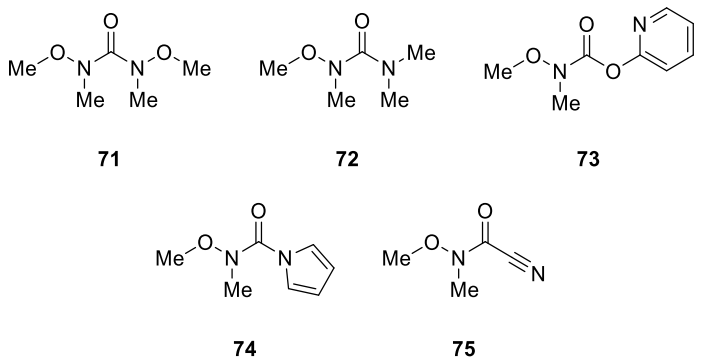
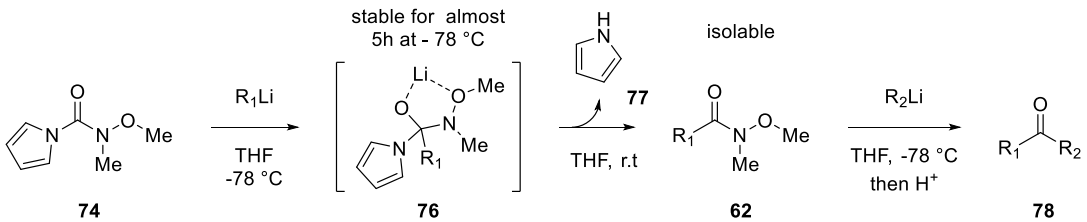


Figure 1.7. Carbonyl dication synthetic equivalents for the preparation of unsymmetrical ketones.

In particular, the *N,O*-dimethylhydroxylamine pyrrole **74** (CLamP) developed by Sarpong *et al.*[98] combined the properties of Weinreb amides and *N*-acylpyrroles, thus allowing the facile one-pot synthesis of unsymmetrical ketones **78**. This carbonyl bis-electrophile reacts rapidly with different organometallic reagents to generate a semipersistent tetrahedral intermediate **76** at -78 °C, and thus allows the selective monoaddition of the first nucleophile. Upon warming to ambient temperature, the putative intermediate readily collapses to exclusively generate a Weinreb amide **62** *in situ*, since the major nucleofugacity of pyrrole **77**, which can react in turn with a suite of organometallic nucleophiles to insert the second carbon ligand and generating asymmetric ketones **78** (Scheme 1.21).

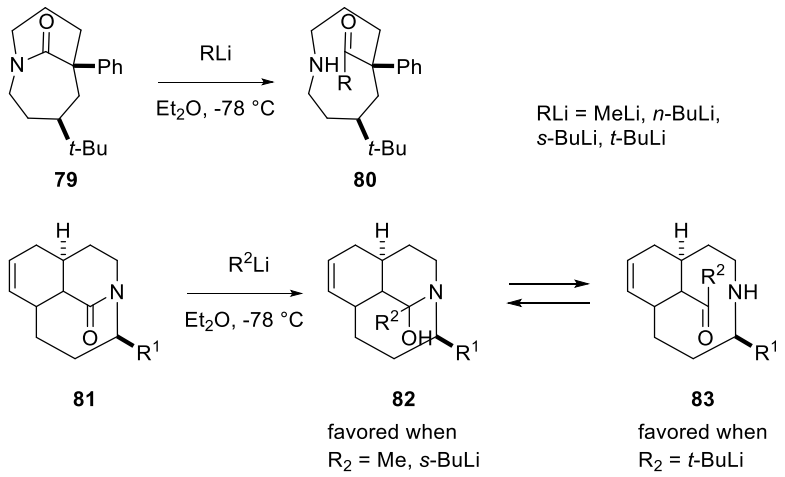


Scheme 1.21. Synthesis of asymmetric ketones **78** using CLamP **74** as carbonyl dication synthetic equivalent.

1.3.3 Nucleophilic addition to twisted amides

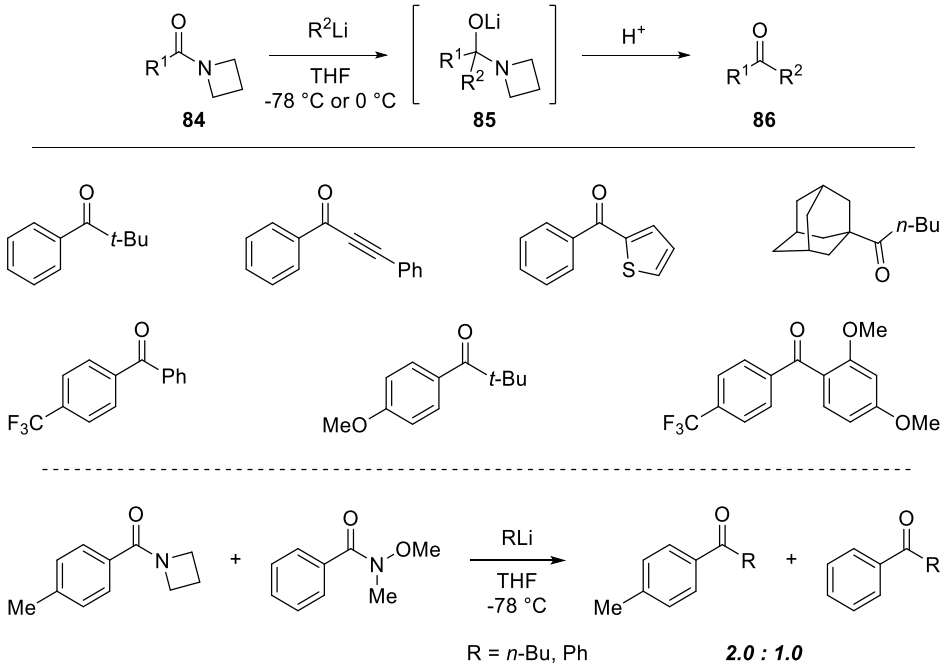
As previously discussed, the major account for the chemical inertness of the amide functional group is attributed to the amide resonance. In this context, the implementation of a steric distortion around the amide bond lowers the planarity of

the system due to the less pronounced amidic resonance, with a consequent increase of the amide reactivity. Preliminary investigations by Aubè *et al.*[100, 101] on the reactivity of bicyclic **79** and tricyclic bridged lactams **81** with various nucleophiles (including organolithiums) showed that distorted amide bonds increase the electrophilicity of the carbonyls which display a reactivity profile analogous to ketones. The results of the addition of organometallics can vary from collapsed amino ketones such as **80** and **83** to stable tetrahedral intermediates (such as hemiaminals **82**). Indeed, addition to bicyclic **79** and tricyclic lactams **81** provided the corresponding amino ketones **80** and **83** respectively with a steric impediment for the overaddition (Scheme 1.22).



Scheme 1.22. Addition of organolithiums to bicyclic **79** and tricyclic lactams **81**.

Despite this limited application, monumental advances in this field have been achieved by Szostak *et al.*, and nowadays the major synthetical importance of this class of non-planar amides relies in metal catalysed cross-coupling methodologies *via* C-N bond cleavage.[102, 103] The same research group also reported the possibility to use *N*-acylazetidines **84** as an alternative to the most common Weinreb amides for direct acylation reactions relying on pyramidalization as reactivity-controlling strategy (Scheme 1.23).[104] The peculiar geometrical proprieties of this substrate are: a) half pyramidalization of the amide bonds allows enhanced N–C(O) reactivity due to diminished amidic resonance, b) the large ring strain in a four-membered ring and high barrier for nitrogen inversion (90° angle) decreases the aptitude for collapse of the tetrahedral intermediate **85**.



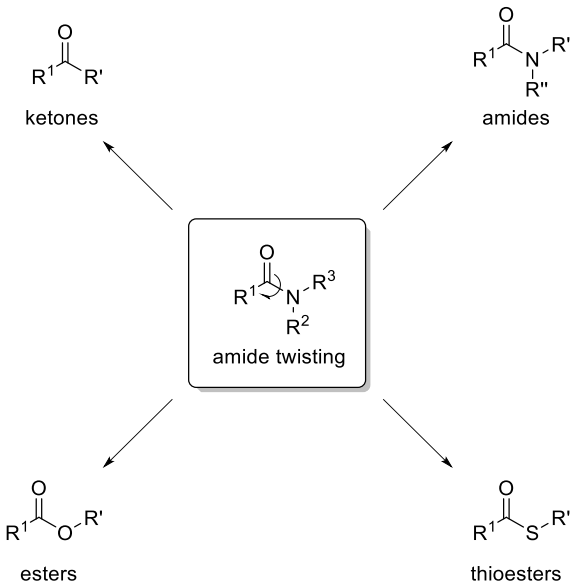
Scheme 1.23. 1,2-Addition of organolithiums to *N*-acylazetidines **84**: synthesis of ketones **86** *via* pyramidalization control strategy.

The method presented wide substate scope and total chemoselectivity for the ketone formation. The synthesis of different ketones **86** using alkyl, alkynyl and (hetero)aryllithiums, starting from both aliphatic and aromatic scaffold bearing both electron donating and electron withdrawing substituents, was reported with good yields. Studies of the stability of **85** were conducted employing a large excess of organolithium and performing the reaction at high temperature with, however, high level of selectivity. Finally, an intermolecular competitive experiment demonstrated the higher reactivity of *N*-acylazetidines **84** than Weinreb amides, showing that nucleophilic addition is kinetically favoured to the *N*-pyramidalized amide bond.

1.3.4 Nucleophilic addition to amides with N-EWG substituents

The easiest method to twist the amide bond relies on the incorporation of the amide function into a rigid cyclic system. However, the synthesis of polycyclic lactams is challenging (due to the severe decrease of the amidic resonance), applications are limited and cannot be adapted to readily available acyclic amides. On the other hand, the presence of easily introducible/removable EWG on the amidic nitrogen considerably enhances the electrophilic character of the carbonyl group, with important structural and reactivity consequences. The first examples of this second class of twisted amides include cyclic amine derivatives such as *N*-

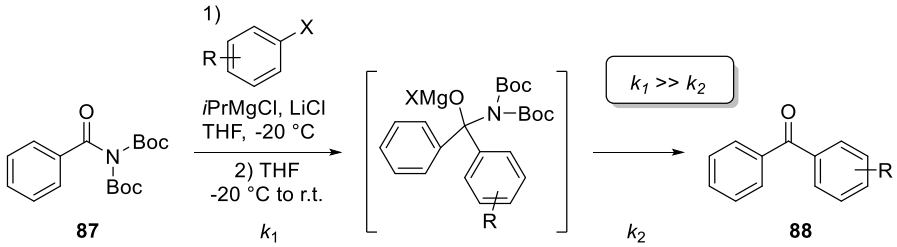
tetramethylpiperidine (TMP), *N*-glutarimide or *N*-succinimide[103, 105] that, however, could suffer of susceptibility to hydrolysis. Recently, Szostak *et al.* proposed the use of amides *N*-EWG_2 (EWG = Boc, Ts, COOEt) as a new generation of twisted acyclic amides.[105] These systems could be easily and reversibly prepared from common primary amides with high level of distortion triggered by the strongly electron withdrawing effect of the nitrogen substituents. Furthermore, a major stability to the hydrolysis compared to the aforementioned bridged lactams was observed. For these reasons, these particular electrophilic amides are an exceptional platform for transition metal- and, more interesting, transition metal-free transformations *via* the notorious complicated C-N cleavage using simple, scalable an mild conditions in the presence of the selected nucleophiles (Scheme 1.24).[106]



Scheme 1.24. Transition-metal free transformations of twisted amides *via* direct nucleophilic addition.

A recent application to the synthesis of aryl ketones *via* direct nucleophilic addition of turbo-Grignard compounds[107] was recently documented by Szostak *et al.* (Scheme 1.25).[108] In this report, the key step to obtain ketones with complete chemoselectivity was the extremely fast addition to the electrophilic *N,N*-Boc_2-benzamide **87**, which is faster than the collapse of the tetrahedral intermediate. Therefore, using a low sub-stoichiometric amount of organometallic reagents, aryl ketones **88** were recovered as the sole products, while an excess of nucleophilic partner led to tertiary alcohols. Considering that a fast addition is crucial to obtain the desired chemoselectivity, the organometallic addition must be fast and the control of temperature was essential (below -20 °C the nucleophilic addition was

extremely slow leading to low conversions, while at room temperature the increased instability of the tetrahedral intermediate led to the formation of a considerable amount of tertiary alcohol). Under the optimized reaction conditions, *N,N*-Boc_2 benzamides **87** have proven to be more reactive than the classical Weinreb amides and even acyl chlorides. However, the methodology is not compatible with alkyl Grignard and organolithiums: using an aryllithium as nucleophilic partner led to the formation of tertiary alcohol as unique product. In any case, this represented the first synthesis of ketones via ultrafast addition of an organometallics to an electrophilic amide *via* transient tetrahedral intermediate.

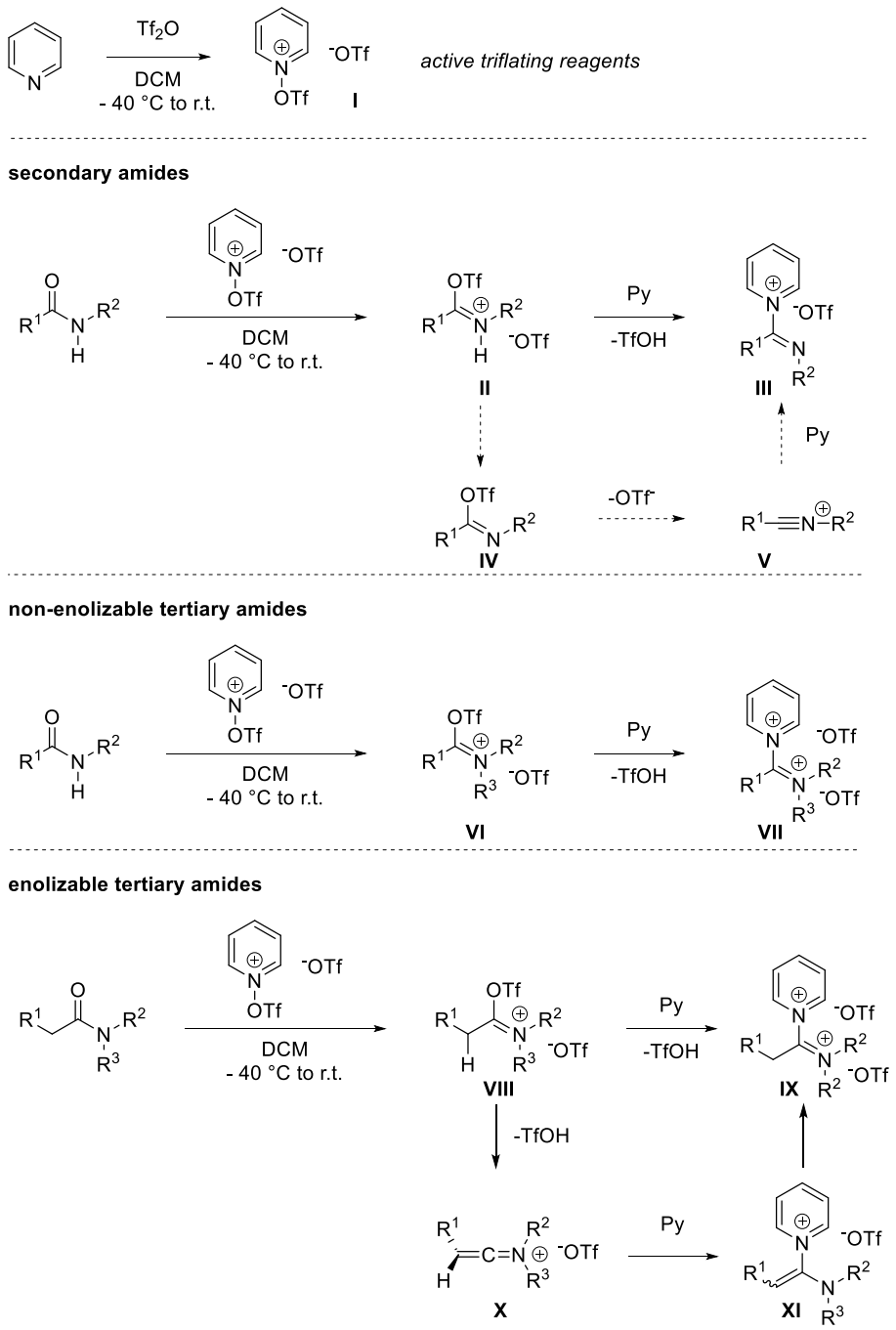


Scheme 1.25. Direct nucleophilic addition of turbo-Grignards to electrophilic amides **87** *via* transient tetrahedral intermediates.

1.3.5 Nucleophilic addition to activated amides

A conceptually distinct approach aimed at increase the reactivity of amides involves their pre-activation with a strong electrophilic agent such as triflic anhydride Tf_2O.[74, 109] The reaction of an amide and Tf_2O in the presence of a base generates a highly electrophilic iminium triflate. In 2001 Charette *et al.*[110] performed an elegant spectroscopic investigation that allowed identification of the intermediates formed in the reaction of different amides with Tf_2O and pyridine. They elucidated the structures of the triflating reagent (*N*-(trifluoromethylsulfonyl)pyridinium triflate) involved in such reactions and the most important intermediates formed under the reaction conditions. As reported in Scheme 1.26, secondary amides react with **I** to give the *O*-trifliminium triflate **II**, which reacts with pyridine yielding pyridinium intermediate **III**. The latter step can alternatively proceed through the elimination of the triflate anion from **IV** with formation of the nitrilium ion **V**. Tertiary amides lacking enolisable protons follow an analogous activation pathway yielding pyridinium triflate **VII**, although the process requires longer reaction times to reach completion. Conversely, in the case of enolisable amides two different routes could lead to pyridinium intermediates **IX** and **XI**. The first route involves the expulsion of TfOH by deprotonation to give keteneiminium triflate **X**, which could further react with excess pyridine providing **XI**. Alternatively, the sequential addition of pyridine

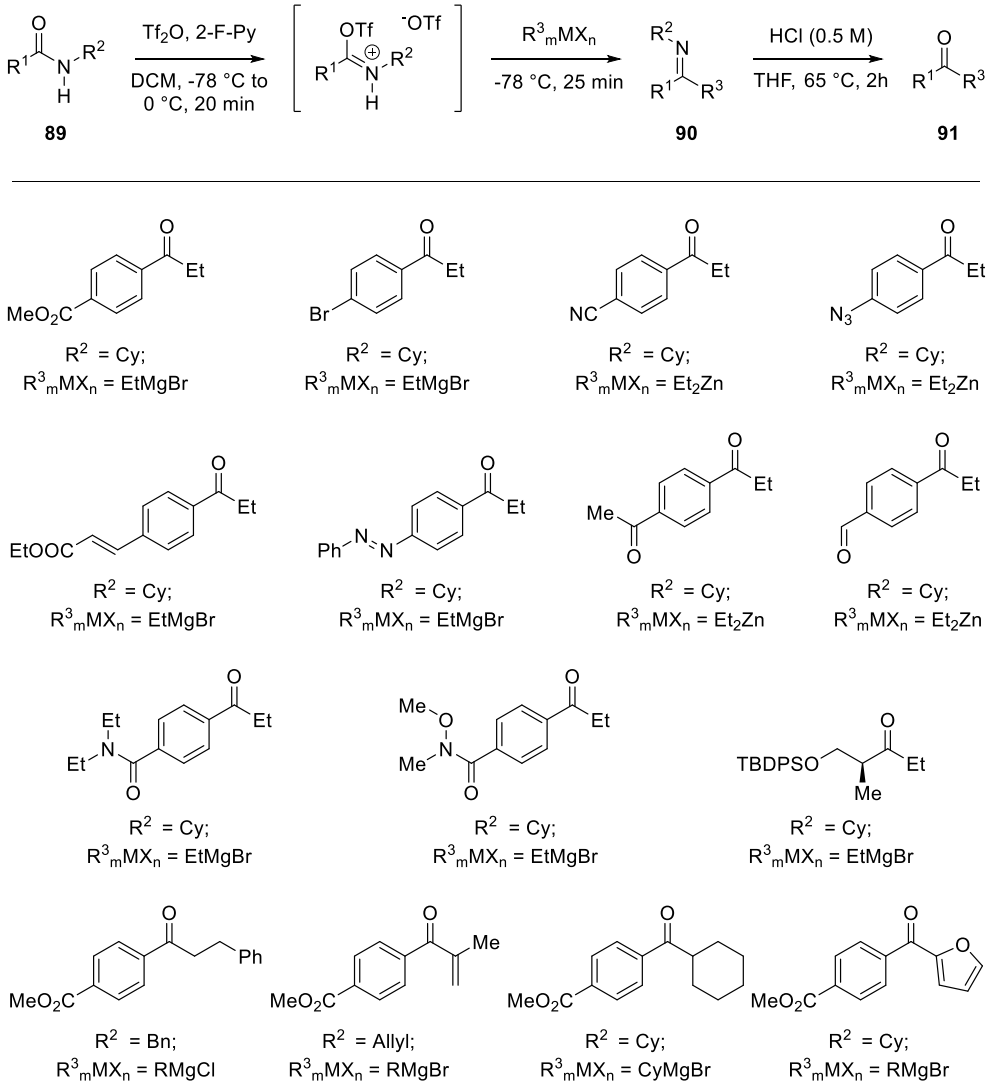
and expulsion of triflate anion could afford intermediate **IX**. Finally, proton removal could form **XI** (Scheme 1.26).



Scheme 1.26. Pyridinium intermediates generated from amide upon activation with Tf_2O/pyridine.

Different research groups combined this strategical activation of amides with different nucleophilic partners thus allowing the synthesis of different classes of products including: amines by reduction with Hantzsch ester[111] or $NaBH_4$,[112] imines or aldehydes by reduction with triethylsilane (Et_3SiH),[113] tertiary alkyl amide by double nucleophilic addition of Grignard reagents,[114, 115] tertiary alkyl amine by single addition of organometallics followed by $NaBH_4$ or $LiAlH_4$ reduction,[116] secondary alkyl amines by single addition of organoceriums followed by $NaBH_4$ reduction.[117] These important findings have been exploited in the synthesis of important intermediates required for the preparation of natural products and biologically active compounds.[118-121] In general, these proposed protocols showed great selectivity and impressive functional groups tolerance due to the selectivity of the electrophilic activation and the reactivity of the iminium intermediate.

The development of iminium triflate intermediates chemistry provided the foundation for the full chemoselective access to generic ketones starting from secondary amides **89** with Grignard or organozinc reagents. Preactivation of the amide with triflic anhydride allowed the fast and extremely chemoselective nucleophilic addition of organometallics, and prevents the formation of overaddition products by providing a stable intermediate ketimine **90**, which release the desired ketone **91** exclusively upon acid hydrolysis (Scheme 1.27).[122] Nevertheless, the use of organolithium in this methodology is limited because of their high intrinsic reactivity.



Scheme 1.27. Charette's synthesis of ketones *via* Grignard or organozinc addition to activated secondary amides **89**.

References

1. U. Wietelmann and J. Klett, *Z. Anorg. Allg. Chem.*, 2018, **644**, 194-204.
2. K. Ziegler and H. Colonius, *Justus Liebigs Ann. Chem.*, 1930, **479**, 135-149.
3. G. Wittig and M. Leo, *Ber. Dtsch. Chem. Ges.*, 1931, **64**, 2395-2405.
4. H. Gilman, E. Zoellner and W. Selby, *J. Am. Chem. Soc.*, 1932, **54**, 1957-1962.
5. H. Gilman, F. W. Moore and O. Baine, *J. Am. Chem. Soc.*, 1941, **63**, 2479-2482.
6. J. Clayden, *Organolithiums: selectivity for synthesis*, Elsevier, 2002.
7. B. J. Wakefield, *Organolithium methods*, Academic Press, 1988.
8. B. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974.
9. G. Hilmersson, P. I. Arvidsson, Ö. Davidsson and M. Håkansson, *J. Am. Chem. Soc.*, 1998, **120**, 8143-8149.
10. R. Luisi and V. Capriati, *Lithium compounds in organic synthesis: from fundamentals to applications*, John Wiley & Sons, 2014.
11. P. v. R. Schleyer, *R. Pure Appl. Chem*, 1984, **56**, 151-162.
12. S. M. Bachrach and A. Streitwieser, *J. Am. Chem. Soc.*, 1986, **108**, 3946-3951.
13. T. L. Brown, in *Organomet. Chem.*, Elsevier, 1970, pp. 447-462.
14. H. Gilman, A. Haubein and H. Hartzfeld, *J. Org. Chem.*, 1954, **19**, 1034-1040.
15. R. Bates, L. Kroposki and D. Potter, *J. Org. Chem.*, 1972, **37**, 560-562.
16. P. Stanetty, H. Koller and M. Mihovilovic, *J. Org. Chem.*, 1992, **57**, 6833-6837.
17. J. S. DePue and D. B. Collum, *J. Am. Chem. Soc*, 1988, **110**, 5518-5524.
18. M. F. Lappert, M. J. Slade, A. Singh, J. L. Atwood, R. D. Rogers and R. Shakir, *J. Am. Chem. Soc.*, 1983, **105**, 302-304.
19. D. B. Collum, *J. Am. Chem. Soc*, 1991, **113**, 5751-5757.
20. J. L. Rutherford and D. B. Collum, *J. Am. Chem. Soc.*, 2001, **123**, 199-202.
21. S. Florio and A. Salomone, *Synthesis*, 2016, **48**, 1993-2008.
22. J. F. Biellmann and J. B. Ducep, *Org. React.*, 2004, **27**, 1-456.
23. D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem. Int. Ed.*, 1990, **29**, 1422-1424.
24. D. Hoppe and T. Hense, *Angew. Chem. Int. Ed.*, 1997, **36**, 2282-2316.
25. J. E. Baldwin, G. A. Hoefle and O. W. J. Lever, *J. Am. Chem. Soc.*, 1974, **96**, 7125-7127.
26. W. C. Still and T. Macdonald, *J. Am. Chem. Soc.*, 1974, **96**, 5561-5563.
27. J. A. Joule, K. Mills and G. F. Smith, *Heterocyclic chemistry*, CRC Press, 2020.
28. D. M. Hodgson and S. L. Norsikian, *Org. Lett.*, 2001, **3**, 461-463.
29. P. Beak and W. J. Zajdel, *J. Am. Chem. Soc.*, 1984, **106**, 1010-1018.
30. R. R. Fraser, G. Boussard, I. D. Postescu, J. J. Whiting and Y. Y. Wigfield, *Can. J. Chem.*, 1973, **51**, 1109-1115.
31. P. Beak and A. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356-363.
32. J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic chemistry*, Oxford university press Oxford, 2001.
33. E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097-4099.
34. A. Streitwieser Jr and S. P. Ewing, *J. Am. Chem. Soc.*, 1975, **97**, 190-191.
35. V. Snieckus, *Chem. Rev.*, 1990, **90**, 879-933.
36. M. Rausch and D. Ciappenelli, *J. Organomet. Chem.*, 1967, **10**, 127-136.
37. F. N. Jones, M. F. Zinn and C. R. Hauser, *J. Org. Chem.*, 1963, **28**, 663-665.
38. R. A. Rennels, A. J. Maliakal and D. B. Collum, *J. Am. Chem. Soc.*, 1998, **120**, 421-422.
39. W. Bauer and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1989, **111**, 7191-7198.

40. N. Hommes and P. v. R. Schleyer, *Tetrahedron*, 1994, **50**, 5903-5916.
41. R. E. Ludt, J. S. Griffiths, K. N. McGrath and C. Hauser, *J. Org. Chem.*, 1973, **38**, 1668-1674.
42. P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2607-2616.
43. P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34-46.
44. P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306-312.
45. J. Clayden, R. P. Davies, M. A. Hendy, R. Snaith and A. E. Wheatley, *Angew. Chem. Int. Ed.*, 2001, **40**, 1238-1240.
46. G. E. Keck, T. T. Wager and J. F. D. Rodriquez, *J. Am. Chem. Soc.*, 1999, **121**, 5176-5190.
47. W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 853-856.
48. H. Butenschön, M. Winkler and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.*, 1986, 388-390.
49. J. Nakano, K. Uchida and Y. Fujimoto, *Heterocycles*, 1989, **29**, 427-430.
50. M. Korb and H. Lang, *Chem. Soc. Rev.*, 2019, **48**, 2829-2882.
51. H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis and D. Slocum, *Can. J. Chem.*, 1969, **47**, 1543-1546.
52. J. G. Lombardino, *J. Org. Chem.*, 1971, **36**, 1843-1845.
53. M. Iwao, T. Iihama, K. Mahalanabis, H. Perrier and V. Snieckus, *J. Org. Chem.*, 1989, **54**, 24-26.
54. J. Clayden, J. J. A. Cooney and M. Julia, *J. Chem. Soc., Perkin Trans. 1*, 1995, 7-14.
55. C. Quesnelle, T. Iihama, T. Aubert, H. Perrier and V. Snieckus, *Tetrahedron Lett.*, 1992, **33**, 2625-2628.
56. S. Cabiddu, L. Contini, C. Fattuoni, C. Floris and G. Gelli, *Tetrahedron*, 1991, **47**, 9279-9288.
57. H. Christensen, *Synth. Commun.*, 1974, **4**, 1-9.
58. R. B. Bates and T. J. Siahaan, *J. Org. Chem.*, 1986, **51**, 1432-1434.
59. F. Faigl and M. Schlosser, *Tetrahedron Lett.*, 1991, **32**, 3369-3370.
60. J. Clayden, M. Helliwell, C. McCarthy and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3232-3249.
61. J. r. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang and M. Campbell, *J. Org. Chem.*, 2015, **80**, 3368-3386.
62. M. Alessi, J. J. Patel, K. Zumbansen and V. Snieckus, *Org. Lett.*, 2020, **22**, 2147-2151.
63. S. L. MacNeil, O. Familoni and V. Snieckus, *J. Org. Chem.*, 2001, **66**, 3662-3670.
64. B. I. Alo and O. B. Familoni, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1835-1838.
65. M. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni and V. Snieckus, *Eur. J. Org. Chem.*, 2018, **2018**, 440-446.
66. M. P. Sibi and V. Snieckus, *J. Org. Chem.*, 1983, **48**, 1935-1937.
67. K. Fries and W. Pfaffendorf, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 212-219.
68. J. C. Riggs, K. J. Singh, M. Yun and D. B. Collum, *J. Am. Chem. Soc.*, 2008, **130**, 13709-13717.
69. H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim and J.-i. Yoshida, *Science*, 2016, **352**, 691-694.
70. A. Kalinin, M. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. Coelho, M. Kerr and V. Snieckus, *Synlett*, 1997, **1997**, 839-841.
71. H. Kim, K. Inoue and J.-i. Yoshida, *Angew. Chem. Int. Ed.*, 2017, **129**, 7971-7974.
72. I. R. Hardcastle and P. Quayle, *Tetrahedron Lett.*, 1994, **35**, 1749-1750.

73. J. J. Patel, T. Blackburn, M. Alessi, H. Sawinski and V. Snieckus, *Org. Lett.*, 2020, **22**, 3860-3864.
74. V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697-3736.
75. L. Claisen, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 646-650.
76. M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **18**, 193-209.
77. E. A. Evans, *J. Chem. Soc.*, 1956, 4691-4692.
78. G. A. Olah, G. Surya Prakash and M. Arvanaghi, *Synthesis*, 1984, 228-230.
79. M. Adler, M. Marsch, N. S. Nudelman and G. Boche, *Angew. Chem. Int. Ed.*, 1999, **38**, 1261-1263.
80. N. F. Scilly, *Synthesis*, 1973, 160-161.
81. D. L. Comins and J. D. Brown, *J. Org. Chem.*, 1986, **51**, 3566-3572.
82. R. Martín, O. Pascual, P. Romea, R. Rovira, F. Urpí and J. Vilarrasa, *Tetrahedron Lett.*, 1997, **38**, 1633-1636.
83. M. Seki and K. Matsumoto, *Tetrahedron Lett.*, 1996, **37**, 3165-3168.
84. J. de Jong, D. Heijnen, H. Helbert and B. L. Feringa, *Chem. Commun.*, 2019, **55**, 2908-2911.
85. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815-3818.
86. R. Senatore, L. Ielo, S. Monticelli, L. Castoldi and V. Pace, *Synthesis*, 2019, **51**, 2792-2808.
87. S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, **2008**, 3707-3738.
88. J. Singh, N. Satyamurthi and I. S. Aidhen, *J. Prakt. Chem.*, 2000, **342**, 340-347.
89. Y. Yanagita, H. Nakamura, K. Shirokane, Y. Kurosaki, T. Sato and N. Chida, *Chem. Eur. J.*, 2013, **19**, 678-684.
90. T. Sato and N. Chida, *Org. Biomol. Chem.*, 2014, **12**, 3147-3150.
91. S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson and V. Pace, *ChemSusChem*, 2019, **12**, 1147.
92. M. Giannerini, C. Vila, V. Hornillos and B. Feringa, *Chem. Commun.*, 2016, **52**, 1206-1209.
93. D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188-3191.
94. L. Castoldi, W. Holzer, T. Langer and V. Pace, *Chem. Commun.*, 2017, **53**, 9498-9501.
95. M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Nat. Chem.*, 2013, **5**, 667-672.
96. D. J. Hlasta and J. J. Court, *Tetrahedron Lett.*, 1989, **30**, 1773-1776.
97. W. L. Whipple and H. J. Reich, *J. Org. Chem.*, 1991, **56**, 2911-2912.
98. S. T. Heller, J. N. Newton, T. Fu and R. Sarpong, *Angew. Chem. Int. Ed.*, 2015, **127**, 9977-9981.
99. J. Nugent and B. D. Schwartz, *Org. Lett.*, 2016, **18**, 3834-3837.
100. M. Szostak and J. Aube, *Chem. Rev.*, 2013, **113**, 5701-5765.
101. M. Szostak, L. Yao and J. Aubé, *J. Am. Chem. Soc.*, 2010, **132**, 2078-2084.
102. C. Liu and M. Szostak, *Chem. Eur. J.*, 2017, **23**, 7157-7173.
103. V. Pace, W. Holzer, G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *Chem. Eur. J.*, 2016, **22**, 14494-14498.
104. C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375-2378.
105. G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *J. Am. Chem. Soc.*, 2018, **140**, 727-734.
106. G. Li and M. Szostak, *Chem. Rec.*, 2020, **20**, 649-659.
107. R. L.-Y. Bao, R. Zhao and L. Shi, *Chem. Commun.*, 2015, **51**, 6884-6900.
108. G. Li and M. Szostak, *Chem. Eur. J.*, 2019, **26**, 611-615.

109. V. Pace and W. Holzer, *Aust. J. Chem.*, 2013, **66**, 507-510.
110. A. B. Charette and M. Grenon, *Can. J. Chem.*, 2001, **79**, 1694-1703.
111. G. Barbe and A. B. Charette, *J. Am. Chem. Soc.*, 2008, **130**, 18-19.
112. S.-H. Xiang, J. Xu, H.-Q. Yuan and P.-Q. Huang, *Synlett*, 2010, **2010**, 1829-1832.
113. G. Pelletier, W. S. Bechara and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817-12819.
114. K.-J. Xiao, J.-M. Luo, X.-E. Xia, Y. Wang and P.-Q. Huang, *Chem. Eur. J.*, 2013, **19**, 13075-13086.
115. K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang and P.-Q. Huang, *Angew. Chem. Int. Ed.*, 2010, **122**, 3101-3104.
116. K.-J. Xiao, Y. Wang, K.-Y. Ye and P.-Q. Huang, *Chem. Eur. J.*, 2010, **16**, 12792-12796.
117. K.-J. Xiao, A.-E. Wang and P.-Q. Huang, *Angew. Chem. Int. Ed.*, 2012, **124**, 8439-8442.
118. H.-H. Huo, X.-E. Xia, H.-K. Zhang and P.-Q. Huang, *J. Org. Chem.*, 2013, **78**, 455-465.
119. H.-H. Huo, H.-K. Zhang, X.-E. Xia and P.-Q. Huang, *Org. Lett.*, 2012, **14**, 4834-4837.
120. K.-J. Xiao, Y. Wang, Y.-H. Huang, X.-G. Wang and P.-Q. Huang, *J. Org. Chem.*, 2013, **78**, 8305-8311.
121. J. W. Medley and M. Movassaghi, *Angew. Chem. Int. Ed.*, 2012, **124**, 4650-4654.
122. W. S. Bechara, G. Pelletier and A. B. Charette, *Nat. Chem.*, 2012, **4**, 228-234.

CHAPTER 2: Deep Eutectic Solvents, CPME and 2-MeTHF: sustainable reaction media for organolithiums chemistry

The growing awareness about the harmful impacts of industrial processes on the environment and human health has laid the foundations for the creation of new sustainable technologies. The reduction of wastes, the use of renewable raw materials and the elimination of toxic or dangerous substances both in industrial and in academic processes are key concepts for a green industrial revolution. In this context, the Green Chemistry[1, 2] offers specific tools aimed at redesign all chemical areas towards a better management of the dangers and risks associated with the production and use of chemicals to obtain "*benign by design*" products, and to reduce the amount of waste generated in production cycles for the development of sustainable processes. The sustainability of a chemical process may be improved from different points of view, among them the choice of the solvent certainly plays a crucial role. This aspect is fundamental especially in organic synthesis, since the solvent usually represents the great majority of the raw material employed in such chemical processes.[3] Volatile organic compounds (VOCs) are the conventional solvents used in most industrial processes as well as in academic research, but they possess many drawbacks both from safety concerns (flammability, tendency to the formation of explosive peroxides, high toxicity) and from an environmental point of view, as they show accumulation in the atmosphere and poor or absent biodegradability. Thus, the use of alternative solvents or green reaction conditions in the development of new synthetic processes concurs to the goal of attaining sustainability. For these reasons, new reaction media have been investigated with a focus on biodegradable, recyclable, safe and low-cost alternatives, and remarkable advances have been achieved by the use of water, supercritical fluids, neat conditions and ionic liquids, among the others.[4-7]

A new class of solvents has rapidly emerged at the beginning of the century as a promising alternative to traditional VOCs, represented by Deep Eutectic Solvents (DESs). As compared to traditional organic solvents, DESs are not volatile, not toxic, not flammable, completely biodegradable and easy to handle and synthesize. For these reasons, they have been recently employed in several synthetic transformations like condensations, conjugated additions, cross-coupling reactions, and multicomponent reactions often showing novel reactivity, selectivity and efficacy compared to traditional VOCs.[8, 9] On the other hand, cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF) have emerged as a feasible sustainable alternative to common ethereal VOCs such as DEE, THF, dioxane, DME and MTBE. Their exploitation as solvents for organolithium chemistry has been

central both for the rethinking of known classic methodologies from a more sustainable perspective and for the design of innovative synthetic protocols.[10-12]

In the present chapter an overview of the properties of DESs, CPME and 2-MeTHF and a comprehensive overview of their applications for an unconventional approach to organolithium chemistry will be provided.

2.1 Deep Eutectic Solvents (DESs): general features

2.1.1 Composition

Deep Eutectic Solvents are generally defined as mixtures of two or more components in a specific molar ratio, where the melting point of the mixture is significantly lower than those of the former components (caused by the formation of an eutectic point), and are usually liquid at room temperature.[8, 13] DESs were initially considered as a new class of ionic liquids (ILs), and they undoubtedly share some proprieties with ILs, such as the negligible vapor pressure, high viscosities and the possibility of tuning their properties by an appropriate molecular design. However, this classification has been overcome and DESs and ILs should be considered as two separate classes of solvents. Indeed, while ILs are molten salts (single ionic compounds of one cation and one anion), DESs are mixtures of more than one compound.[14]

The components constituting a DES are small organic molecules able to interact through hydrogen bonding. In most cases the mixture is composed by a Brønsted or Lewis acid acting as hydrogen bond donor (HBD) and a Brønsted or Lewis base acting as hydrogen bond acceptor (HBA). The HBA is typically an ionic halide salt, such as an ammonium or phosphonium salt. Choline chloride (ChCl), a quaternary ammonium salt, is one of the most employed HBAs for the formation of DESs, since it fulfils several sustainability principles due to its reduced costs, high biodegradability, low toxicity and bioavailability (Figure 2.1). In the seminal work by Abbott *et al.* in 2003[15] the authors reported that mixing ChCl (mp 303 °C) with urea as HBD (mp 134 °C) in 1:2 molar ratio[16] resulted in the formation of a liquid with a mp of 12 °C. Other common HBDs are short-chain polyols, such as glycerol or xylitol, carboxylic acids, sugars and even water. Metal halides, such as $ZnCl_2$, $FeCl_3$, $CrCl_3$ and others, can also be combined with organic molecules to form DESs.[8, 13, 17]

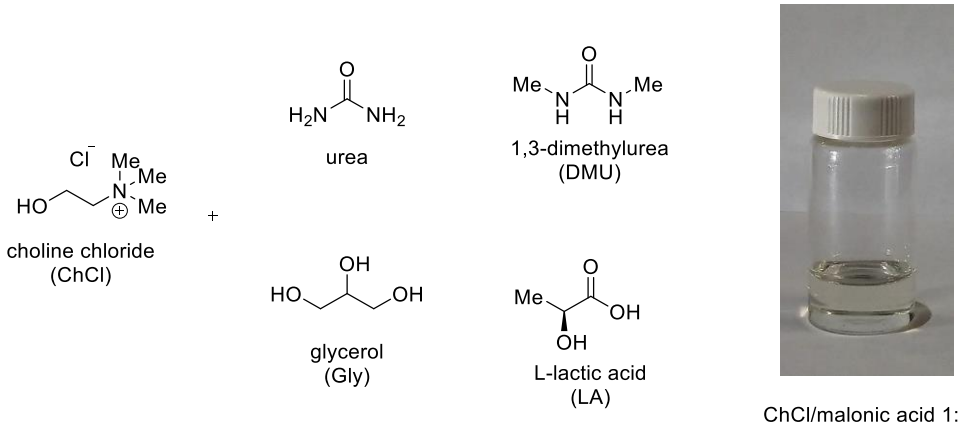


Figure 2.1. Examples of the most common DESs components: choline chloride as HBA and some HBDs. A picture of the DES composed by ChCl (mp 303 °C) and malonic acid (mp 136 °C) in 1:1 molar ratio.

Hydrogen bonding interactions strongly characterize the nature of Deep Eutectic Solvents. The significant lowering in the melting point of the mixture, compared to its single components, has been attributed indeed to the formation of a network of hydrogen bonds between the components.[8, 18] More recently, the concept of natural deep eutectic solvent (NaDES) has been proposed. In 2011 Verpoorte *et al.* observed that a small number of primary metabolites, such as carboxylic acids, choline, sugars and some amino acids are found in unexpected high amounts in a wide number of living organisms. The hypothesis advanced was that these compounds could be the base to form eutectic mixtures that would serve as reaction media for the biosynthesis of non-water-soluble molecules.[19] Taking inspiration from nature, several eutectic mixtures of bioderived compounds have been prepared, studied and employed for different applications.[20-23] The term NaDES is thus generally intended to designate Deep Eutectic Solvents composed only by naturally occurring compounds.

2.1.2 Green credentials

Deep Eutectic Solvents have emerged as an alternative to conventional solvents and as an improvement in terms of sustainability, often in comparison with ionic liquids. The first appealing difference between DESs and ILs is that the latter are synthesised by chemical reactions, such as alkylation of imidazole for the imidazolium-based ones. The synthetic steps imply the use of solvents and reagents, mostly with high toxicity, for reaction, extraction and purification steps, and disposal of the waste material (often non-biodegradable) is absolutely required.[24] By comparison, the preparation of a DES is much simpler and safer: the components

are mixed and stirred under heating (often 60-100 °C) until a clear liquid is formed and no further purification is generally required. The method is intrinsically 100% atom economic. Alternatively, it is also possible to dissolve the components in water and obtain the eutectic mixture by evaporation of water under reduced pressure. The intrinsic high thermodynamic stability of DESs consequently facilitates their storage without any precautions.

Among the reasons why Deep Eutectic Solvents are diffusely considered as green solvents is their supposed low toxicity. Similarly to ILs, DESs display negligible vapour pressure, resulting in a low risk for atmospheric pollution and low flammability. On the other hand, a substantial difference is found in the intrinsic safety of many DES components, which are often biocompatible, towards human health. It should be noted that this does not necessarily imply a low toxicity of their combination in the eutectic mixture. Nowadays, evaluations of DESs toxicity have been performed on microorganisms, human cell lines, plants and mice, and the preliminary results suggest that the initial assumption of DESs as "biocompatible solvents" needs deeper investigations.[25-29] Anyway, DESs appear to be safer than conventional solvents and ionic liquids, in particular when their components are essential ingredients of cellular metabolism.[30, 31] Furthermore, applications of DESs as media for drug solubilization and delivery have already been investigated.[32, 33]

In order to evaluate the sustainability of Deep Eutectic Solvents, their whole lifecycle should be considered. In this context, NaDESs certainly constitute an attractive option, since their components derive from potentially renewable sources and often are biodegradable. Biodegradability is a relevant issue, as it reduces not only the impact on human health and the environment, but also the costs for waste disposal. Studies employing the closed bottle test, a standard method in which the substrate is added to an aerobic aqueous medium inoculated with wastewater microorganisms, indicated several DESs as "readily biodegradable".[25-27]

2.1.3 Practical aspects

The physicochemical properties and the chemical behaviour of DESs influence the laboratory practices that need to be adopted for the use of these solvents.

The first relevant propriety for organic synthesis is viscosity. In analogy with ionic liquids, DESs often exhibit high viscosities, as shown in Table 2.1. The typical values are in the range of 101-103 cP; by comparison, dichloromethane (0.45 cP at 20 °C), toluene (0.59 cP), ethyl acetate (0.46 cP) and other common organic solvents are much less viscous.

Table 2.1 Viscosity of some DESs determined by NMR diffusion at 25 °C.[34]

DES components		Ratio	Viscosity (cP)[a]
ChCl	Gly	1:2	259
ChCl	ethylene glycol	1:2	37
ChCl	urea	1:2	750
ChCl	malonic acid	1:1	1124

[a] cP = g s-1 cm-1

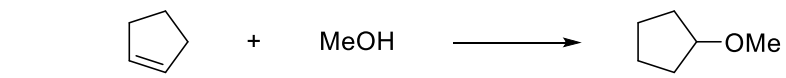
The viscosity of DESs has been attributed to the hydrogen bonding network that characterizes the melt. The chemical nature of the components is important since their volume determines the availability of holes in the structure of the fluid, which allow suitable motion.[13, 35, 36] This parameter is significant for the application of DESs in organic synthesis, because it dramatically influences the ability to ensure proper mechanical stirring to the reaction mixture. The stirring may be crucial for the outcome of the reaction, since the organic substrates are often not completely soluble in the polar DES medium. However, it should be noted that the viscosity of DESs may also be influenced both by the water content in the eutectic mixture and additives eventually employed.[37, 38]

When working with Deep Eutectic Solvents, a central aspect is represented by the work-up procedure at the end of the reaction. From this point of view, this class of solvents appears to be particularly appealing, because the components of the DES are usually water-soluble. The addition of water disrupts the structure of the eutectic mixture, and the components are dissolved into the aqueous layer where the organic product of the reaction is often insoluble. Thus, under optimal conditions a solid organic product can precipitate and can be collected by simple filtration or, in case it is an oil, it forms a separate layer. This procedure not only avoids the use of extraction solvents, but also enables the recycle of the DES. Indeed, the removal of water restores the eutectic mixture, that can be used for anthers reaction cycle, usually up to 3-5 consecutive runs. It should be noted that other recycling procedures are also feasible: the product can be directly extracted from the reaction mixture by washing with an organic solvent (such as DEE or CPME) able to dissolve the product but not the DES components; alternatively, a classical water/organic solvent extraction is always possible, followed by evaporation of the aqueous layer to restore the DES.

2.2 Cyclopentyl methyl ether (CPME): general features

Among the possible alternatives to VOCs, the research for new sustainable organic solvents represents an important perspective as they feature physico-chemical properties similar to VOCs, but with a reduced overall toxicological and environmental impact.[39]

Typical ethereal solvents such as DEE, THF, DME, and dioxane have been widely used in synthesis. However, their major drawbacks such as low boiling points, high volatility, easy peroxide (PO) formation, and partial solubility in water often lead to an inefficient recovery. To overcome these disadvantages, MTBE has been proposed as an alternative. However, MTBE has some limitations related to its use, such as general low solubility of organic compounds, instability under acidic conditions, and low flash point. Cyclopentyl methyl ether (CPME) has proven to be a more promising alternative to common VOCs as reaction media in organic synthesis since it does not suffers of the drawbacks associated with the other classical ethereal solvents.[40] CPME is industrially produced *via* the 100% atom economical addition of MeOH (employed both as reagent and solvent) to readily available cyclopentene by Zeon Corporation (Scheme 2.1).[12] The primary source for CPME generation arises however from petrochemicals, but several biomass-based routes have been explored for the generation of chemical precursors that may be used for CPME production, such as cyclopentanone or cyclopentanol.[41, 42] Both precursors can be synthesized from biomass-derived furfural thus creating a potential biogenic pathway for CPME that could be developed in biorefinery in future.



M.W.	68.12	+	32.04	100.16

Scheme 2.1. Zeon production process of CPME.

As shown in Table 2.2, CPME is characterized by high boiling and low melting points, low heat of vaporization and formation of a positive azeotrope with H_2O. These proprieties make CPME exploitable as a new reaction medium within a range of temperatures. Additionally, its impressive hydrophobicity allows its use as an extraction solvent by limiting the necessary quantities (sometimes eliminating the washing process of the aqueous phase during the final work-up) and making it easy to recover by simple anhydrification and distillation, particularly in industrial scale applications. Furthermore, the possibility to easily obtain anhydrous CPME by simple drying with molecular sieves, more efficiently compared with well-used anhydrous

THF, gives the choice of CPME particularly attractive for organometallic chemistry (Figure 2.2 a).

Table 2.2. Physical proprieties of CPME.[12, 40]

Boiling point (°C)	106
Melting point (°C)	<-140
Density (20 ° C, g/mL)	0.86
Solubility in H_2O (23 °C, g/100g)	1.1
Azeotropic boiling point with H_2O (°C)	83
Azeotropic composition (w/w%, CPME: H_2O)	83.7:16.3
Dielectric constant (25 °C, Debye)	4.76
Explosion range (vol%, lower limit, upper limit)	1.84-9.9
Latent heat of vaporization (kcal/kg, at the bp)	69.2
Ignition point (°C)	180
Flash point (°C)	-1

Safety concerns for ethereal solvents are closely related to their explosive nature which arises from the esaily peroxides (POs) generation. CPME shows a particularly high resistance to POs formation, compared to other ethereal solvents due to the high bond dissociation energy of the secondary α-CH bond (Figure 2.2 b). For further safety reasons, however, CPME is commercially supplied with about 50 ppm butylated hydroxytoluene (BHT) as a peroxide inhibitor, while the commercially available THF contains 250 ppm BHT. The latter propriety combined with its narrow explosion range makes CPME an ethereal solvent particularly safe to be stored and handled.

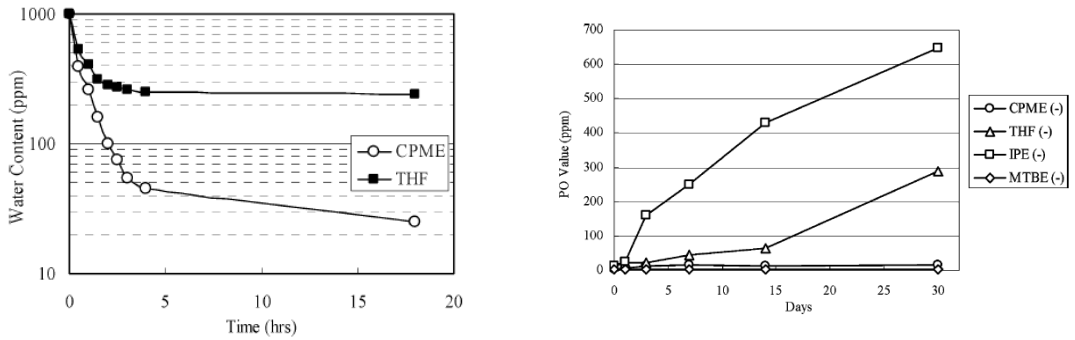


Figure 2.2. a) Drying by 4Å-MS of CPME (compared to THF); **b)** peroxide formation for common ethereal solvents. Imagines adapted from ref.[40]

In general, many ethers are susceptible to acidic conditions: MTBE is sensible to a cleavage into alcohols; THF is also prone to ring opening followed by a facile polymerization. On the other hand, CPME is relatively stable to acids in both homogeneous and heterogeneous conditions.[43] Watanabe *et al.*[40] studied the relative stability of CPME in presence of Brønsted acids commonly employed in acid catalysed reaction or during the classical quenching operation of base-mediated transformations, such as camphorsulfonic acid, H_2SO_4 and HCl. In every case, CPME showed an exceptional stability under acidic condition, also at high temperatures.

CPME is additionally extremely stable under strong basic conditions.[40] This parameter is fundamental to plan new organometallic reaction using unconventional solvents. Half-lives of *n*-BuLi in various ethereal solvents (THF, DEE, CPME) were compared to ascertain the different stability under strong basic conditions. As previously discussed, *n*-BuLi cannot be compatible with THF at high temperatures because of the undesired deprotonation followed by ring opening.[43] On the contrary, in CPME *n*-BuLi has sufficient half-life even at 40 °C (Figure 2.3) comparable to the DEE solution. For this reason, CPME has emerged as a promising solvent for polar organometallic chemistry.[12]

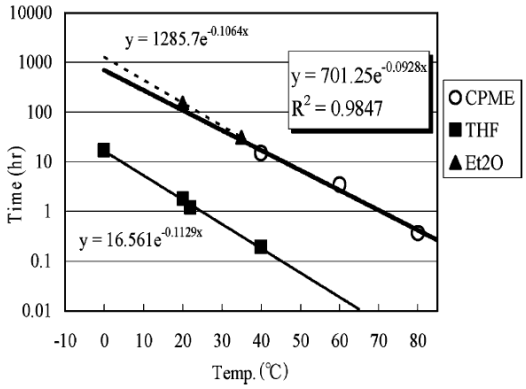


Figure 2.3. Half-lives of *n*-BuLi in various ethereal solvents. Imagines adapted from ref.[40]

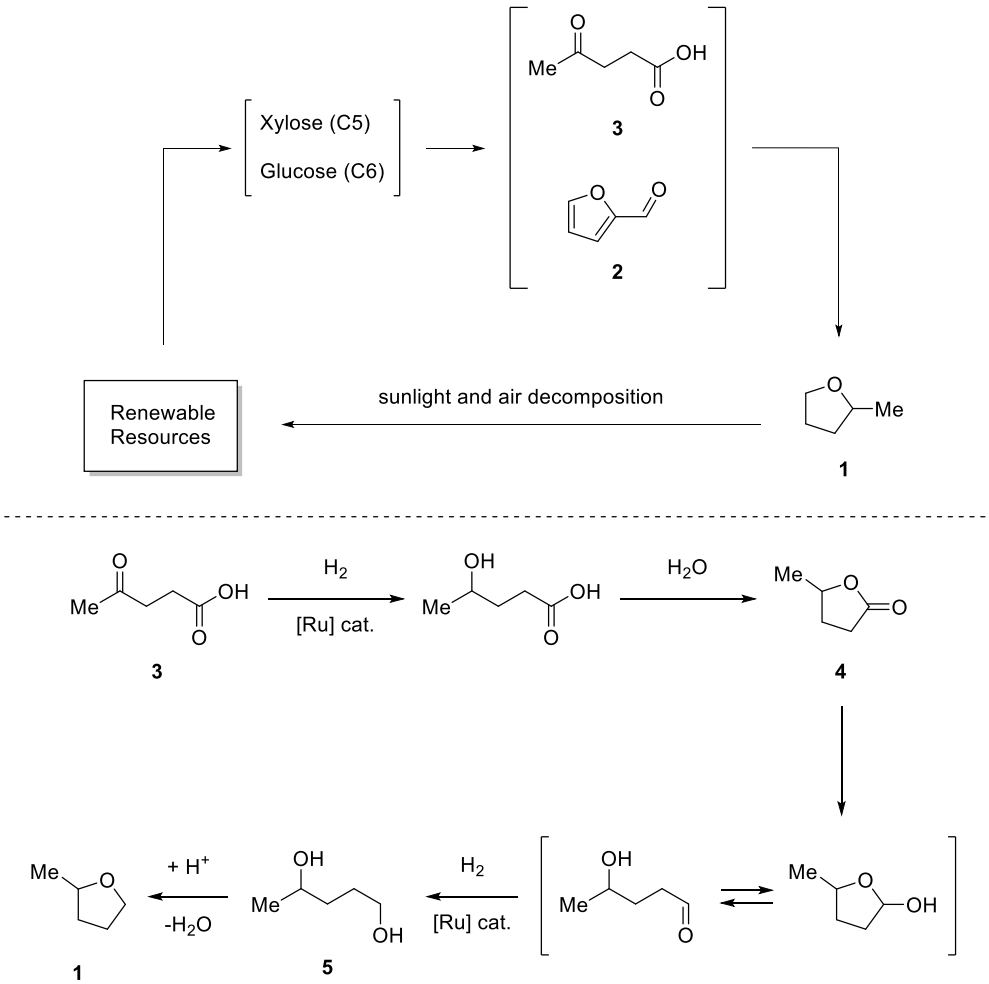
In general, no detailed studies are reported in the literature about the toxicity of CPME. To the best of our knowledge, only Scott *et al.* in 2011 in his important study reported that, from a toxicological point of view, CPME has low acute or subchronic toxicity, with moderate irritation and negative genotoxicity and mutagenicity.[44]

2.3 2-MeTHF: general features

Analogously to CPME, 2-MeTHF is emerging in recent years as a valid sustainable alternative to common aprotic solvents (THF and DEE above all) for

organometallic-promoted reactions.[10, 11] Its recent use as a reaction medium has significantly increased in accordance with the growing demand for procedures in line with sustainability principles of green chemistry.[4]

The most attractive feature of 2-MeTHF **1** (in comparison for example with CPME) is its accessibility from renewable resources. It can be easily synthesized either by a two-steps hydrogenation of biomass-derived furfural **2**[45] *via* the formation of 2-methylfuran as an intermediate, and from levulinic acid **3** with a sequence of reduction-hydration steps, in which other interesting biomass-derived products are produced, such as γ-valerolactone **4** and 1,4-pentanediol **5**.[46] Moreover, 2-MeTHF has some intrinsic instability in the presence of air and sunlight, so it can be abiotically degraded (Scheme 2.2).



Scheme 2.2. Conceptual cycle for production and degradation of 2-MeTHF **1** (up) and synthesis of 2-MeTHF starting from levulinic acid **3**.

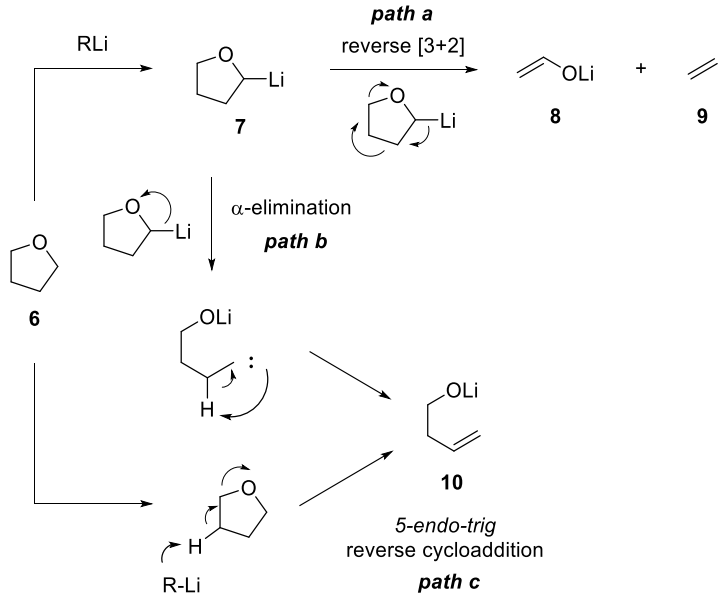
As shown in Table 2.3, the most important difference between 2-MeTHF and its demethylated analogue THF is the water miscibility.[47] The strong miscibility of THF in water often causes some troubles during classical work-up procedures, and the employment of other VOCs for the extraction process is mandatory. In the case of 2-MeTHF, its high hydrophobicity allows easy work-up procedures avoiding additional organic washes of the water phase. In analogy with DEE, 2-MeTHF is a water-immiscible monodentate alkyl ether, however with a significantly minor volatility and high boiling point (see Table 2.3). These properties, together with the polarity and the intrinsic Lewis basicity (the available data place 2-MeTHF between THF and DEE as Lewis base strength), make it suitable for pilot plant applications. Unfortunately, in analogy to THF, the formation of peroxides cannot be avoided, but the use of stabilizers can positively modulate this drawback.[47]

Table 2.3. Physical proprieties of 2-MeTHF compared to THF.[47]

Proprieties	**2-MeTHF**	**THF**
Boiling point (°C)	80	66
Melting point (°C)	<-136	-108
Density (20 ° C, g/mL)	0.85	0.89
Viscosity (20 °C, cP)	0.60	0.55
Solubility in H_2O (23 °C, g/100g)	14	soluble
Azeotropic boiling point with H_2O (°C)	71	64
Azeotrope composition (% water)	10.6	-
Dielectric constant (25 °C, Debye)	6.97	7.58
Latent heat of vaporization (kcal/kg, at the bp)	87.1	98.1
Flash point (°C)	-11	-14.5

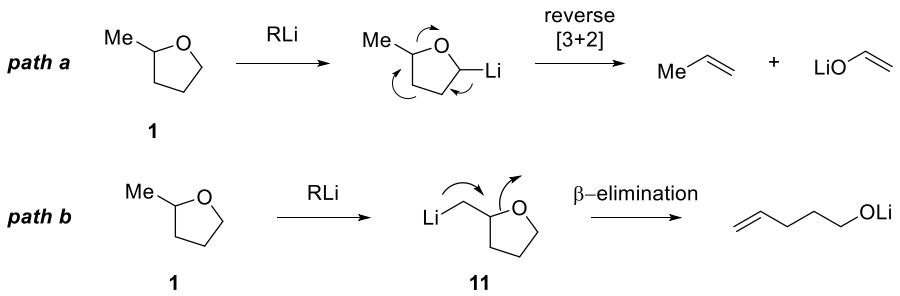
One of the most important propriety of an ethereal solvent which is required for its application with organolithiums is the capability to disaggregate such species increasing their reactivity. Furthermore, common solvents suffer of some tendency to react themselves with organolithiums (see paragraph 1.1). It was observed that the half-life of the *n*-BuLi in 2-MeTHF at 35 °C is almost 13 times higher compared with THF solution.[43] The principal pathway for decomposition of THF **6** by alkyllithiums involves the initial α-lithiation to oxygen, followed by a reverse [3+2] cycloaddition of the resulting anion **7** to yield one molecule of ethylene **9** and one molecule of the lithium enolate of acetaldehyde **8** (Scheme 2.3, path a), in the so-called α-cleavage. Especially in the presence of highly basic organolithiums-additive mixture, such as *t*-BuLi/HMPA 6/1, an alternative pathway is possible, leading to the

formation of but-3-en-1-oxide **10**, *via* an alternative α-elimination (Scheme 2.3, path b) or reverse *5-endo-trig* cyclization (Scheme 2.3, path c).[48] These mechanisms were proved by trapping the THF-decomposed lithiated species.[49]



Scheme 2.3. THF degradation pathways.

By contrast, the presence of a methyl group in 2-MeTHF **1** decreases the polarity, and the α-cleavage is considerably suppressed (Scheme 2.4, top). In the same way, the decomposition pathway *via* β-elimination, which involves the abstraction of a β-proton from the external methyl group and entails the formation of a very unstable primary carbanion **11**, is partially reduced compared to THF (Scheme 2.4, bottom).[43]



Scheme 2.4. 2-MeTHF **1** degradation pathways.

For these reasons, 2-MeTHF has already found wide use in organolithium-promoted reactions, with notable advantages in both efficiency and sustainability.[10, 11]

Finally, it is notorious that water-miscible cyclic ethers, such as THF, are not stable under acidic aqueous conditions, being degraded by ring opening. Herein, replacing THF with 2-MeTHF is advantageous due to the low miscibility with water of 2-MeTHF. The biphasic system thus formed preserves the latter from the acidic hydrolytic action. As a result, in 2 N HCl at 60 °C, THF degrades 9 times faster than is methylated analogue.[47]

2.4 Reactivity of organolithium reagents under sustainable reaction conditions

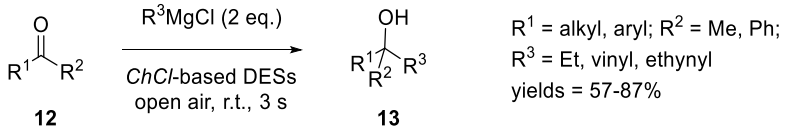
Owing to the pronounced polarity of the C-Li bond, the use of polar organolithium compounds implies some efforts in order to control the high reactivity of these species; side reactions such as hydrolysis/oxidation of reagents, decomposition of intermediates, undesired rearrangements, and side reaction of sensitive functional groups are quite common. In addition, these reagents manifest a high tendency to hydrolyse in the presence of air and moisture. In order to overcome some of these drawbacks, polar organometallic reagents are usually employed at very low temperatures (such - 78°C or below) using strictly anhydrous conditions, under inert atmosphere and carefully dried non protic organic solvents. These selectivity problems can also lead to the formation of complex mixtures with associated low product yields, which require additional separation steps producing lots of waste. These limitations can greatly impact large scale processes in industry due to the extra costs and time incurred to solve these problems. In addition, this chemistry requires hazardous volatile organic compounds (VOCs), in particular ethereal solvents owing to their Lewis basicity and attitude to activate organolithiums by disaggregation, incrementing the environmental impact of this chemistry. In this contest, important advances achieved by several research groups, to limit the use of toxic reagents, polluting solvents and energetically expensive conditions, have been made in the last two decades. Consequently, many efforts have been focussed on the design of organic processes that can take place: a) under aerobic ambient conditions and with energy efficiency (operating at room temperature and under atmospheric pressure); b) using sustainable solvents; and c) under safe conditions (for both human beings and the environment).[1, 2, 50] However, important progresses towards an upgrade of organolithiums chemistry under greener conditions have been limited until recently, since *a priori*, the cannon of this type of chemistry is incompatible with these conditions.

Pioneering independent studies by Álvarez, Hevia and Capriati *et al.*[51-55] have shown, for the first time, the possibility of using polar organolithium reagents in sustainable conditions, under air, in the presence of moisture and at room

temperature, thus breaking the traditional paradigm that provided their use limited only to classical strict Schlenk conditions to better control their reactivity and stability. Furthermore, making this step possible, they have demonstrated that replacing of traditional coordinating ethereal solvents with polar protic biocompatible DESs or aprotic bio-based 2-MeTHF and CPME is possible, also, for some organolithiums processes, opening the door for a new era of the organolithiums chemistry.

2.4.1 Direct nucleophilic addition to ketones and esters in DESs

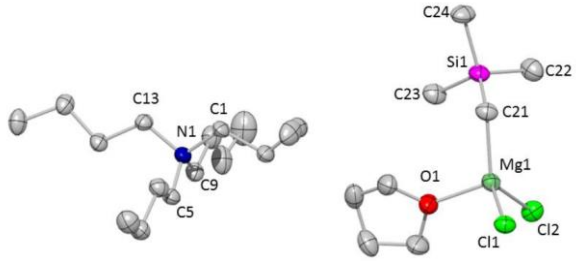
The study of new sustainable *s*-block organometallic-based reaction started in 2014 by Hevia and Álvarez *et al.* with the nucleophilic addition of Grignard reagents to aromatic and aliphatic ketones **12** to the corresponding tertiary alcohols **13** using ChCl-based DESs as reaction media.[56] Excellent yields and selectivity for the preparation of alcohols have been achieved under air and at room temperature, in a very short reaction time (3 s) without the expected competitive hydrolysis of the Grignard reagents employed (Scheme 2.5). Remarkably, the formation of reduction and/or enolization by-products under these conditions was completely suppressed.



Scheme 2.5. Addition of Grignard to ketones **12** in *ChCl*-based DESs.

Notably, the reaction requires two equivalents of nucleophile to obtain good conversions without negative impact on the selectivity of the reaction. The scope of this methodology was studied with regard to the nature of the deep eutectic mixture, the Grignard reagent, and the carbonyl compound. The positive role of the DES as reaction medium was evaluated by adding the Grignard reagent to a bulk water suspension of ketone with a detrimental effect on the yield (10%). This result suggested a possible kinetic activation of the Grignard reagents favoured by the interaction with ChCl. This hypothesis could be in good agreement with the previous report by Song *et al.* about the positive chemoselective effect of an ammonium salt (tetrabutylammonium chloride, TBACl) as stochiometric additive in the alcohols synthesis starting from ketones using Grignard reagents in THF.[57] Trying to shed some light in this activation process, the co-complexation of several Grignard reagents with TBACl in anhydrous THF has been investigated by X-ray and DOSY

NMR experiments, revealing the formation of mixed ammonium magnesiate [{*N*(*n*-Bu_4)}$^+${$RMgCl_2$}$^-$] **14** species (Figure 2.4).

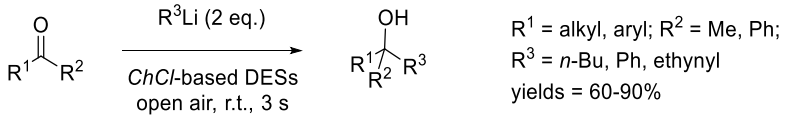


14

Figure 2.4. Molecular structure of [{*N*(*n*-Bu)$_4$}$^+$-{(THF)$MgCl_2$(CH_2SiMe_3)}$^-$] **14**. Picture adapted from ref.[56]

Unfortunately, analogous data in ChCl-based solvents have been not obtained so far, anyway the authors hypothesized a similar interaction of the Grignard reagent with choline quaternary ammonium salt forming an activated species that exhibits enhanced nucleophilic power. In this case, ChCl could have a double effect being not only a constituent of DES, but also a source of halide for the organometallic reagent. This could explain the vary fast addition rate observed in DESs over the competing hydrolysis process. In any case, other factors, including hydrogen bond interactions or the heterogeneous character of these reactions (THF in which Grignard reagents are stored and DESs are not miscible), cannot be excluded and could be additional positive effects both activating the substrate and shielding the organometallic reagents to the protonolysis.

The reaction was also extended to organolithium reagents with good results in terms of yield and chemoselectivity compared with the previous synthesis of alcohols reported under classical Schlenk conditions (Scheme 2.6).[58]



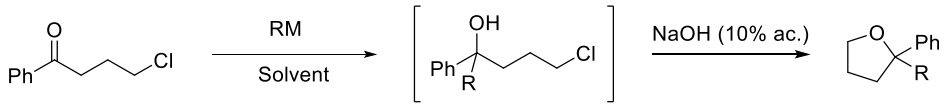
Scheme 2.6. Addition of organolithiums to ketones in *ChCl*-based DESs.

Again, the replacement of the DESs with pure bulk water lead to a dramatically decrease of the yield. The authors proposed a rationalization of this unexpected reactivity in terms of activation effect of *n*-BuLi in presence of the quaternary ammonium salt (ChCl). NMR studies on the co-complexation between $TMSCH_2Li$ and TBACl in anhydrous THF were consistent with the formation of dianionic halolithiate species [{*N*(*n*-Bu)$_4$}$_2^+${$LiCl_2$-(CH_2SiMe_3)$^{2-}$]} where two Cl^-

anions have been transferred to lithium. In strong relation with the notorious positive effect of chloride salts (such as LiCl) to the reactivity of organolithiums,[59] the authors hypothesized a similar halide-mediated accelerating effect to favour the addition reaction in DES over the competing protonation process.

In order to underline the green aspects of the methodology, the authors reported a very easy work-up procedure for this DESs-mediated nucleophilic addition. When the desired alcohols were obtained as solids the final products were isolated by simple addition of brine to the reaction mixture (to favour the precipitation) and filtration. On the other hand, when the final products were obtained as oils, an extraction with the environmentally friendly CPME could be easily employed. An elegant application of this chemistry was shown by Capriati *et al.* in 2016 for the synthesis of tetrahydrofurans **17** (Table 2.4).[60]

Table 2.4. Addition of organolithiums and Grignard reagents *en route* to substituted tetrahydrofurans **17** under different reactions conditions.

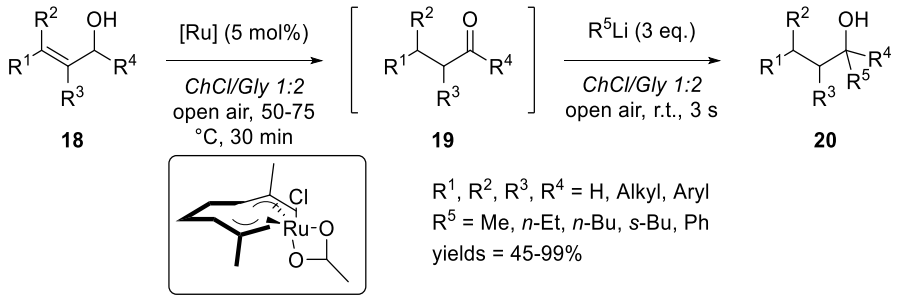


15 **16** **17**

Entry	R-M (eq.)	Solvent	T (°C)	Time conditions	**15** (%)	**16** (%)	**17** (%)
1	MeMgCl (3)	THF	- 40	12 h, under argon	-	-	60
2	MeMgCl (6)	THF	- 40	12 h, under argon	-	-	80
3	MeMgCl (3)	THF	r.t.	12 h, under argon	-	-	10
4	MeLi (6)	THF	-40	12 h, under argon	-	-	85
5	MeLi (3)	THF	r.t.	12 h, under argon	-	-	30
6	MeMgCl (3)	ChCl/Gly 1:2	r.t.	10 min, under air	15	-	85
7	MeLi (3)	ChCl/Gly 1:2	r.t.	10 min, under air	10	-	73
8	MeMgCl (3)	H_2O	r.t.	10 min, under air	-	-	72
9	MeLi (3)	H_2O	r.t.	10 min, under air	-	-	75

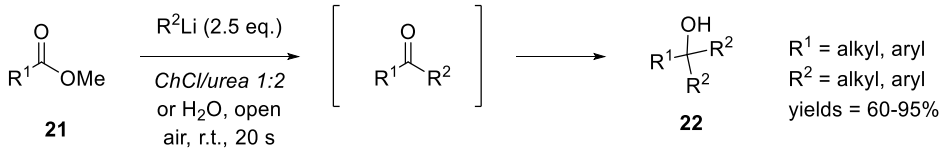
As depicted in Table 2.4 an extensive comparison between classical low temperature conditions and sustainable open air conditions is reported. Interestingly, the use of protic conditions (DESs or water) gave an important benefit on the reaction outcome in terms of yield, reaction time and temperature. Differently from the previous reported results by Hevia and Álvarez *et al.*,[56] this reaction proceeded smoothly also using water as solvent. Moreover, water/DESs mixture cannot be simply replaced by bulk alcohols (*e.g.* MeOH), suggesting that the strong and three-dimensional intermolecular hydrogen bond established between water/DESs and the substrate may play a crucial role in promoting this transformation. This special H-bonding scenario could induce not only the activation of the C=O bond on the substrate towards the nucleophilic addition, but also shield the organometallic reagent from competitive hydrolysis processes.

The facile access to tertiary alcohols by simple direct addition of organolithiums to carbonyl compounds in DESs inspired Alvarez *et al.* to develop tandem protocols in which other DESs-compatible reactions (such as bio- or metal catalysed transformations) promoted the conversion of the substrate into an intermediate which is *in situ* converted in the final product. Recently, the one-pot synthesis of tertiary alcohols **20** by combining the ruthenium-catalysed isomerisation of allylic alcohols **18** and chemoselective addition of organolithiums to intermediate ketone **19** in DESs was reported (Scheme 2.7).[61]



Scheme 2.7. One-pot tandem combination of Ru-catalysed isomerisation of allylic alcohols **18** with chemoselective addition of RLi in DESs.

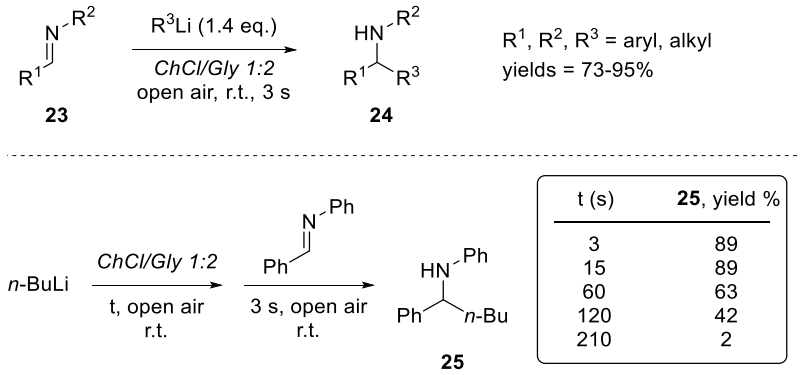
More recently, the possibility to use methyl or ethyl esters such as **21** as electrophilic platform to perform an easy double addition of organolithiums (or Grignard) *en route* to the corresponding tertiary alcohols **22** was reported.[62] The reaction proceeded very fast (20 s) using both ChCl/urea 1:2 or water as solvents, in presence of air, at room temperature, with good yield (Scheme 2.8). However, a limit of this methodology consists in the consecutive and non-controllable double addition of the same organolithium, while the installation of two different nucleophiles is prevented.



Scheme 2.8. Double addition of organolithiums to esters **21** in ChCl/urea 1:2 or water.

2.4.2 Direct nucleophilic addition to imines and nitriles in DESs and glycerol

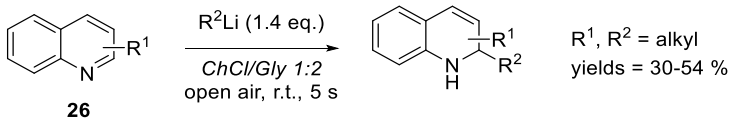
Compared to their corresponding ketone counterparts, the synthesis of amines by 1,2 direct addition of organolithiums to imines suffers of some limitations due to the lower electrophilicity of the iminic carbon and the tendency to undergo some side reaction (such as reduction or enolization).[63] For these reasons, the employment of Lewis acids[64, 65] or more electrophilic imines with *N*-EWG substituents[65] is necessary to overcome these limitations. In this context, an elegant and sustainable protocol was proposed by Hevia and Álvarez *et al.* for the direct synthesis of secondary amine **24** exploiting the ChCl/Gly eutectic mixture to activate these substrates (Scheme 2.9).[66]



Scheme 2.9. Nucleophilic addition of organolithium reagents to imines **23** in ChCl/Gly 1:2 (top) and time-dependent formation of the addition product when the addition order of reagents is reversed (bottom).

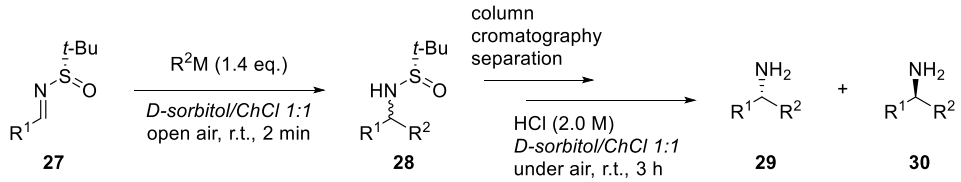
Again, addition reaction take place much faster than the competing protonolysis process, giving the secondary amines **24** in good yield after very short reaction time (3 s), under air at room temperature, without any additives, starting from simple and non-activate imines with good chemoselectivity (only unreacted starting material and product were observed in the reaction crude). In this work, little progresses in terms of functional group tolerance were realized: in the presence of a bromoaryl imine no metal-halogen exchange byproducts were detected, despite the thermodynamic condition adopted. Notably, with respect to

the other citated methodology, in this case, with this less electrophilic platform, only more reactive organolithiums gave satisfactory results. A life-time experiment by reversing the addition order of the reagents was used to corroborate the stability of organolithiums in these protic reaction media. As shown Scheme 2.9 (bottom), after 15 seconds under air, amine **25** was still recovered in remarkably high 89% yield. This experiment revealed an unexpected high kinetic stability of *n*-BuLi in the ChCl/Gly 1:2 eutectic mixture. In fact, only after 3.5 minutes the addition to the imine was completely supressed. This approach was finally extended to the more challenging alkylation/arylation of quinoline **26**, leading to similar results in term of yield (however lower compared to imines) and chemoselectivity (Scheme 2.10).[66]

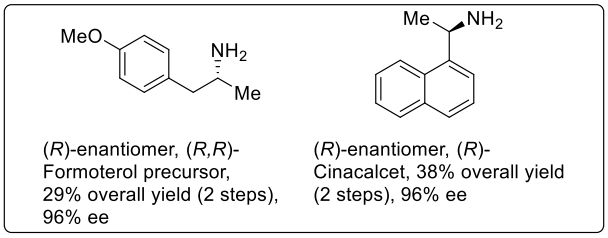


Scheme 2.10. Addition of alkyllithiums to quinoline **26** in ChCl/Gly 1:2.

More recently, the synthetic potential of this approach has been further expanded by Álvarez and Capriati *et al.* The direct addition of both organolithiums and Grignards to enantiopure *N*-*tert*-butanesulfinyl imines **27** was performed in DESs, working at room temperature in the presence of air, for the preparation of chiral amines **29**, **30** of pharmaceutical interest (Scheme 2.11).[67]



R^1 = Ph, 4-$OMeC_6H_4$, 4-$CF_3C_6H_4$, *t*-Bu
R^2 = Me, Et, *i*Pr, *n*-Bu, *t*-Bu, allyl
M = Li, MgCl
dr = from 68:32 to 50:50
yields = 74-98%



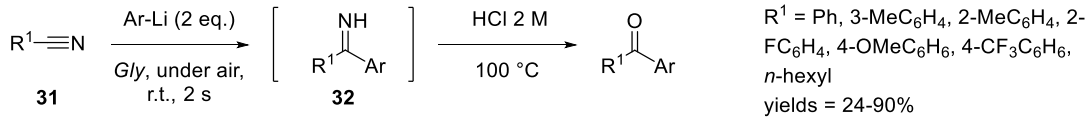
Scheme 2.11. Addition of organolithiums and Grignard reagents to *N*-*tert*-butanesulfinyl imines **27** in DESs. Some relevant API precursors synthesized are shown.

The principal limitation of this protocol is the poor diastereoselectivity observed in the addition step, compared to the classical methods, while total integrity was observed on the preinstalled chiral position. However, the two obtained diastereomers could be easily separated by column chromatography and,

subsequently, the cleavage of the chiral auxiliary in the intermediate sulfinamide **28** was achieved under acidic conditions in the same D-sorbitol/ChCl 1:1 eutectic mixture with quantitative yields and excellent enantioselectivity.

Finally, Capriati *et al.* shown that also water can be used as sustainable reaction media to promote a fast and chemoselective direct 1,2 addition of organolithium to aldimine at room temperature under "on-water" conditions.[68]

Another promising eco-friendly biomass-derived solvent aforementioned as DES-component, namely glycerol, was used for the first time as reaction medium in the direct addition of aryllithiums to nitriles **31** by Álvarez *et al.* (Scheme 2.12).[69]



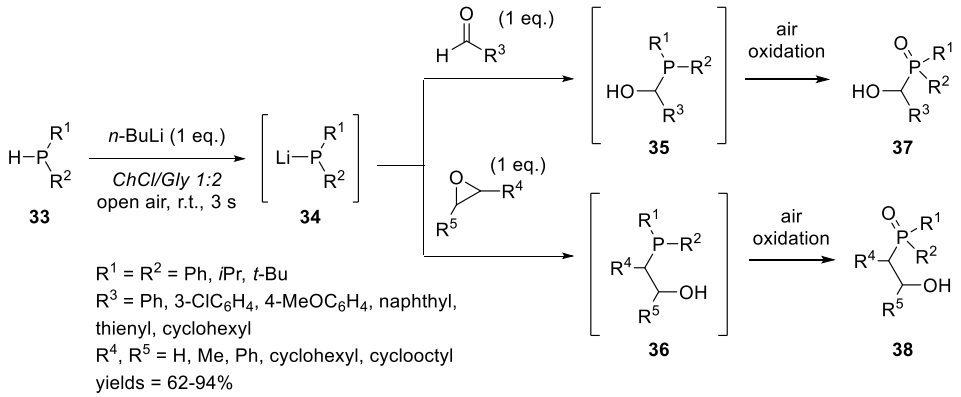
Scheme 2.12. Addition of aryllithiums to nitriles **31** in glycerol.

As described in the previous cited examples using DESs or water, these reactions are ultrafast (2-3 s) and compatible with the presence of air and moisture. Arylation of nitriles generates *in situ* the relevant NH-imines **32** which resist to a second nucleophilic attack, and it is then converted into the corresponding ketones by acidic hydrolysis in moderate to good yields. Interestingly, only nitriles insoluble in Gly were effective towards these arylation processes. Furthermore, good results were achieved using water or ChCl/Gly 1:2 as solvent, while both a 'normal stirring' and replacing Gly with protic methanol or aprotic 2-MeTHF (solvents in which benzonitrile is completely soluble) lead to a dramatic decrease of the yield. These findings suggest that this addition protocol takes place under "on-glycerol" conditions. Again, the authors proposed an inverse addition experiment to corroborate the stability of PhLi to hydrolysis in this protic medium. In fact, when PhLi was added to Gly and stirred for 15 seconds before addition of benzonitrile, benzophenone was recovered in 74% yield after acidic hydrolysis of the imine intermediate. Anyway, this protocol was unsuccessful using alkyllithiums that are more sensitive to the Gly-promoted hydrolysis.

2.4.3 Aerobic addition of lithium phosphides to aldehydes and epoxides in DESs

The development of sustainable and effective transition-metal-free protocols for the selective formation of new C-P bonds is highly desirable especially because phosphorous-containing organic molecules are key scaffolds in medicine, biochemistry, material science, catalysis, and organic synthesis.[70, 71] In a recent publication, Álvarez and Capriati *et al.* reported the possibility to generate high

reactive lithium phosphide **34** starting from corresponding phosphine **33** directly in DESs under bench conditions (under air, at room temperature). These species are used as source of nucleophilic phosphorus and easily trapped in the same eutectic mixture with aldehydes or epoxides to generate the corresponding α- or β-hydroxy phosphine oxide **37** and **38** with high efficiency in very short reaction time (Scheme 2.13).[72] This work open the door to the generation of high reactive organolithium species directly in these unconventional protic media.



Scheme 2.13. Generation and addition of $LiPR_2$ **34** to aldehydes and epoxides in DESs.

Replacing **33** with the corresponding phosphine oxide and reacting with *n*-BuLi under the same reaction condition in order to generate the corresponding lithiated phosphine oxide, no evidence of the formation of the desired products after the addition of the selected electrophiles was observed. This gives the elucidation on the *in situ* air-oxidation of the non-isolable phosphines **35** and **36**, generated upon addition to **34** of the selected aldehyde and epoxide respectively.

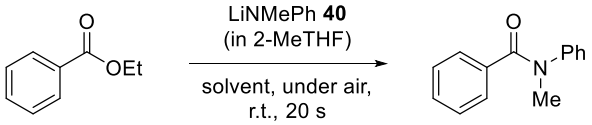
Other interesting features of this report are: a) the possibility to replace DESs with water or Gly with a limited decrease of reaction yields; b) the possibility to generate the active P-species with bases such as NaH or KH with a limited decrease of reaction yields; c) an easy work-up procedure, by simple adding water to promote the precipitation of the product; d) the life-time study of the lithiated phosphide by changing the electrophile addition time is reported.

2.4.4 Direct addition of lithium amides $LiNR_2$ to esters, amides and olefins in 2-MeTHF

Because of their minor reactivity due to the less polarized Li-N bond compared to the corresponding C-Li species, the development of bench and sustainable methodologies using nucleophilic lithium amides slowly emerged on the

panorama of the air-moisture compatible reactions. The first experimental evidence of the possibility to use nucleophilic lithium amides such as **40** at room temperature, in presence of air was reported by Hevia and Álvarez *et al.* describing the direct transamination of esters.[73]

Table 2.5. Study of solvent-compatibility in the direct addition of lithium *N*-methylanilide **40** to ethyl benzoate **39**.

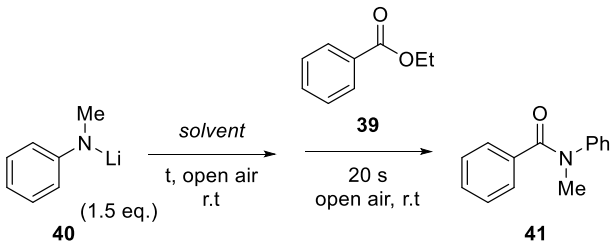


39 **41**

Entry	Solvent	LiNMePh (eq.)	**41**, yield %
1	THF	2	93
2	2-MeTHF	1.5	80
3	2-MeTHF	2	81
4	2-MeTHF	3	80
5	ChCl/Gly 1:2	3	83
6	ChCl/H_2O 1:2	3	81
7	H_2O	3	36
8	Gly	3	75
9[a]	2-MeTHF	1.5	82
10[a]	Gly	1.5	47

[a] solid LiNMePh was used

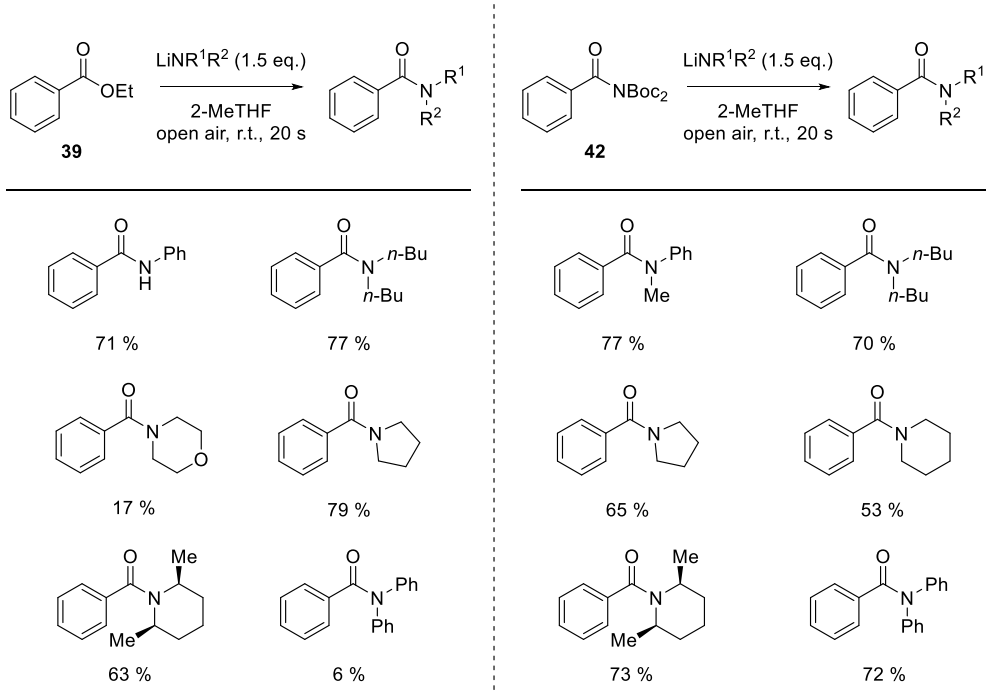
As shown in Table 2.5, nucleophilic lithium *N*-methylanilide **40** showed a good tolerance and stability under this bench conditions, and it was able to promote the direct amidation in very fast reaction time using different unconventional solvents, among them both polar aprotic (2-MeTHF and THF) (Table 2.5, entry 1-4), polar protic (Gly) (Table 2.5, entry 8) and eutectic mixtures (ChCl/Gly 1:2 and ChCl/H_2O 1:2) (Table 2.5, entry 5-6), while bulk water led to an important decrease of yield (Table 2.5, entry 7). Furthermore, the best features of 2-MeTHF over Gly were demonstrated a) in the classical inverse-sequence experiment (Scheme 2.14), showing an expected major resistance of **40** to protonolysis in 2-MeTHF compared to Gly and b) the possibility to use **40** in a solid aggregated form without significant differences in terms of yield was feasible only in 2-MeTHF (Table 2.5, entry 9,10).



t (s)	solvent	**41**, yield %
10	Gly	32
30		3
1 min	2-MeTHF	70
2 min		62
5 min		42
10 min		13

Scheme 2.14. Assessing the time-dependent formation of **41** when the order of addition of reagents is reversed in both Gly and 2-MeTHF.

The reaction was successfully extended to several ethyl benzoates decorated with different functionalities on the aromatic ring (methyl, fluorine and methoxy). Also heteroaromatic (3-furyl and 3-pyridyl) and aliphatic (cyclohexyl and heptyl) ethyl esters were used with high yield and chemoselectivity. More interesting, different lithium amides were used as nucleophilic nitrogen sources for the direct amidation of ethyl esters **39** and for the transamidation of high activated *N*-Boc_2 electrophilic twisted amides **42** (Scheme 2.15).

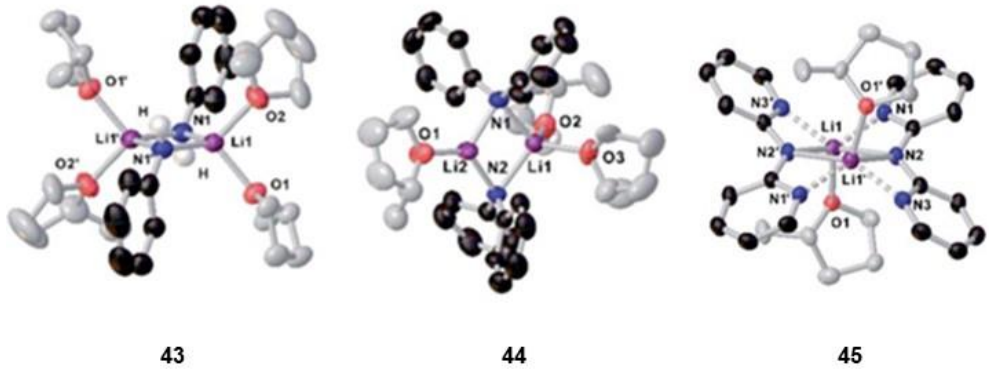


Scheme 2.15. Addition of different $LiNR_2$ to ethyl benzoate **39** (left) and to *N*-Boc_2 benzamide **42** (right).

The reaction was compatible with sterically hindered lithium *cis*-2,6-dimethylpiperidide and with the less basic lithium secondary amides and

diphenylamide. The latter reacted smoothly only with the strong electrophilic *N*-Boc_2 benzamide **42** that show a superior reactivity compared to the corresponding ethyl esters. Anyway, highly hindered non-nucleophilic lithium amides (such LDA and LiTMP) were not compatible with this protocol.

By structural and spectroscopic studies, authors revealed that 2-MeTHF plays a key role in these reactions, ensuring full solubilisation of the lithium amides and favouring the formation of small kinetically activated aggregates. Furthermore, while LiNHPh **43** and $LiNPh_2$ **44** exhibit dimeric structures in the solid state solvated by three and two molecules of 2-MeTHF respectively (Figure 2.5), DOSY NMR studies are consistent with the formation of trisolvated $[Li(NR_2)(2\text{-MeTHF})_3]$ monomers. Monomer formation should lead to more powerful nucleophilic lithium amides that can react faster with the unsaturated organic substrate (ester or amide) to add across its C=O bond, favouring the addition over competing degradation by oxygen or moisture.

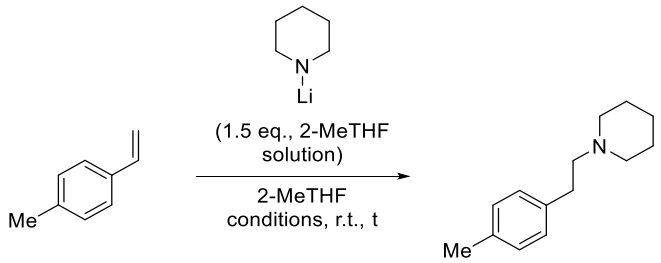


43 44 45

Figure 2.5. Molecular structures of dimeric (left to right) lithium anilide **43**, lithium diphenylamide **44** and lithium 2,2′-bipyridylamide **45** crystallised from anhydrous 2-MeTHF. Imagines adapted from ref.[73]

The applicability of this bench conditions to the chemistry of nucleophilic lithium amides was further detailed by the same authors with a moisture-promoted hydroamination of olefins such as **46** in wet 2-MeTHF (Table 2.6).[74]

Table 2.6. Experimental details of air-moisture benefits for the hydroamination of 4-methylstyrene **46** in 2-MeTHF.



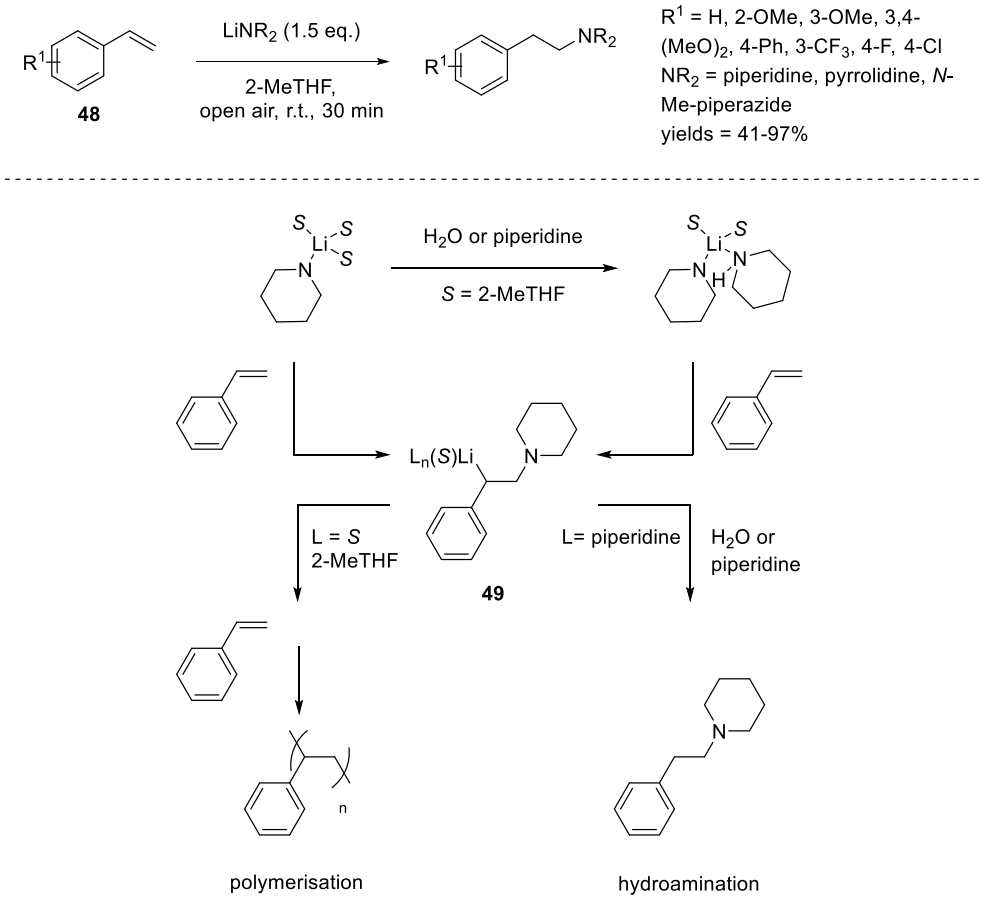
46 **47**

Entry	Conditions	t (min)	**47**, yield %
1	open air, wet solvent	30	90
2	$CaCl_2$ trap attached to the top of the reaction vial, wet solvent	240	35
3	N_2, dried solvent	30	28
4	N_2, dried solvent	120	28
5	wet N_2, dried solvent	120	75
6	N_2 + 1.5 eq. of piperidine, dried solvent	30	98

Surprisingly, the best results were obtained operating under bench conditions (open air, wet solvent) (Table 2.6, entry 1), while every strategy adopted to remove air and moisture in the reaction vessel (Table 2.6, entry 2-4) lead to a dramatic decrease of **47** yield. Interestingly, the addition of a stochiometric amount of free piperidine under anhydrous condition lead again to a quantitative recovery of the hydroamination product **47** (Table 2.6, entry 6).

In order to explain these experimental evidences, the authors proposed an *in situ* NMR monitoring of the reaction combined with DOSY NMR studies, revealing that the presence of free piperidine combined with the ability of 2-MeTHF to generate small kinetically activated monomeric aggregates[73] are the key to promote the hydroamination reactivity. When the reaction is carried out under air, the presence of moisture can generate free piperidine; the latter is able to coordinate the lithium piperidide, which in turn reacts with styrene to form selectively the hydroamination product *via* an intermediate lithiated species **49** that can be rapidly quenched by piperidine or traces of moisture. On the opposite, when the reaction was carried out under strictly anhydrous conditions, **49** become more stable and reacts with another units of styrene to generate polystyrene, that was observed as principal product under these conditions (Scheme 2.16).

Finally, the reaction was easily extended to different vinyl arenes **48** and lithium amides, to demonstrate the applicability of this unprecedent moisture-accelerated hydroamination protocol (Scheme 2.16).



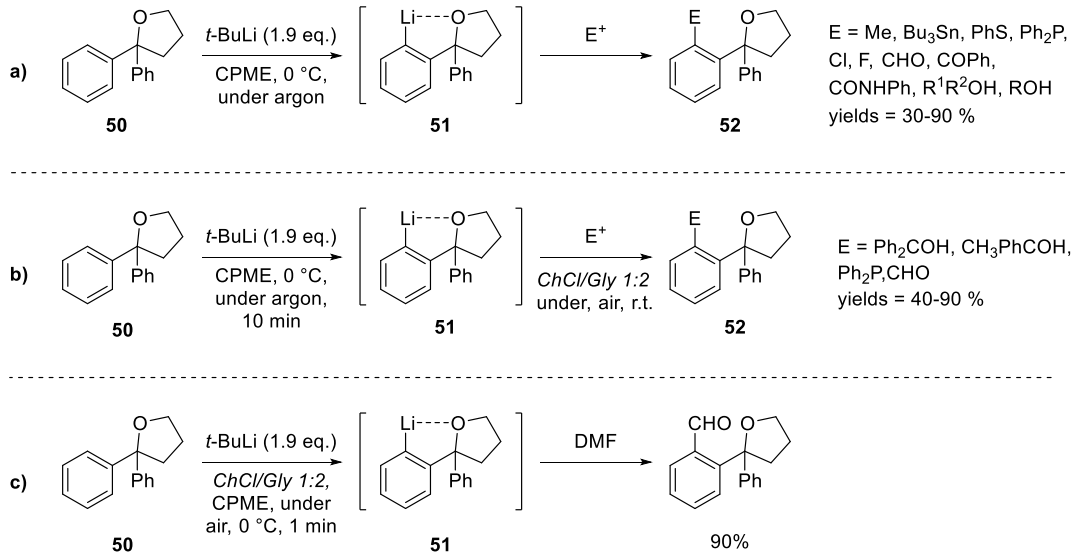
Scheme 2.16. Proposed pathway for the reaction of lithium piperidide with styrene in 2-MeTHF showing how the excess piperidine or ambient moisture supply is necessary to favour hydroamination over polymerisation.

On the basis of these results, and motivated to discover new bio-compatible strategies to synthesize polymers, the same authors subsequently developed an unprecedent *n*-BuLi-promoted anionic polymerization in DESs in high yields and with low polydispersity.[75]

2.4.5 Directed ortho-metalation and lateral lithiation of diaryltetrahydrofurans in DESs

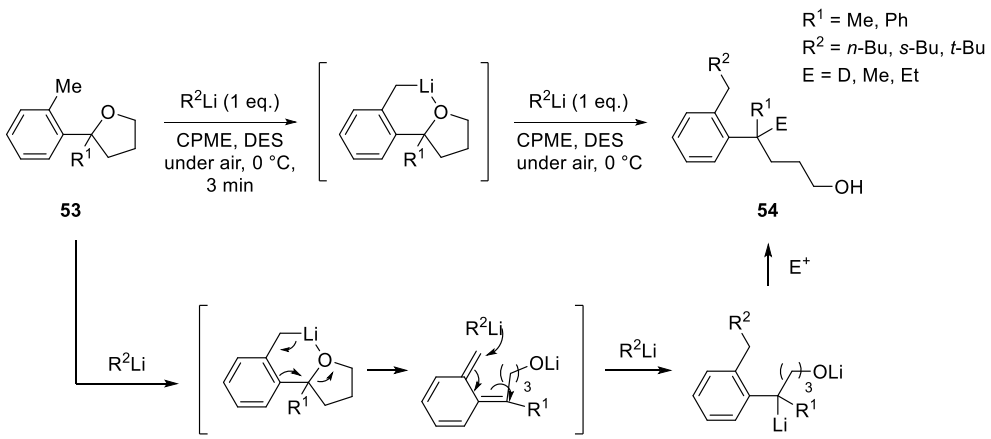
Compared to the nucleophilic reactivity of organolithiums, examples about the basic behaviour of these highly polar compounds in sustainable reaction media still remain scarce. This lack is easily understandable considering the counterintuitive nature of the proposed challenge. In fact, if the organolithiums nucleophilicity could be exalted by co-complexation with an ammonium salt or by H-bond interaction in the interface of a heterogeneous mixture under vigorous stirring, the classical deprotonation/electrophilic trapping sequence involves the formation of a high reactive C-Li species that requires a proton-free environment to overcome re-protonation events leading to a recover of the unreacted starting material.

Only recently, Capriati *et al.* showed the first experimental evidence of basic organolithiums reactivity using protic DESs as reaction media under sustainable conditions. During the optimization of the D*o*M of diaryltetrahydrofurans **50** promoted by *t*-BuLi, the authors observed that replacement of toxic and volatile DEE with environmental-friendly CPME led good results in term yields and efficiency of the *ortho*-functionalization, under argon (Scheme 2.17 a).[76] Motivated by this result, with the aim of further simplify the methodology, the authors performed the electrophilic quenching in DESs of the pre-generated active *ortho*-lithiated species **51** (in CPME), with both good recovery of the desired product **52** and with some advantages (depending on the nature of the electrophile used) respect to the classical approach under strictly anhydrous conditions (Scheme 2.17 b). Unfortunately, the *ortho*-deprotonation/electrophilic-functionalization directly in DESs, under air, at room temperature was effective only using the strong formylating agent DMF (Scheme 2.17 c). Nevertheless, this report represents the very first example of a successful D*o*M strategy in a polar protic environment.



Scheme 2.17. D*o*M of diaryltetrahydrofurans **50** performed in **a)** CPME under anhydrous conditions; **b)** CPME under anhydrous conditions followed by electrophilic trapping in DES; **c)** in DES under air.

A further extension of this work has demonstrated that the LL of *o*-tolyltetrahydrofurans **53** undergoes a spontaneous C-C bond formation step. This process takes place using CPME/DESs as sustainable reaction media, with the initial regioselective lithiation of the activated benzylic position of **53**, followed by addition of the second equivalent of the RLi reagent (*s*-BuLi, *i*PrLi, or *t*-BuLi), which finally promote the ring-opening of the furan ring leading the primary alcohol **54** in good to quantitative yields (Scheme 2.18).[77]



Scheme 2.18. Lateral lithiation-ring opening of *o*-tolyltetrahydrofurans **53** in CPME/DES and proposed mechanism.

The peculiar nature of this proposed mechanism, together with the limited choice of suitable electrophiles, requires future developments and investigations to fulfil the necessity of develop novel general and efficient methodologies for the generation and functionalization of high reactive C-Li species directly under protic bench conditions using these bio-compatible solvents.

References

1. P. T. Anastas and J. C. Warner, *Principles of green chemistry*, Oxford University Press, Oxford, 1998.
2. M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807-810.
3. F. Roschangar, J. Colberg, P. J. Dunn, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg and J. L. Tucker, *Green Chem.*, 2017, **19**, 281-285.
4. C. J. Clarke, W.-C. Tu, O. Levers, A. Brohl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747-800.
5. J. H. Clark and S. J. Tavener, *Org. Process. Res. Dev.*, 2007, **11**, 149-155.
6. R. A. Sheldon, *Green Chem.*, 2005, **7**, 267-278.
7. B. H. Lipshutz, F. Gallou and S. Handa, *ACS Sustain. Chem. Eng.*, 2016, **4**, 5838-5849.
8. Q. Zhang, K. D. O. Vigier, S. Royer and F. Jerome, *Chem. Soc. Rev.*, 2012, **41**, 7108-7146.
9. D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem.*, 2016, **2016**, 612-632.
10. V. Pace, P. Hoyos, L. Castoldi, P. Dominguez de Maria and A. R. Alcántara, *ChemSusChem*, 2012, **5**, 1369-1379.
11. S. Monticelli, L. Castoldi, I. Murgia, R. Senatore, E. Mazzeo, J. Wackerlig, E. Urban, T. Langer and V. Pace, *Monatsh. Chem.*, 2017, **148**, 37-48.
12. U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta and V. Pace, *ChemSusChem*, 2019, **12**, 40-70.
13. E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 11060-11082.
14. M. A. Martins, S. P. Pinho and J. A. Coutinho, *J. Solut. Chem.*, 2019, **48**, 962-982.
15. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70-71.
16. All DESs composition are reported as molar ratios throughout the whole thesis, unless otherwise specified
17. C. Ruß and B. König, *Green Chem.*, 2012, **14**, 2969-2982.
18. M. Francisco, A. van den Bruinhorst and M. C. Kroon, *Angew. Chem. Int. Ed.*, 2013, **52**, 3074-3085.
19. Y. H. Choi, J. van Spronsen, Y. Dai, M. Verberne, F. Hollmann, I. W. Arends, G.-J. Witkamp and R. Verpoorte, *Plant Physiol.*, 2011, **156**, 1701-1705.
20. Y. Dai, J. van Spronsen, G.-J. Witkamp, R. Verpoorte and Y. H. Choi, *Anal. Chim. Acta*, 2013, **766**, 61-68.
21. Y. Liu, J. B. Friesen, J. B. McAlpine, D. C. Lankin, S.-N. Chen and G. F. Pauli, *J. Nat. Prod.*, 2018, **81**, 679-690.
22. H. Vanda, Y. Dai, E. G. Wilson, R. Verpoorte and Y. H. Choi, *C. R. Chimie*, 2018, **21**, 628-638.
23. A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis and A. R. C. Duarte, *ACS Sustain. Chem. Eng.*, 2014, **2**, 1063-1071.
24. M. Deetlefs and K. R. Seddon, *Green Chem.*, 2010, **12**, 17-30.
25. Z. Yang, in *Deep Eutectic Solvents: Synthesis, Properties, and Applications*, Wiley, 2019, pp. 43-60.
26. B.-Y. Zhao, P. Xu, F.-X. Yang, H. Wu, M.-H. Zong and W.-Y. Lou, *ACS Sustain. Chem. Eng.*, 2015, **3**, 2746-2755.

27. I. Juneidi, M. Hayyan and M. A. Hashim, *RSC Adv.*, 2015, **5**, 83636-83647.
28. R. F. Frade, S. Simeonov, A. A. Rosatella, F. Siopa and C. A. Afonso, *Chemosphere*, 2013, **92**, 100-105.
29. X.-D. Hou, Q.-P. Liu, T. J. Smith, N. Li and M.-H. Zong, *PLOS ONE*, 2013, **8**.
30. B. Kudłak, K. Owczarek and J. Namieśnik, *Environ. Sci. Pollut. Res.*, 2015, **22**, 11975-11992.
31. Y. P. Mbous, M. Hayyan, W. F. Wong, C. Y. Looi and M. A. Hashim, *Sci. Rep.*, 2017, **7**, 1-14.
32. M. Faggian, S. Sut, B. Perissutti, V. Baldan, I. Grabnar and S. Dall'Acqua, *Molecules*, 2016, **21**, 1531.
33. S. Sut, M. Faggian, V. Baldan, G. Poloniato, I. Castagliuolo, I. Grabnar, B. Perissutti, P. Brun, F. Maggi and D. Voinovich, *Molecules*, 2017, **22**, 1921.
34. C. D'Agostino, R. C. Harris, A. P. Abbott, L. F. Gladden and M. D. Mantle, *Phys. Chem. Chem. Phys.*, 2011, **13**, 21383-21391.
35. A. P. Abbott, R. C. Harris and K. S. Ryder, *J. Phys. Chem. B*, 2007, **111**, 4910-4913.
36. A. P. Abbott, G. Capper and S. Gray, *ChemPhysChem*, 2006, **7**, 803-806.
37. C. Ma, A. Laaksonen, C. Liu, X. Lu and X. Ji, *Chem. Soc. Rev.*, 2018, **47**, 8685-8720.
38. A. Yadav, S. Trivedi, R. Rai and S. Pandey, *Fluid Phase Equilib.*, 2014, **367**, 135-142.
39. R. Bijoy, P. Agarwala, L. Roy and B. N. Thorat, *Org. Process. Res. Dev.*, 2021, DOI: 10.1021/acs.oprd.1c00246.
40. K. Watanabe, N. Yamagiwa and Y. Torisawa, *Org. Process. Res. Dev.*, 2007, **11**, 251-258.
41. G. de Gonzalo, A. R. Alcántara and P. Domínguez de María, *ChemSusChem*, 2019, **12**, 2083-2097.
42. P. D. de María, *Industrial biorenewables: a practical viewpoint*, John Wiley & Sons, 2016.
43. R. Bates, L. Kroposki and D. Potter, *J. Org. Chem.*, 1972, **37**, 560-562.
44. V. Antonucci, J. Coleman, J. B. Ferry, N. Johnson, M. Mathe, J. P. Scott and J. Xu, *Org. Process. Res. Dev.*, 2011, **15**, 939-941.
45. G. W. Huber, S. Iborra and A. Corma, *Chem. Rev.*, 2006, **106**, 4044-4098.
46. F. M. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer and W. Leitner, *Angew. Chem. Int. Ed.*, 2010, **49**, 5510-5514.
47. D. F. Aycock, *Org. Process. Res. Dev.*, 2007, **11**, 156-159.
48. J. Clayden and S. A. Yasin, *New J. Chem.*, 2002, **26**, 191-192.
49. I. Fleming, S. R. Mack and B. P. Clark, *Chem. Commun.*, 1998, 715-716.
50. M. Lancaster, *Green chemistry: an introductory text*, Royal society of chemistry, 2020.
51. S. E. García-Garrido, A. Presa Soto, E. Hevia and J. García-Álvarez, *Eur. J. Inorg. Chem.*, 2021, **2021**, 3116-3130.
52. J. García-Álvarez, E. Hevia and V. Capriati, *Chem. Eur. J.*, 2018, **24**, 14854-14863.
53. J. García-Álvarez, E. Hevia and V. Capriati, *Eur. J. Org. Chem.*, 2015, **2015**, 6779-6799.
54. F. M. Perna, P. Vitale and V. Capriati, *Curr. Opin. Green Sustain. Chem.*, 2020, **21**, 27-33.
55. F. M. Perna, P. Vitale and V. Capriati, *Curr. Opin. Green Sustain. Chem.*, 2021, **30**, 100487.
56. C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy and E. Hevia, *Angew. Chem. Int. Ed.*, 2014, **126**, 6079-6083.

57. H. Zong, H. Huang, J. Liu, G. Bian and L. Song, *J. Org. Chem.*, 2012, **77**, 4645-4652.
58. I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127-2198.
59. E. Hevia and R. E. Mulvey, *Angew. Chem. Int. Ed.*, 2011, **50**, 6448-6450.
60. L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Sci.*, 2016, **7**, 1192-1199.
61. L. Cicco, M. J. Rodríguez-Álvarez, F. M. Perna, J. García-Álvarez and V. Capriati, *Green Chem.*, 2017, **19**, 3069-3077.
62. A. F. Quivelli, G. D'Addato, P. Vitale, J. García-Álvarez, F. M. Perna and V. Capriati, *Tetrahedron*, 2021, **81**, 131898.
63. J. S. Dickstein and M. C. Kozlowski, *Chem. Soc. Rev.*, 2008, **37**, 1166-1173.
64. V. Pace, L. Castoldi, P. Hoyos, J. V. Sinisterra, M. Pregnolato and J. M. Sánchez-Montero, *Tetrahedron*, 2011, **67**, 2670-2675.
65. A. W. Patterson and J. A. Ellman, *J. Org. Chem.*, 2006, **71**, 7110-7112.
66. C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy and E. Hevia, *Angew. Chem. Int. Ed.*, 2016, **55**, 16145-16148.
67. L. Cicco, A. Salomone, P. Vitale, N. Ríos-Lombardía, J. González-Sabín, J. García-Álvarez, F. M. Perna and V. Capriati, *ChemSusChem*, 2020, **13**, 3583-3588.
68. G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati and F. M. Perna, *Angew. Chem. Int. Ed.*, 2017, **56**, 10200-10203.
69. M. J. Rodríguez-Álvarez, J. García-Álvarez, M. Uzelac, M. Fairley, C. T. O'Hara and E. Hevia, *Chem. Eur. J.*, 2018, **24**, 1720-1725.
70. S. Van der Jeught and C. V. Stevens, *Chem. Rev.*, 2009, **109**, 2672-2702.
71. C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981-8006.
72. J. García-Álvarez, L. Cicco, A. Fombona-Pascual, G. Carriedo, F. Perna, V. Capriati, A. P. Soto and A. Sánchez-Condado, *ChemSusChem*, 2020, **13**, 4967-4973.
73. M. Fairley, L. J. Bole, F. F. Mulks, L. Main, A. R. Kennedy, C. T. O'Hara, J. García-Alvarez and E. Hevia, *Chem. Sci.*, 2020, **11**, 6500-6509.
74. F. F. Mulks, L. J. Bole, L. Davin, A. Hernán-Gómez, A. Kennedy, J. García-Álvarez and E. Hevia, *Angew. Chem. Int. Ed.*, 2020, **59**, 19021-19026.
75. A. Sánchez-Condado, G. A. Carriedo, A. Presa Soto, M. J. Rodríguez-Álvarez, J. García-Álvarez and E. Hevia, *ChemSusChem*, 2019, **12**, 3134-3143.
76. V. Mallardo, R. Rizzi, F. C. Sassone, R. Mansueto, F. M. Perna, A. Salomone and V. Capriati, *Chem. Commun.*, 2014, **50**, 8655-8658.
77. F. C. Sassone, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Commun.*, 2015, **51**, 9459-9462.

Abstract

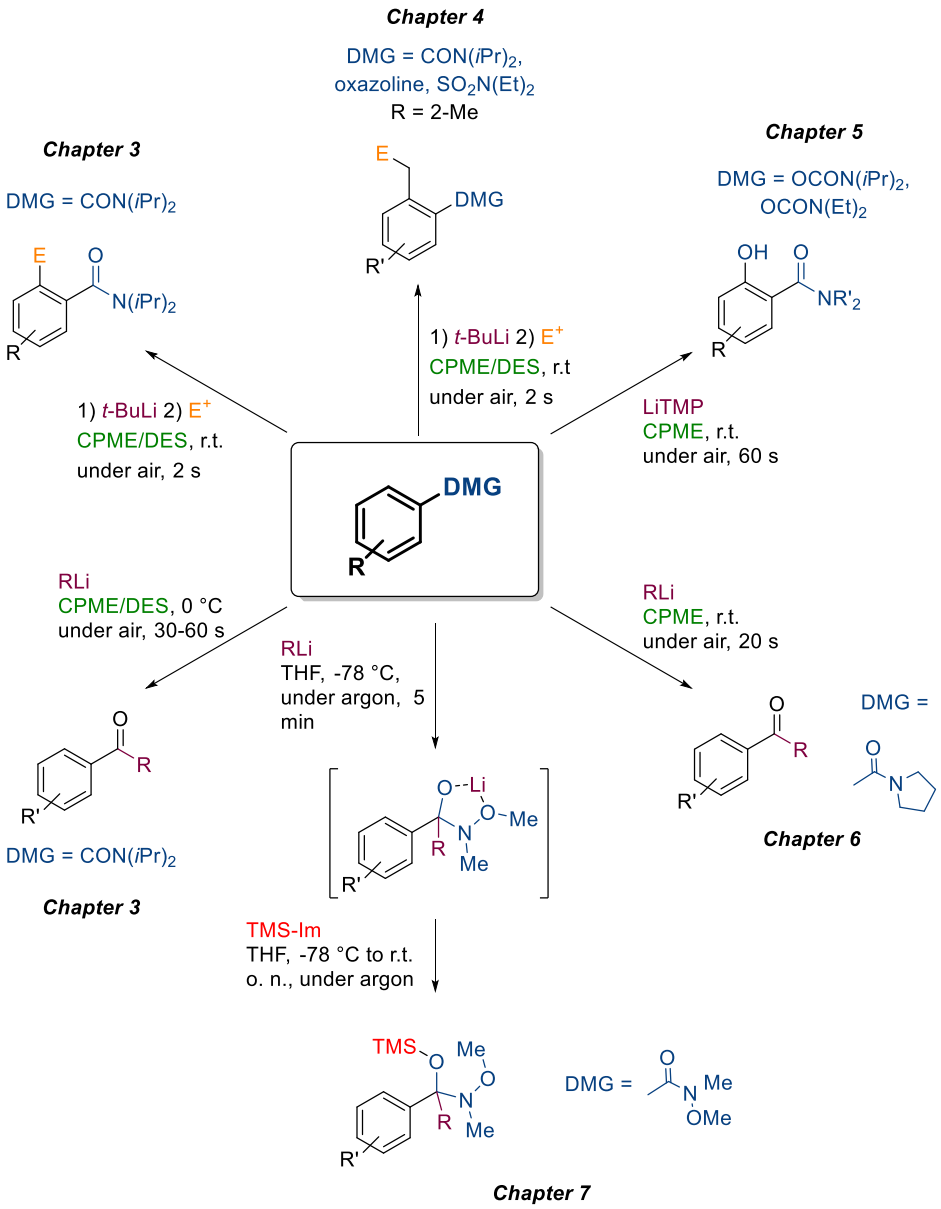
One of the main goals of modern synthetic chemistry is the development of new and efficient chemical processes under sustainable conditions. Recently, the chemistry of highly polar *s*-block organometallic compounds has proven to be compatible with exquisitely environmentally friendly operating conditions: the feasibility of running organometallic-mediated transformations under air, at room temperature using new protic 'green' reaction media, has broken the traditional paradigm which impose the handling of both organolithiums and Grignard reagents under strictly anhydrous conditions, using dangerous and toxic dry ethereal solvents at low temperatures to better control their reactivity.

My PhD project was mainly focused on the development of new organolithium-mediated synthetic strategies under unconventional bench conditions, in order a) to extend the portfolio of air-moisture compatible organolithium reactions and b) deepen our knowledge on the mechanistic principle on which this new and complex scenario of organolithium chemistry is based.

In **Chapter 3**, the chemoselective Directed *ortho* Metalation (D*o*M) or nucleophilic acyl substitution (S_NAc) reaction starting from the same aromatic carboxylic acid amide, in a choline chloride-based eutectic mixture, is reported. The D*o*M or S_NAc processes, *en route* to functionalized amides and ketones, can be conveniently and chemoselectively carried out under air, at room temperature or 0 °C, within a reaction time of up to 60 seconds and using environmentally friendly eutectic mixtures in combination with CPME, depending on the nature of the organolithium reagent. Next, a systematic study of new metalation/functionalization strategies using DESs as sustainable reaction media has been undertaken for promoting the regioselective lateral lithiation (LL) of substituted toluene derivatives, and the results are summarized in **Chapter 4**. In this work, we have shown that under exceedingly mild reaction conditions and ultrafast reaction times the most widely used DMGs in *ortho*- and lateral lithiation reactions (tertiary amides, sulfonamides and oxazolines) preserve their relative directing abilities and efficiently promote the LL under these conditions. Finally, the possibility to manipulate *O*-aryl carbamates under unconventional conditions to promote D*o*M functionalization strategies and anionic *ortho*-Fries (A*o*F) rearrangement sequences is illustrated in **Chapter 5**. We have shown that the reactivity of *O*-arylcarbamates with polar organolithium reagents can be conveniently controlled by changing the reaction conditions in the presence of air and moisture using eco-friendly unconventional solvents, at room temperature and in very short reaction times. Remarkably, high chemo- and regioselectivities using for the first time the hindered lithium amide

LiTMP as metalating agent under these unconventional conditions have been disclosed.

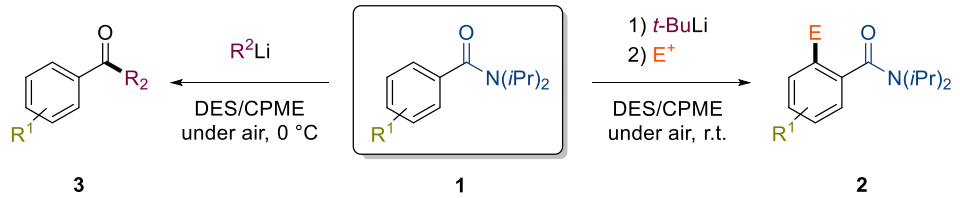
The nucleophilic reactivity of organolithium reagents has been also deeply investigated, with a particular focus on the chemoselective synthesis of ketones by 1,2-nucleophilic addition to carboxylic acid amides *via* stable tetrahedral intermediates. More in details, in **Chapter 6** the fast addition of organolithiums to simple amides in environmentally friendly CPME, at ambient temperature and under air, is reported. Our results disclosed that there is no need to make use of chemically modified or activated amides as well as transition metal-catalyzed C-N activation processes to promote and privilege nucleophilic acyl substitution reactions by organolithium reagents. The method provides the desired ketones with an effective suppression of the notorious over-addition reaction, and the experimental results are nicely supported by detailed DFT calculations that show how CPME stabilizes the dimeric tetrahedral intermediate, and by NMR spectroscopic investigations, which provide insights into the stability of the tetrahedral intermediate in CPME solution. Finally, a general and efficient protocol to access stable *O*-trimethylsilyl protected hemiaminals obtained upon addition of organolithiums to aromatic Weinreb amides is detailed in **Chapter 7**. The reaction has proven to be highly chemoselective allowing the formation of a plethora of derivatives presenting different functionalities., and the possibility to obtain single crystals of some selected compounds, together with their X-Ray analysis, gave further evidence of their chemical stability and easy handling, which allowed an unprecedent crystallographic analysis of these stable tetrahedral intermediates. This last part of the project was carried out during my period as PhD visiting scholar in the group of Prof. Vittorio Pace at the Pharmaceutical Department of the University of Vienna, Austria.


Chapter 4
DMG = CON(iPr)2, oxazoline, SO2N(Et)2
R = 2-Me
Chapter 3
DMG = CON(iPr)2
Chapter 5
DMG = OCON(iPr)2, OCON(Et)2
1) t-BuLi 2) E+
CPME/DES, r.t
under air, 2 s
1) t-BuLi 2) E+
CPME/DES, r.t.
under air, 2 s
LiTMP
CPME, r.t.
under air, 60 s
DMG
RLi
CPME/DES, 0 °C
under air, 30-60 s
RLi
THF, -78 °C,
under argon, 5 min
RLi
CPME, r.t.
under air, 20 s
DMG =
DMG = CON(iPr)2
Chapter 3
Chapter 6
TMS-Im
THF, -78 °C to r.t.
o. n., under argon
DMG =
Chapter 7

CHAPTER 3: Chemoselective directed *ortho*-metalation and nucleophilic acyl substitution of hindered carboxamides in Deep Eutectic Solvents

Part of the results presented in this chapter are published in *Chem. Commun*. **2019**, *55*, 7741-7744.

Amides are excellent starting materials and intermediates for organic synthesis due to their easy availability and preparation,[1-3] and versatile reactivity.[3-6] The reaction of highly reactive organolithiums compounds with aromatic amides has two different outcomes: directed *ortho* metalation with aromatic C-H functionalization (see section 1.2.2) or nucleophilic acyl substitution (S_NAc) (see paragraph 1.3). Interestingly, the reactivity of this versatile electrophilic platform has not been yet investigated under unconventional bench conditions (room temperature in the presence of air and moisture). Motivated by the experience of our research group[7-11] in polar organometallic chemistry and by the recent findings in using water or DESs as privileged reaction media with organometallic reagents (see paragraph 2.4), in this chapter a systematic study on the usefulness of protic DESs as sustainable reaction media to promote a high chemoselective D*o*M-S_NAc of hindered carboxamides **1** (Scheme 3.1) is presented.



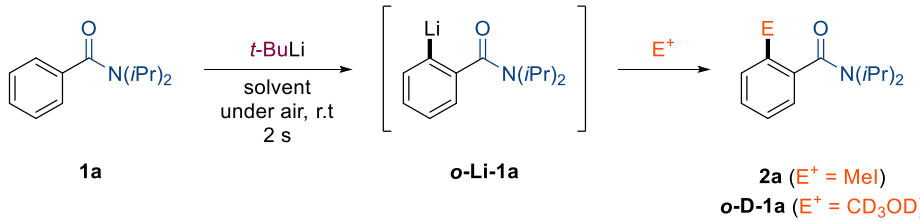
Scheme 3.1. *Ortho*-lithiation and nucleophilic acyl substitution of benzamide derivatives **1** in ethereal/eutectic mixtures.

3.1 D*o*M: optimization of the reaction conditions

We started our investigation using unsubstituted *N,N*-diisopropylbenzamide **1a** as a model substrate since it is known to be completely resistant to nucleophilic attack by alkyllithiums at the amide carbonyl, and to be easily *ortho*-functionalized in a total chemoselective fashion with *t*-BuLi, *s*-BuLi or even *n*-BuLi under classical condition (THF, -78 °C, under nitrogen).[12-14] In a preliminary experiment, amide **1a** (0.2 mmol) was suspended in a prototypical ChCl/Gly 1:2 eutectic mixture and then reacted at room temperature in air with commercially available *t*-BuLi (2 eq.) under vigorous stirring. Quenching the reaction mixture with MeI (5 eq.) after 2 seconds,

however, led to quantitative recovery of **1a** after work up (Table 3.1, entry 1). When *t*-BuLi (2 eq.) was added in one portion to **1a** (0.2 mmol), previously solubilized in a small amount of environmentally friendly CPME (0.2 mL, 1 M), in the above eutectic mixture, under air at room temperature with vigorous stirring in order to generate an emulsion between the two immiscible phases, and then quenched after 2 seconds with MeI (5 eq.), the *ortho*-methylated adduct **2a** was this time isolated in 70% yield as the sole product (Table 3.1, entry 2). Interestingly, no traces of any nucleophilic addition product were detected by ^{1}H NMR and GC-MS analyses of the crude reaction mixture when amide **1a** was treated with *t*-BuLi either in the presence or in the absence of electrophile. Furthermore, no evidence by ^{1}H NMR and GC-MS of bis methylated adduct were detected, despite the excess of base and electrophile used, indicated the extremely high instability of a bis-lithiated species under these experimental conditions (Figure 3.1). The regioselectivity of the lithiation was next confirmed by ^{2}H NMR analysis of the deuterated product ***o*-D-1a**, resulting from the treatment of **1a** with *t*-BuLi followed by quench with CD_3OD, that showed a total regioselective incorporation of deuterium at a single *ortho* position in 66% yield (86% deuterium incorporation) (Table 3.1, entry 3 and Figure 3.2). No significant changes were observed when the reaction was run at 0 °C (Table 3.1, entry 4), while lowering the organolithium from 2 to 1.5 eq., the electrophile from 5 to 3 eq. and the amount of CPME amounts from 0.2 mL to 0.1 mL led to a small decrease of conversion (Table 3.1, entries 5-8). Using ChCl/urea 1:2 as DES led to similar results (Table 3.1, entry 9), whereas the use of water as HBD (Table 3.1, entry 10) as well as the replacement of the eutectic mixture with water or Gly was ineffective (Table 3.1, entries 8-10). Furthermore, performing the reaction using a 'normal stirring', the recovery of **2a** noticeably decreased (Table 3.1, entry 14). These experimental results are in strong agreement with the previous studies on the beneficial effect of the H-bond interaction at the interphase area both on the substrate activation and on shielding the organolithiums from the competitive protonolysis.[15-17] The features of these '*on-DES*' procedures have been also observed for this unprecedented DES-compatible D*o*M: a) a heterogenous mixture is required; b) the outcome of the reaction is dependent by the stirring-efficiency; c) the replacement with other protic solvent with a minor H-bond network lead to a decrease of the reaction performance. Consequentially, using pure CPME as solvent the *ortho*-functionalized product **2a** was obtained, albeit in 41% yield (Table 3.1, entry 14).

Table 3.1. Metalation reaction of *N,N*-diisopropylbenzamide **1a** using *t*-BuLi under different conditions.[a]



1a **o-Li-1a** **2a** (E^+ = MeI) ***o*-D-1a** (E^+ = CD_3OD)

Entry	Solvent	*t*-BuLi (eq.)	E^+ (eq.)	Product (%)[b]
1	ChCl/Gly 1:2	2	MeI (5)	-
2	CPME,[c] ChCl/Gly 1:2	2	MeI (5)	**2a** (70)
3	CPME,[c] ChCl/Gly 1:2	2	CD_3OD (5)	***o*-D-1a** (83)[d]
4	CPME,[c, e] ChCl/Gly 1:2	2	MeI (5)	**2a** (67)
5	CPME,[c] ChCl/Gly 1:2	1.5	MeI (5)	**2a** (60)
6	CPME,[c] ChCl/Gly 1:2	2	MeI (3)	**2a** (63)
7	CPME,[f] ChCl/Gly 1:2	2	MeI (5)	**2a** (34)
8	CPME,[g] ChCl/Gly 1:2	2	MeI (5)	**2a** (60)
9	CPME,[c] ChCl/urea 1:2	2	MeI (5)	**2a** (67)
10	CPME,[c] ChCl/H_2O 1:2	2	MeI (5)	**-**
11	H_2O	2	MeI (5)	**-**
12	Gly	2	MeI (5)	**-**
13	CPME	2	MeI (5)	**2a** (41)
14[h]	CPME, ChCl/Gly 1:2	2	MeI (5)	**2a** (60)

[a] Reaction conditions: 1.0 g DES per 0.2 mmol of **1a.** DESs: ChCl/Gly 1:2; ChCl/urea 1:2; ChCl/H_2O 1:2. Stirring at 900 rpm. [b] Determined by ^1H NMR using CH_3NO_2 as the internal standard. [c] CPME: 0.2 mL. [d] 66% isolated yield, 86% D incorporation. [e] T = 0 °C. [f] CPME: 0.1 mL. [g] CPME: 0.15 mL. [h] 'normal stirring' at 400 rpm.

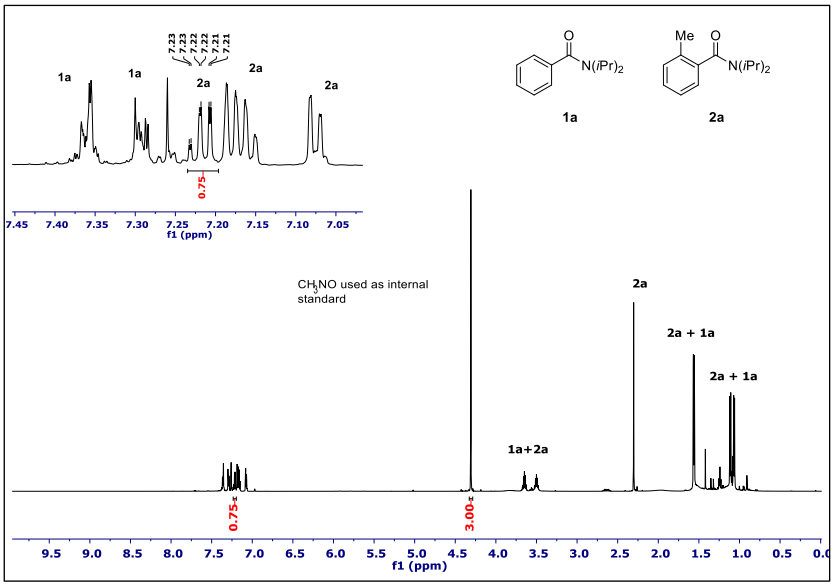


Figure 3.1. ^{1}H NMR of D*o*M crude reaction mixture reported in Table 3.1, entry 2: only signals of amide **1a** and **2a** were observed. Inset: expansion of the aromatic region with integration of the reference signal of **2a** used for ^{1}H NMR SI yield analysis.

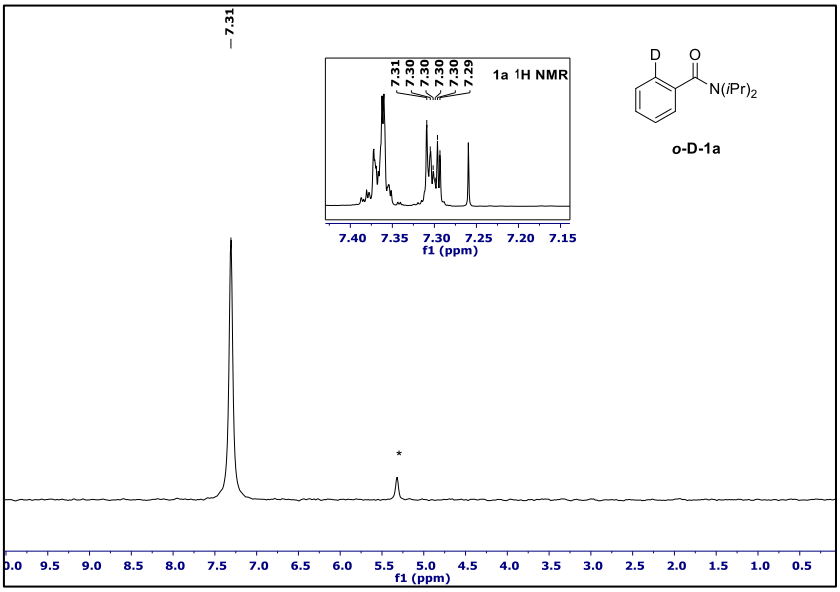
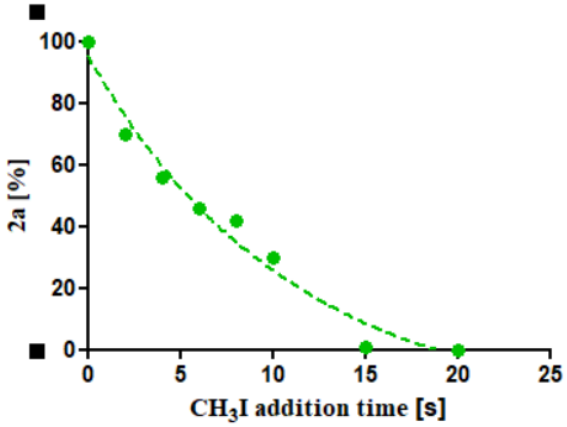


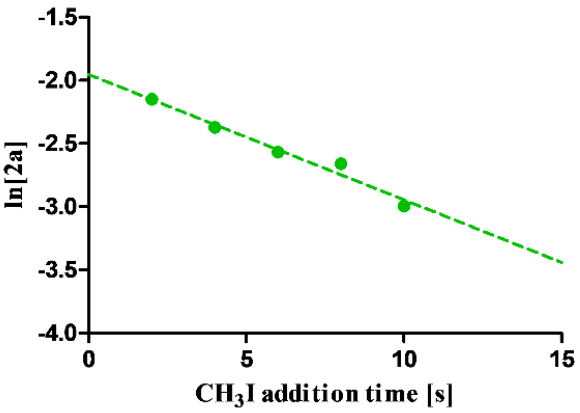
Figure 3.2. ^{2}H NMR of ***o*-D-1a**: total regioselective incorporation at *ortho*-position was observed. Inset: ^{1}H NMR spectra expansion of aromatic region of **1a**. *: residual CD_2Cl_2 solvent peak.

Next, the half-life of ***o*-Li-1a** was evaluated in the above protic medium. Experiments were designed to show the reaction progress over time with reaction

samples quenched with MeI at different times following treatment of the substrate **1a** with *t*-BuLi. The first-order plot obtained indicated an estimated half-life for ***o*-Li-1a** of 6.26 seconds (Figure 3.3). This very short half-life is due the presence of accessible protons in the eutectic mixture but, however is long enough to obtain the desired *ortho*-functionalized compounds after electrophilic quench. To the best of our knowledge, this is the first experimental evidence of the generation of a high reactive C-Li species under these protic and moisture-compatible experimental conditions. The presence of the amide directing group and the strict control of the experimental condition (*vide supra*) are crucial to yield stabilized ***o*-Li-1a** species.



CH_3I addition time (s)	**2a**, yield %
2	70
4	56
6	46
8	42
10	32
15	1
20	0



CH_3I addition time (s)	ln [**2a**]
2	-2.15
4	-2.37
6	-2.57
8	-2.66
10	-3.00

Figure 3.3. Kinetic analysis of the directed *ortho*-metalation of **1a**.

3.2 D*o*M: reaction substrate scope

The scope and limitations of this transformation were evaluated for a series of electrophiles and benzamide decorated with different functional group on the aromatic ring (Scheme 3.2). Strong electrophiles such as benzaldehyde and DMF reacted smoothly with anion ***o*-Li-1a**, thereby providing the expected *ortho*-functionalized adducts **2b**,**c** in good yield (60% and 68% respectively). In similar way, halogenating ($BrCH_2CH_2Br$), sulfurylating (S_2Me_2) and silylating (TMSI) agents could be used in slight excesses (1.5 eq.) to functionalize ***o*-Li-1a**, limiting remarkably the impact of the transformation, leading to the corresponding adducts **2b**,**f**,**g** in good yields (63-70%). Furthermore, 2 M solution of I_2 in 2-MeTHF was used to generate the corresponding *ortho*-iodo derivative **2c** in 62% yield. On the opposite, quenching of ***o*-Li-1a** with less electrophilic ethyl benzoate or with gaseous CO_2 (directly bubbled in the reaction mixture) were less favorable and furnished the corresponding aromatic ketone **2h** and the carboxylic acid derivative **2i** in lower yields (23-34%) (Scheme 3.2). The synthetic importance of these *ortho*-acyl derivatives motivated us to further optimize the reaction conditions to increase the yields. Unfortunately, the use of acetyl chloride to generate the methylated analogous of **2h** was ineffective, probably due to the high tendency of this electrophile to hydrolize under the reaction conditions, while changing the CO_2 addition protocol (*e.g.* using CO_2-presaturated DESs or dry-ice as CO_2 sources) after metalation only lead to the recovery of **2i** in lower yield compared to the aforementioned bubbling technique. Unfortunately, attempts with other electrophiles conventionally employed as trapping agents under classical Schenk conditions, including long-chain alkyl iodides (such as EtI and BuI), formates or carbonates, borates (such as $B(OMe)_3$ and $B(O\textit{i}Pr)_3$), benzonitrile and Ph_2PCl were unsuccessful, and the starting material **1a** was always recovered unreacted.

We next evaluated the impact of some functional group on the (hetero)aromatic ring on the reaction outcomes (Figure 3.4).

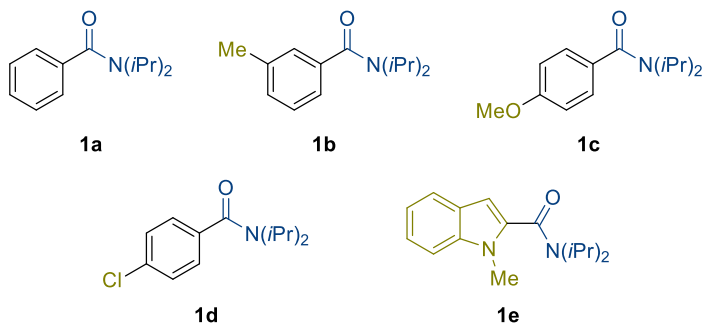
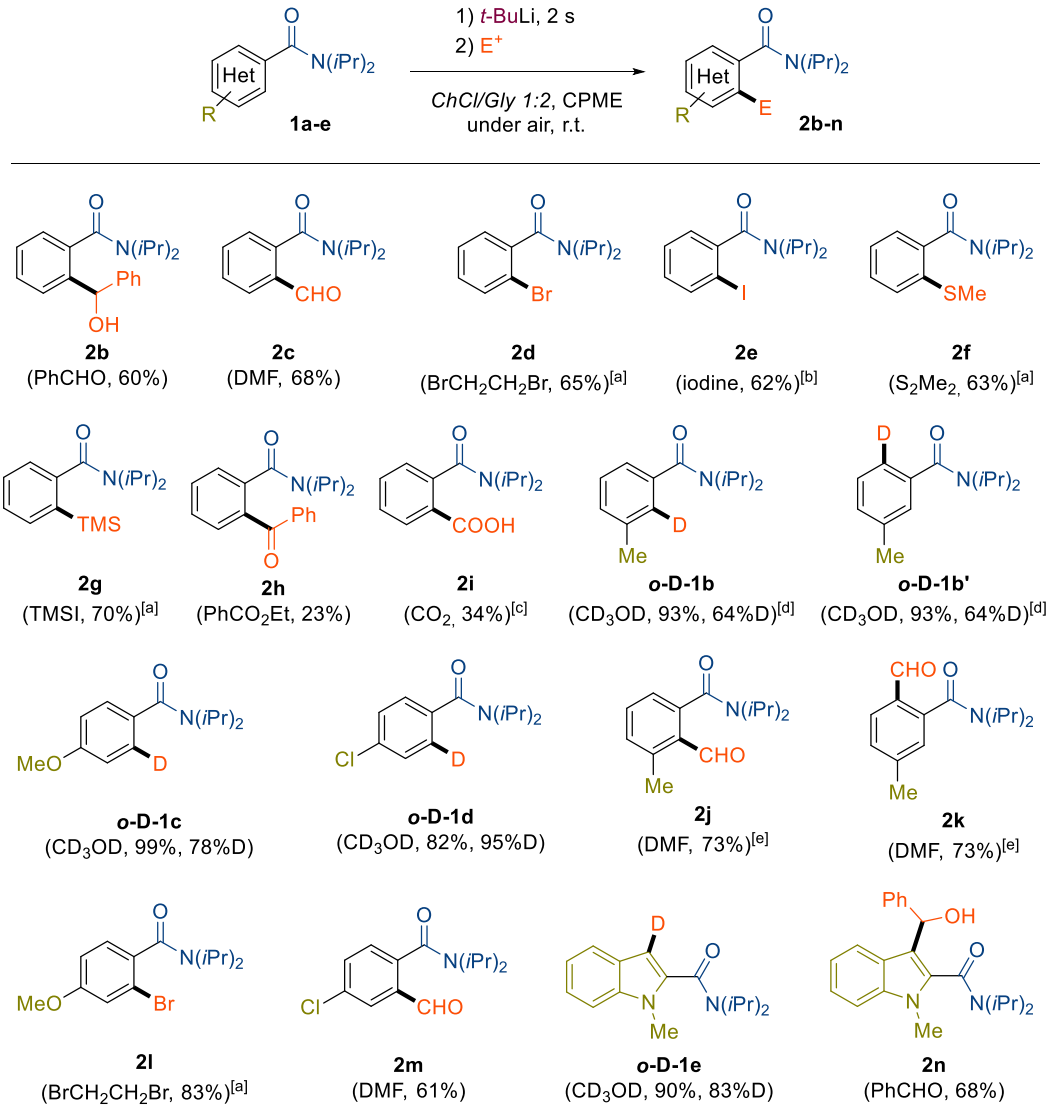


Figure 3.4. *N,N*-diisopropylamides **1a-e** used for the scope analysis.



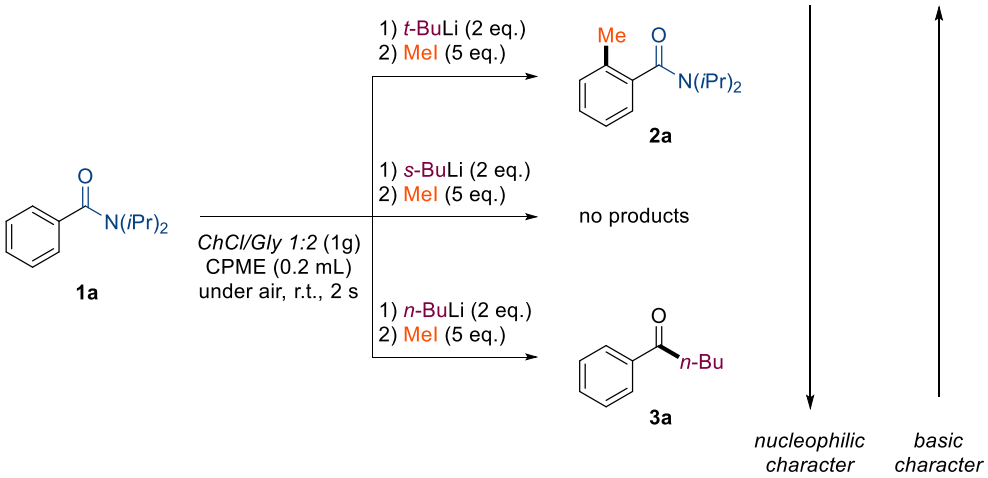
Scheme 3.2. Scope of the *ortho*-lithiation reaction of *N,N*-diisopropylbenzamides **1a-e** in a CPME/DES (ChCl/Gly 1:2) mixture. Reaction conditions: **1a-e** (0.2 mmol, 1.0 eq.), *t*-BuLi (1.7 M in pentane, 0.4 mmol, 2.0 eq.), CPME (0.2 mL, 1 M), ChCl/Gly 1:2 (1.0 g), electrophile (1.0 mmol., 5 eq., unless otherwise stated). The yields reported are for products isolated after flash column chromatography on silica gel. [a] The amount of the electrophile can be reduced to 1.2 eq. without any loss in terms of yield. [b] I_2 was added as a 2 M solution in 2-MeTHF. [c] CO_2 was bubbled for 15 s. [d] Overall percentage yield and overall percentage deuteration (ratio ***o*-D-1b**: ***o*-D-1b'** = 1:1). [e] Overall percentage yield (ratio **2j:2k** = 1:1).

Metalation-deuteration of **1b-d** took place in a total regioselective fashion proximal to the amide moiety (up to 95% D), (a) both at the *ortho* and at the *ortho'*-

position in the case of **1b** (and not in competition with lateral lithiation) and (b) leaving the chloride unreacted in the case of **1d**, and thus available for further functionalization. Formylation of *ortho*-lithiated ***o*-Li-1b** with DMF afforded products **2j**,**k** in 73% yield, however as an inseparable 1:1 mixture of regioisomers. On the other hand, bromination and formylation of *ortho*-lithiated ***o*-Li-1c** and ***o*-Li-1d** led to products **2l**,**m** in 83% and 61% yield, respectively. Interestingly, indole derivative **1e** showed 90% deuterium incorporation at the 3-position when sequentially treated with *t*-BuLi and CD_3OD, while provided product **2n** in 68% yield when anion ***o*-Li-1e** was quenched with PhCHO (Scheme 3.2).

3.3 Chemoselective S_NAc in eutectic/ethereal mixture

The reactivity of the model substrate **1a** was then explored toward other organolithium reagents. When amide **1a** was treated in a CPME/DES (ChCl/Gly 1:2) mixture at room temperature under air with *s*-BuLi either in the presence or in the absence of MeI as the electrophile, only the starting material was recovered. Alternatively, using *n*-BuLi (2 eq.) as the nucleophilic reagent, only a mixture of valerophenone **3a** and alcohol **4a** in 85:25 molar ratio (85% conversion) was detected (Table 3.2, entry 1) in the crude reaction mixture. Notably, when amide **1a** was treated with *n*-BuLi (2 eq.) in a CPME/DES (ChCl/Gly 1:2) mixture and quenched after 2 seconds using MeI as the electrophile, ketone **3a** and alcohol **4a** were again recovered as the sole products. These results clearly indicated how the basicity/nucleophilicity of the organolithium dictates the chemoselectivity of the reaction outcomes (Scheme 3.3). In the presence of a strong basic (and sterically hindered) organolithium such as *t*-BuLi only the metalation occurs, while using the less basic (and more nucleophilic) alkyllithium of the series, namely *n*-BuLi, only the S_NAc pathway is feasible. Interestingly, using a middle-ground organolithium (*s*-BuLi) neither metalation nor nucleophilic substitution occur under these unconventional conditions (Scheme 3.3).

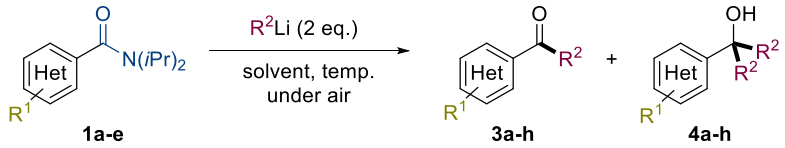


Scheme 3.3. High chemoselective D*o*M-S$_N$Ac in eutectic/ethereal mixture: the organolithium dictates the reaction outcome.

The good results observed in the preliminary experiment using *n*-BuLi as nucleophile showed an unexpected tetrahedral intermediate stability despite the protic environment. Therefore, we next explored different reaction conditions for the S$_N$Ac pathway in other to increase the ketone **3a**/alcohol **4a** ratio. Coherently with the D*o*M reaction, the use of pure ChCl/Gly 1:2 as solvent without CPME as an additive led to an important decrease of conversion (Table 3.2, entry 2). A remarkable chemoselectivity toward the S$_N$Ac pathway was similarly observed upon replacing the Gly component of the DES with urea (Table 3.2, entry 3), whereas the use of water or lactic acid (LA) as the HBD led to a lower or no conversion (Table 3.2, entries 4 and 5). The conversion was increased up to 90% and the ketone to alcohol ratio improved up to 86:14 by running the acyl substitution at 0 °C (Table 3.2, entry 6). Even in this case, the stirring speed is crucial for the reactivity under these heterogeneous conditions (Table 3.2, entry 7). Remarkably, the replacement of the CPME/DES mixture with pure solvents such as CPME, 2-MeTHF and Gly led to a significant decrease in terms of conversion and/or chemoselectivity (Table 3.2, entries 8-10).

Under the optimized reaction conditions, other aliphatic and aromatic commercially available organolithium reagents, ranging from MeLi to *n*-HexLi and PhLi, have been reacted with **1a** leading to the desired ketone derivatives **3b-d** in satisfactory yields (60-70%) (Table 3.2, entries 11-13). Pleasingly, also the treatment of substituted (hetero)aryl amides (see Figure 3.4) **1b-e** with *n*-BuLi afforded the corresponding ketones **3e-h** in yields up to 50% after column chromatography (Table 3.2, entries 14-17).

Table 3.2. Nucleophilic acyl substitution promoted by organolithiums on *N,N*-diisopropylcarboxamides **1a**-**e** in different unconventional solvents.[a]

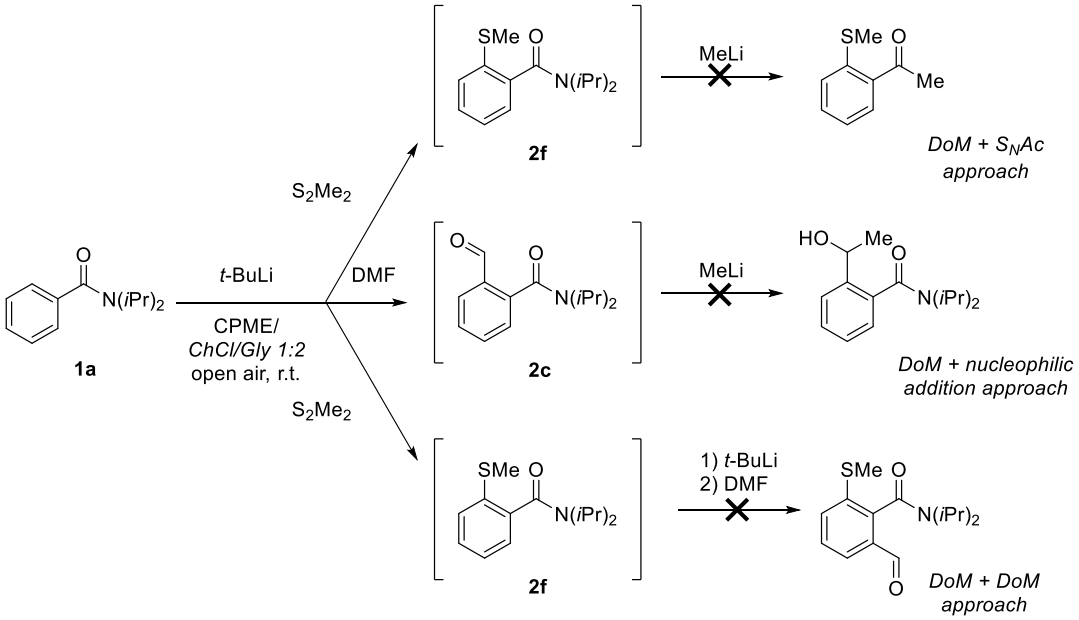


Entry	Solvent	**1**	R^2	T (° C)	Conv. (yield)% [c,d]	**3**	**3:4** ratio[c]
1	ChCl/Gly 1:2[b]	**1a**	*n*-Bu	25	85	**3a**	83:17
2	ChCl/Gly 1:2	**1a**	*n*-Bu	25	20	**3a**	50:50
3	ChCl/urea 1:2[b]	**1a**	*n*-Bu	25	80	**3a**	83:17
4	ChCl/H_2O 1:2[b]	**1a**	*n*-Bu	25	50	**3a**	66:33
5	ChCl/LA 1:2[b]	**1a**	*n*-Bu	25	-	**3a**	-
6	ChCl/Gly 1:2[b]	**1a**	*n*-Bu	0	90 (65)	**3a**	86:14
7	ChCl/Gly 1:2[b,g]	**1a**	*n*-Bu	0	60	**3a**	75:25
8	CPME	**1a**	*n*-Bu	0	100	**3a**	75:25
9	2-MeTHF	**1a**	*n*-Bu	0	70	**3a**	66:34
10	Gly	**1a**	*n*-Bu	25	24	**3a**	50:50
11	ChCl/Gly 1:2[b]	**1a**	Me[e]	0	70 (60)	**3b**	83:17
12	ChCl/Gly 1:2[b]	**1a**	*n*-Hex	0	87 (69)	**3c**	83:17
13	ChCl/Gly 1:2[b]	**1a**	Ph[f]	0	89 (70)	**3d**	86:14
14	ChCl/Gly 1:2[b]	**1b**	*n*-Bu	0	70 (50)	**3e**	86:14
15	ChCl/Gly 1:2[b]	**1c**	*n*-Bu	0	78 (56)	**3f**	80:20
16	ChCl/Gly 1:2[b]	**1d**	*n*-Bu	0	74 (50)	**3g**	83:17
17	ChCl/Gly 1:2[b]	**1e**	*n*-Bu	0	90 (60)	**3h**	88:12

[a] Conditions: **1a-e** (0.2 mmol, 1.0 eq.), DES or solvent (1 g). Reaction time of 20 s unless otherwise stated. Commercially available solutions of *n*-BuLi (2.5 M in hexanes), PhLi (1.8 M in dibutyl ether), *n*-HexLi (2.3 M in hexane), MeLi (1.6 M in DEE), *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane) were used (0.4 mmol, 2 eq.). [b] CPME 0.2 mL. [c] Conversions and **3:4** ratios were determined by GC-FID analysis and/or ^{1}H NMR spectroscopy. [d] In brackets, isolated yield of ketone **3** after flash column chromatography on silica gel. [e] Reaction time: 60 s. [f] Reaction time: 30 s. [g] 'normal stirring'.

3.4 Tandem approach

An interesting potentiality of this approach is the possibility to develop multistep synthetic sequences exploiting the natural quenching of the lithiated species under air-moisture without the necessity of adding water. As a basic principle, *ortho*-functionalized carboxamides **2** obtained by directed *ortho* metalation of **1** under our optimized reaction conditions could undergo other organolithium-promoted transformations *in situ* by treatment with an appropriated organometallic agent. To this purpose, we designed a series of experiments combining the two chemoselective methodologies previously developed in order to obtain more functionalized product in one synthetic operational step (Scheme 3.4).

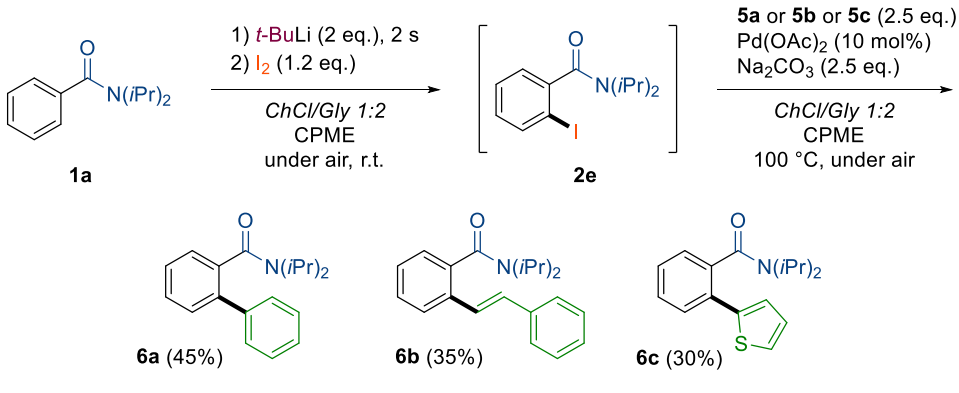


Scheme 3.4. Unsuccessful attempts to combine sequential organolithium-promoted reactions in CPME/DES.

Unfortunately, all the attempts were unsuccessful as a probable consequence of the reduced reactivity of the high hindered *ortho*-position, or a possible breaking of the H-bond network of the DES promoted by the high reactivity of strong basic compounds, or a combination of both.

Finally, we decided to combine our metalation protocol with another DES-compatible reaction, such as metal catalyzed cross coupling, developed by several research groups in recent years.[18-21] We thus targeted tandem D*o*M/ Suzuki-Miyaura (SM) approaches based on a preliminary regioselective *ortho*-lithiation/iodination of amide **1a** followed by an *in situ* Pd-catalyzed SM reaction in the above-described

eutectic mixture using different borates/boronic acids **5a-c** (Scheme 3.5) as nucleophilic partners. The resulting *ortho*-iodo derivative **2e** was subjected to a SM coupling reaction using 10 mol% of $Pd(OAc)_2$, thereby affording valuable *ortho*-functionalized styryl or (hetero)aryl derivatives **6a-c** in yields of up to 45% after two steps in one pot.



5a: phenylboronic acid; **5b**: styryl-BF_3K; **5c**: 2-thienylboronic acid pinacol ester

Scheme 3.5 Telescoped D*o*M/SM arylation/vinylation reactions starting from amide **1a** in a CPME/ChCl/Gly 1:2 mixture, and leading to adducts **6a-c**.

3.5 Conclusion

Directed *ortho* metalation or nucleophilic acyl substitution processes, *en route* to functionalized amides and ketones, can be conveniently carried out with high chemo control starting from the same aromatic carboxylic acid amide, under air, at room temperature or 0 °C, within a reaction time of up to 60 seconds and using environmentally friendly eutectic mixtures in combination with CPME, depending on the nature of the organolithium reagent. The use of *t*-BuLi led to *ortho*-lithiation processes, whereas the employment of less sterically encumbered organolithium reagents favoured S_NAc reaction. This work provides new insights for the metalation of arenes bearing a DMGs under bench conditions without a strict control of the experimental conditions (temperature and atmosphere) and the use of expensive and toxic additives such as bidentate diamino ligands (TMEDA among others). On the other hand, the low levels of tertiary alcohol by-products suggest that DES plays a prominent role in stabilizing the tetrahedral intermediates. Furthermore, both reactions proceed 'on DES' and the control of some operational aspect (*e.g.* the vigorous stirring of the heterogeneous mixture, the use of an ethereal additive) are crucial to obtain good level of reproducibility. In addition, we have demonstrated the possibility of performing one-pot, telescoped *ortho*-

lithiation/Pd-catalyzed Suzuki-Miyaura coupling reactions in DES mixtures, which are of great value in terms of efficiency and environmental sustainability.

3.6 Experimental section

3.6.1 General information

Materials and methods. Unless specified, all reagents were used as received without further purifications. *N,N*-dimethylformamide was distilled under vacuum from CaH_2 prior to use. Ethyl benzoate and benzaldehyde were distilled under vacuum prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. The following solutions of organolithium reagents were furnished by Aldrich and were used with the following concentration: *n*-BuLi 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane, *n*-HexLi 2.3 M in hexane, MeLi 1.6 M in DEE, and PhLi 1.8 M in dibutyl ether. The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[22] *N,N*-diisopropylbenzamides **1a-e** were synthesized according to the procedures reported in the literature.[23-26] Deep Eutectic Solvents (ChCl/LA 1:2; ChCl/urea 1:2; ChCl/Gly 1:2, ChCl/H_2O 1:2) were prepared by heating under stirring at 60-80 °C for 10-30 min the corresponding individual components until a clear solution was obtained.[27] Full characterization data have been reported for both the newly synthesized compounds and the known compounds.

Instrumentation. ^{1}H NMR (600 MHz) and $^{13}C\{^{1}H\}$ (150 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. ^{2}H NMR (92.07 MHz) spectra were obtained in DCM using residual CD_2Cl_2 as an internal reference. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad). Low-resolution MS spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI) or on a Micromass Quattro microTM API instrument (ESI, Waters Corporation, Milford, MA, USA). GC analyses were performed on a PerkinElmer Autosistem XL chromatographic system equipped with a methyl silicone capillary column. The MS flow-injection analyses were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an a ESI ion source. The samples were analyzed in acetonitrile solution using a syringe pump at a flow rate of 5 μL/min. The tuning parameters adopted for the ESI source were source voltage 4.0 kV. The heated capillary temperature was maintained at 275 °C. The mass accuracy of the recorded ions (vs. the calculated ones) was ± 2.5 mmu (milli-mass units). Analyses were run using both full MS (150-2000 m/z range) and MS/MS acquisition, at 500000 resolutions (200 m/z). Nitromethane was used as internal standard for quantitative NMR analyses on crude reaction

mixtures. For each ^{1}H NMR the amount of product was determined by applying the following equation (Eq. 1):

$$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)}\ \cdot\ f\ \cdot\ 100$$

where:

- *x* is the value of integral/number of protons;
- *n* is the amount of starting material or CH_3NO_2 in mmol;
- *f* the diluting factor used for the preparation of the sample

*3.6.2 Synthesis of N,N-diisopropylcarboxamides **1a-e**: general procedure*

The appropriate carboxylic acid (10.0-50.0 mmol, 1.0 eq.) was dissolved in thionyl chloride (10 eq.) and the solution was heated at reflux (80 °C) overnight. The solution was cooled to room temperature and the excess of thionyl chloride was removed under vacuum. The resulting acyl chloride was dissolved in dichloromethane (10-40 mL) then triethylamine (1.5 eq.) and diisopropylamine (1.2 eq.) were sequentially added dropwise at 0 °C. The mixture was warmed at room temperature and stirred until the reaction was completed (TLC, 4-5 hours). The mixture was washed with 1 M aq. HCl (2 x 10-30 mL), then with a saturated solution of Na_2CO_3 (2 x 10-30 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the corresponding amides **1a-e** that were purified by flash column chromatography and/or by recrystallization.

*3.6.3 Directed ortho-metalation in DESs: synthesis and analysis of products **2a-n***

Reactions were performed under air at room temperature. In an open screw cap vial, *N,N*-diisopropylcarboxamides **1a**-**e** (0.2 mmol, 1 eq.) were dissolved in CPME (0.2 mL, 1 M), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. *t*-BuLi (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of a selected electrophile after 2 seconds. The mixture was diluted with water (5 mL) and extracted with DEE (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

***N,N*-Diisopropyl-2-methylbenzamide (2a):** general procedure starting from **1a** and CH_3I (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2a** as a white solid (31 mg, 70%, R_f = 0.33 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.21 (m, 1H), 7.19-7.16 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 3.65 (sept, *J* = 6.7 Hz, 1H), 3.50 (sept, *J* = 6.7 Hz, 1H), 2.31 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H) superimposed to 1.57 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.8, 138.8, 133.7, 130.5, 128.2, 125.9, 124.8, 50.9, 45.9, 21.1, 20.9, 20.8, 20.7, 18.9. EI-MS *m/z* (%): 219 (M^+, 19), 218 (11), 176 (19), 119 (100), 91 (25).[28]

2-Deuterio-*N,N*-diisopropylbenzamide (*o*-D-1a): general procedure starting from **1a** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave ***o*-D-1a** (86% D incorporation) as a white solid (27 mg, 66%, R_f = 0.32 PE/EtOAc 8/2 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.38-7.35 (m, 3H), 7.31-7.29 (m, 1H), 3.99-3.29 (br m, 2H), 1.68-0.99 (br m, 12H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 171.2, 139.0 (t, *J* = 15.1 Hz, 1C), 128.7, 128.6, 128.5, 125.4 (t, *J* = 24.3 Hz, 1C), 51.0, 46.0, 20.9. ^2H NMR (92.07 MHz, dc): δ 7.31 (s). EI-MS *m/z* (%): 206 (M^+, 10), 163 (21), 107 (48), 106 (100), 105 (39).[28]

2-(Hydroxy(phenyl)methyl)-*N,N*-diisopropylbenzamide (2b): general procedure starting from **1a** and PhCHO (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2b** as a yellow semisolid (37 mg, 60%, R_f = 0.13 PE/EtOAc 9/1 v/v). ^1H NMR (600 MHz, $CDCl_3$, mixture of rotamers): δ 7.53 (dd, *J* = 7.7, 1.3 Hz, 2H minor), 7,41 (td, *J* = 7.6, 1.5 Hz, 2H minor), 7.37-7.33 (m, 4H major), 7.31-7.28 (m, 2H minor), 7.29-7.25 (m, 4H major), 7.19-7.16 (m, 1H major), 7.17-7.15 (m, 2H minor), 7.13-7.09 (m, 1H minor), 5,97 (s, 1H minor), 5.74 (s, 2H major), 4.09 (br s, 1H minor), 3.86 (sept, *J* = 6.7 Hz, 1H minor), 3.56-3.49 (m, 1H minor), 3.50-3.43 (m, 1H major), 3.25 (sept, *J* = 6.8 Hz, 1H major), 1.58 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.56 (d, *J* = 6.8 Hz, 3H minor), 1.41 (d, *J* = 6.9 Hz, 3H major), 1.28 (d, *J* = 6.8 Hz, 3H major), 1.19 (d, *J* = 6.6 Hz, 3H minor), 1.07 (d, *J* = 6.7 Hz, 3H major), 0.97 (d, *J* = 6.7 Hz, 3H minor), 0.39 (d, *J* = 6.7 Hz, 3H major). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$, mixture of rotamers): δ 172.1, 171.5, 144.3, 143.0, 141.9, 141.6, 137.8, 136.6, 131.4, 129.6, 129.2, 128.5, 128.4, 128.2, 127.5, 127.5, 127.3, 127.3, 127.2, 126.7, 126.2, 124.9, 77.1 (major), 72.9 (minor), 51.5 (minor), 51.2 (major), 46.3 (minor), 46.3 (major), 20.8 (minor), 20.6 (minor), 20.6 (major), 20.5 (minor), 20.2 (major), 20.2 (major). EI - MS *m/z* (%): 311 (M^+, 3), 210 (83), 209 (100), 194 (23), 181 (18), 165 (24), 133 (32). ESI-HRMS $[M+Na]^+$: *m/z* 334.1780, $C_{20}H_{25}NO_2Na^+$ requires 334.1778.

2-Formyl-*N,N*-diisopropylbenzamide (2c): general procedure starting from **1a** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 6/4 v/v) gave **2c** as a white solid (32 mg, 68%, R_f = 0.34 PE/EtOAc 6/4 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.92 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H) 7.50 (td, *J* = 7.6, 0.6 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 3.60-3.54 (m, 2H), 1.60 (d, *J* = 6.6 Hz, 6H), 1.09 (d, *J* = 6.7 Hz, 6H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.8, 168.4, 141.30, 134.4, 132.7, 129.8 128.8, 126.1, 51.3, 46.3, 20.6. EI-MS *m/z* (%): 233 (M^+, 1), 190 (42), 148 (33), 133 (100), 105 (37), 100 (17).[29]

2-Bromo-*N,N*-diisopropylbenzamide (2d): general procedure starting from **1a** and 1,2-dibromoethane (1.2 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2d** as a white solid (37 mg, 65%, R_f = 0.40 DCM/EtOAc 96/4 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.32 (td, *J* = 7.5, 1.0 Hz, 1H), 7.21-7.17 (m, 2H) 3.60 (sept, *J* = 6.7 Hz, 1H), 3.52 (sept, *J* = 6.7 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H) superimposed to 1.56 (d, *J* = 6.9 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 168.3, 140.3, 133.0, 129.6, 127.7, 126.7, 119.1,

51.3, 46.1, 20.9, 20.8, 20.8, 20.2. EI-MS *m/z* (%): 285 (M^+, 13), 283 (M^+, 13), 242 (29), 240 (29), 185 (95) 183 (100).[23]

2-Iodo-*N,N*-diisopropylbenzamide (2e): general procedure starting from **1a** and I_2 (5 eq.) in 2-MeTHF (2 M) solution. Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2e** as a white solid (41 mg, 62%, R_f = 0.46 DCM/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.35 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.03 (td, *J* = 7.6, 1.6, 1H), 3.58 (sept, *J* = 6.6 Hz, 1H), 3.51 (sept, *J* = 6.6 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.0, 144.4, 139.5, 129.6, 128.3, 126.0, 92.4, 51.4, 46.1, 20.9, 20.8, 20.2. EI-MS *m/z* (%): 331 (M^+, 18), 330 (16), 288 (31), 231 (100), 203 (17).[28]

***N,N*-Diisopropyl-2-(methylthio)benzamide (2f):** general procedure starting from **1a** and $(SMe)_2$ (1.2 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2f** as a white solid (32 mg, 63%, R_f = 0.10 PE/EtOAc 9/1 v/v), mp 132.1-133.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.3 Hz, 2H), 7.18-7.15 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 3.60 (sept, *J* = 6.8 Hz, 1H), 3.51 (sept, *J* = 6.8 Hz, 1H), 2.47 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H) superimposed to 1.56 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 169.1, 139.2, 134.7, 128.7, 127.6, 125.7, 125.5, 51.2, 46.0, 20.9, 20.4, 16.7. EI - MS *m/z* (%): 253 (M^+, 1), 251 (M^+, 17), 250 (14), 153 (6), 151 (100). ESI-HRMS $[M+Na]^+$: *m/z* 274.1237, $C_{14}H_{21}NOSNa^+$ requires 274.1236.

***N,N*-Diisopropyl-2-(trimethylsilyl)benzamide (2g)** general procedure starting from **1a** and TMSI (5 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2g** as a white solid (39 mg, 70%, R_f = 0.23 DCM/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61-7.59 (m, 1H), 7.34-7.29 (m, 2H), 7.17-7.14 (m, 1H), 3.80 (sept, *J* = 6.6 Hz, 1H), 3.49 (sept, *J* = 6.6 Hz, 1H), 1.56 (br s, 6H), 1.15 (br s, 6H), 0.31 (s, 9H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 172.4, 144.2, 138.3, 135.4, 128.3, 127.8, 125.3, 51.0, 45.9, 20.8, 0.3. EI-MS *m/z* (%): 277 (M^+, 14), 262 (42), 218 (60), 204 (29); 178 (46), 177 (100), 160 (25).[28]

2-Benzoyl-*N,N*-diisopropylbenzamide (2h): general procedure starting from **1a** and PhCOOEt (5 eq.). Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2h** as a white solid (14 mg, 23%, R_f = 0.20 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.51 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48-7.42 (m, 3H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1H) 7.33 (d, *J* = 7.6 Hz, 1H), 3.84 (sept, *J* = 6.7 Hz, 1H), 3.45 (sept, *J* = 6.7 Hz, 1H), 1.43 (br s, 6H), 1.20 (br s, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 196.9, 169.7, 140.0, 137.5, 136.9, 133.0, 130.9, 130.5, 130.1, 128.4, 127.6, 126.2, 51.5, 45.9, 20.3. EI-MS *m/z* (%): 309 (M^+, 2), 210 (41), 209 (100), 152 (23), 100 (30).[30]

2-(Diisopropylcarbamoyl)benzoic acid (2i): general procedure starting from **1a** and CO_2 (bubbled for 15 seconds). Purification by flash column chromatography (PE/EtOAc 1/1

v/v + HCOOH 0.5%) gave **2i** as a white solid (17 mg, 34%, R_f = 0.32 PE/EtOAc 1/1 v/v + HCOOH 0.5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (br s, 1H), 8.07 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.43 (td, *J* = 7.4, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.5, 0.9 Hz, 1H), 3.58 (sept, *J* = 6.6 Hz, 1H) superimposed to 3.52 (sept, *J* = 6.6 Hz, 1H), 1.58-1.56 (br m, 6H), 1.14-1.07 (br m, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.3, 170.2, 140.7, 133.4, 131.6, 128.4, 126.4, 126.2, 51.4, 46.0, 20.8, 20.6, 20.1, 19.9. ESI-MS *m/z*: 248.17 $[M-H]^-$.[31]

2-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (*o*-D-1b) and **6-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (*o*-D-1b')**: general procedure starting from **1b** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave an inseparable mixture of ***o*-D-1b** (30% D incorporation) and ***o*-D-1b'** (34% D incorporation) as a white solid (41 mg, 93%, R_f = 0.20 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26-7.23 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H, 30%D), 7.08 (d, *J* = 7.6 Hz, 1H, 34%D), 3.95-3.38 (br m, 2H), 2.35 (s, 3H), 1.77-0.94 (br m, 12H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.3, 139.1, 139.0, 138.4, 138.3, 129.4, 128.4, 128.3, 126.4, 122.3 (t, *J* = 23.8 Hz, 1C), 50.9, 45.9, 21.5, 21.5, 20.8. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.11 (s). EI-MS *m/z* (%): 220 (M^+, 17), 176 (24), 177 (22), 120 (86), 119 (100), 91 (27). ESI-HRMS $[M+Na]^+$: *m/z* 243.1571, $C_{14}H_{20}DNONa^+$ requires 243.1578.

2-Deuterio-*N,N*-diisopropyl-4-methoxybenzamide (*o*-D-1c): general procedure starting from **1c** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave ***o*-D-1c** (78% D incorporation) as a yellow oil (47 mg, 99%, R_f = 0.25 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, acetone-d_6): δ 7.27-7.25 (m, 1H), 6.95-6.94 (m, 2H), 3.86-3.62 (br m, 2H) superimposed to 3.82 (s, 3H), 1.32 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, acetone-d_6): δ 171.0, 160.9, 132.9 (t, *J* = 13.9 Hz, 1C), 128.0 (t, *J* = 21.1 Hz, 1C), 114.5, 114.4, 55.7, 49.2, 21.1. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.27 (s). EI-MS *m/z* (%): 236 (M^+, 10), 193 (20), 137 (36), 136 (100). ESI-HRMS $[M+Na]^+$: *m/z* 259.1527, $C_{14}H_{20}DNO_2Na^+$ requires 259.1527.

4-Chloro-2-deuterio-*N,N*-diisopropylbenzamide (*o*-D-1d): general procedure starting from **1d** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave ***o*-D-1d** (95% D incorporation) as a white solid (39 mg, 82%, R_f = 0.22 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.34 (m, 2H), 7.25-7.24 (m, 1H), 3.76-3.46 (br m, 2H), 1.49-1.15 (br m, 12H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.0, 137.3 (t, *J* = 13.3 Hz, 1C), 134.7, 128.9, 128.8, 127.0 (t, *J* = 24.6 Hz, 1C), 51.1, 46.1, 20.8. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.27 (s). EI-MS *m/z* (%): 242 (M^+, 4), 240 (M^+, 10), 199 (9), 197 (22), 143 (14), 142 (36), 141 (58), 140 (100). ESI-HRMS $[M+Na]^+$: *m/z* 263.1033, $C_{13}H_{17}DClNONa^+$ requires 263.1032.

2-Formyl-*N,N*-diisopropyl-3-methylbenzamide (2j) and **2-formyl-*N,N*-diisopropyl-5-methylbenzamide (2k)**: general procedure starting from **1b** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 75/25 v/v) gave an inseparable

mixture of regioisomers **2j** and **2k** in 1:1 ratio as a white solid (36 mg, 73%, R_f = 0.25 PE/EtOAc 75/25 v/v).^{1}H NMR (600 MHz, $CDCl_3$): δ 10.33 (s, 1H), 10.02 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9, 1H), 7.23 (d, *J* = 7.6, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 3.60-3.52 (m, 4H), 2.66 (s, 3H), 2.42 (s, 3H), 1.65-1.52 (br m, 12H), 1.13-1.04 (br m, 12H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 191.7, 190.4, 169.3, 168.6, 145.7, 142.8, 141.5, 141.4, 133.5, 131.9, 130.3, 130.1, 129.9, 129.6, 126.6, 123.9, 51.3, 51.3, 46.2, 46.1, 22.0, 20.8, 20.7, 20.6, 20.5. EI-MS *m/z* (%): **2j**: 247 (M^+, 1), 204 (65), 162 (58), 147 (100), 119 (36); **2k**: 247 (M^+, 1), 204 (53), 162 (41), 147 (100), 119 (39).[32]

2-Bromo-*N,N*-diisopropyl-4-methoxybenzamide (2l): general procedure starting from **1c** and 1,2-dibromoethane (1.2 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2l** as a white solid (52 mg, 83%, R_f = 0.30 DCM/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09-7.08 (m, 2H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.62 (sept, *J* = 6.7 Hz, 1H), 3.49 (sept, *J* = 6.7 Hz, 1H), 1.56 (d, *J* = 6.8 Hz, 3H) superimposed to 1.54 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6,7 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 168.4, 159.8, 132.9, 127.4, 119.6, 118.0, 113.8, 55.7, 51.3, 46.0, 21.0, 20.8, 20.8, 20.2. EI-MS *m/z* (%): 315 (M^+, 9), 313 (M^+, 10), 272 (27), 270 (28), 258 (4), 256 (4), 215 (97), 213 (100).[33]

4-Chloro-2-formyl-*N,N*-diisopropylbenzamide (2m): general procedure starting from **1d** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2m** as a white solid (32 mg, 61%, R_f= 0.30 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.90 (d, *J* = 2.1 Hz, 1H), 7.58 (dd, *J* = 8.1, 2.2 Hz, 1H) 7.24 (d, *J* = 8.0 Hz, 1H), 3.56 (sept, *J* = 6.6 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.7 Hz, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 189.3, 167.3, 139.6, 135.2, 134.2, 133.8, 129.3, 127.6, 51.4, 46.4, 20.6, 20.5. EI-MS *m/z* (%): 267 (M^+, 1), 226 (13), 224 (41), 184 (10), 182 (31), 169 (33), 167 (100), 141 (11), 139 (36).[34]

3-Deuterio-*N,N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (*o*-D-1e): general procedure starting from **1e** and CD_3OD. Purification by flash column chromatography (PE/DEE 8/2 v/v) gave ***o*-D-1e** (83% D incorporation) as a white solid (47 mg, 90%, R_f = 0.20 PE/DEE 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.29-7.26 (m, 1H), 7.16-7.12 (m, 1H), 4.47-3.38 (br m, 2H) superimposed to 3.78 (s, 3H), 1.85-0.96 (br m, 12H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 164.1, 137.3, 134.9, 126.9, 122.6, 121.4, 120.2, 109.8, 99.9 (t, *J* = 26.2 Hz, 1C), 51.0, 45.9, 30.9, 21.0. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 6.49 (s), 3.73 (t, *J* = 2.0 Hz). EI-MS *m/z* (%): 259 (M^+, 22), 159 (100), 132 (73), 90 (38). ESI-HRMS $[M + Na]^+$: *m/z* 282.1684, $C_{16}H_{21}DN_2ONa^+$ requires 282.1687.

3-(Hydroxy(phenyl)methyl)-*N,N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (2n): general procedure starting from **1e** and PhCHO (5 eq.). Purification by flash column chromatography (PE/EtOAc 75/25 v/v) gave **2n** as a white solid (50 mg, 68%, R_f = 0.25 PE/EtOAc 75/25 v/v), mp 59.0-60.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$, mixture

of rotamers): δ 7.61-6.91 (m, 18H major + minor), 6.12 (d, *J* = 6.0 Hz, 1H major), 6.07 (d, *J* = 4.2 Hz, 1H minor), 3.88-3.75 (m, 2H minor), 3.71 (s, 3H minor), 3.70 (s, 3H major), 3.60-3.43 (m, 3H major), 2.76 (br s, 1H minor), 1.62 (d, *J* = 6.8 Hz, 3H minor) superimposed 1.59 (d, *J* = 6.8 Hz, 3H major) superimposed to 1.57 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.55 (d, *J* = 6.8 Hz, 3H major), 1.18 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.16 (d, *J* = 6.6 Hz, 3H major), 1.03 (d, *J* = 6.6 Hz, 3H minor), 0.79 (d, *J* = 6.6 Hz, 3H major). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, mixture of rotamers): δ 164.5, 144.4, 143.2, 137.0, 136.8, 134.3, 133.6, 128.5, 128.2, 127.6, 127.2, 126.8, 126.0, 125.8, 125.5, 122.9, 122.6, 121.1, 120.4, 120.1, 116.9, 114.7, 109.8, 109.6, 70.3 (minor), 69.0 (major), 51.5 (minor), 51.4 (minor), 46.5 (major), 46.4 (major), 31.1 (major), 30.8 (minor), 21.0 (major), 20.7 (minor), 20.5 (major + minor), 20.5 (major + minor), 20.3 (minor). EI-MS *m/z* (%): 364 (M^+, 22), 263 (89), 262 (100), 247 (27), 218 (20), 158 (38). ESI-HRMS $[M+Na]^+$: *m/z* 387.2043, $C_{23}H_{28}N_2O_2Na^+$ requires 387.2043.

*3.6.3 Nucleophilic acyl substitutions in DES: synthesis and analysis of ketones **3a-h***

Reactions were performed under air at 0 °C. In an open screw cap vial, *N,N*-diisopropylcarboxamides **1a-e** (0.2 mmol, 1 eq.) were dissolved in CPME (0.2 mL, 1 M), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. The appropriate organolithium reagent (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was vigorously stirred for 20 s (30 s for PhLi, 60 s for MeLi) and then diluted with water. The mixture was extracted with DEE (3 x 5 mL), the combined organic layers were washed twice with 1 M HCl (5 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude ketones were purified by flash column chromatography on silica gel.

1-Phenylpentan-1-one (3a): general procedure starting from **1a** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3a** as colourless liquid (21 mg, 65%, R_f = 0.54 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.73 (quint, *J* = 7.3 Hz, 2H), 1.42 (sext, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 200.8, 137.2, 133.0, 128.7, 128.2, 38.5, 26.6, 22.6, 14.1. EI-MS *m/z* (%): 162 (M^+, 80), 120 (49), 105 (100), 77 (46).[35]

Acetophenone (3b): general procedure starting from **1a** and MeLi. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **3b** as colourless liquid (15 mg, 60%, R_f = 0.46 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 2.61 (s, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 198.4, 137.2, 133.3, 128.7, 128.5, 26.8. EI-MS *m/z* (%): 120 (M^+, 34), 105 (100), 77 (75), 51 (24).[36]

1-Phenylheptan-1-one (3c): general procedure starting from **1a** and *n*-HexLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3c** as colourless liquid

(26 mg, 69%, R_f = 0.57 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.41-1.30 (m, 6H), 0.91-0.88 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 200.8, 137.2, 133.0, 128.7, 128.2, 38.8, 31.8, 29.2, 24.5, 22.7, 14.2. δ. EI-MS *m/z* (%): 190 (M^+, 10), 120 (77), 105 (100), 77 (40).[37]

Benzophenone (3d): general procedure starting from **1a** and PhLi. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **3d** as white solid (25 mg, 70%, R_f = 0.50 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83-7.78 (m, 4H), 7.61-7.58 (m, 2H), 7.50-7.47 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 196.9, 137.7, 132.6, 130.2, 128.4. EI-MS *m/z* (%): 182 (M^+, 74), 105 (100), 77 (56), 51 (18).[36]

1-(*m*-Tolyl)pentan-1-one (3e): general procedure starting from **1b** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3e** as colourless liquid (18 mg, 50%, R_f = 0.60 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.37-7.33 (m, 2H), 2.95 (t, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.71 (quint, *J* = 7.6 Hz, 2H), 1.40 (sext, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 201.0, 138.5, 137.3, 133.7, 128.7, 128.5, 125.4, 38.5, 26.7, 22.6, 21.5, 14.1. EI-MS *m/z* (%): 176 (M^+, 13), 134 (42), 119 (100), 91 (44).[38]

1-(3-Methoxyphenyl)pentan-1-one (3f): general procedure starting from **1c** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 9/1 v/v) gave **3f** as colourless liquid (21 mg, 56%, R_f = 0.37 PE/DEE 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 6.94-6.91 (m, 2H), 3.86 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.70 (quint, *J* = 7.5 Hz, 2H), 1.40 (sext, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.4, 163.4, 130.5, 130.3, 113.8, 55.6, 38.2, 26.9, 22.7, 14.1. EI-MS *m/z* (%): 192 (M^+, 4), 150 (46), 135 (100), 107 (8).[38]

1-(3-Chlorophenyl)pentan-1-one (3g): general procedure starting from **1d** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3g** as colourless liquid (20 mg, 50%, R_f = 0.57 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91-7.88 (m, 2H), 7.44-7.42 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.71 (quint, *J* = 7.3 Hz, 2H), 1.40 (sext, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.5, 139.4, 135.5, 129.6, 129.0, 38.5, 26.5, 22.6, 14.1. EI-MS *m/z* (%): 196 (M^+, 1), 156 (19), 154 (56), 141 (34), 139 (100), 113 (10), 111 (31).[38]

1-(1-Methyl-*1H*-indol-2-yl)pentan-1-one (3h): general procedure starting from **1e** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 9/1 v/v) gave **3h** as white solid (26 mg, 60%, R_f = 0.43 PE/DEE 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.40-7.37 (m, 2H), 7.30 (s, 1H), 7.18-7.14 (m, 1H), 4.08 (s, 3H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.76 (quint, *J* = 7.7 Hz, 2H), 1.44 (sext, *J* = 7.7 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 194.6, 140.1, 135.1, 125.9, 125.9, 123.0, 120.8,

111.3, 110.5, 39.9, 32.3, 27.5, 22.7, 14.1. EI-MS *m/z* (%): 215 (M^+, 59), 173 (39), 159 (41), 158 (100), 144 (16), 131 (27), 89 (50).[39]

*3.6.4 Telescoped DoM/Suzuki-Miyaura coupling reaction: synthesis and analysis of compounds **6a-c***

In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (0.2 mmol, 1.0 eq.) was dissolved in CPME (0.2 mL, 1 M), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. *t*-BuLi (0.4 mmol, 2.0 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring then quenched by addition of iodine (2 M solution in 2-MeTHF, 0.24 mmol, 1.2 eq., 0.12 mL) after 2 seconds. Then the selected boronic coupling partner **5a-c** (0.5 mmol, 2.5 eq.), Na_2CO_3 (0.5 mmol, 2.5 eq.) and $Pd(OAc)_2$ (0.02 mmol, 0.1 eq.) were sequentially added and the reaction mixture was stirred overnight at 100 °C under air. The mixture was cooled to room temperature, filtered through a Celite pad, then extracted with 1 mL of CPME and concentrated under reduced pressure. Purification by flash column chromatography give the pure product **6a-c**.

***N,N*-Diisopropyl-[1,1'-biphenyl]-2-carboxamide (6a):** General procedure using phenyl boronic acid **5a**. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) gave **6a** as a white solid (25 mg, 45%, R_f = 0.38 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.42-7.26 (m, 7H), 3.43 (sept, *J* = 6.8 Hz, 1H), 3.22 (sept, *J* = 6.7 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.32 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.4, 140.0, 138.1, 137.8, 129.5, 129.4, 128.6, 128.4, 127.7, 127.7, 126.7, 50.7, 45.7, 21.0, 20.9, 19.6, 19.6. EI-MS *m/z* (%): 281 (M^+, 23), 280 (25), 238 (31), 181 (100), 152 (36).[28]

***(E)*-*N,N*-Diisopropyl-2-styrylbenzamide (6b):** General procedure using potassium styryltrifluoroborate **5b**. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) give **6b** as a white solid (22 mg, 35%, R_f = 0.40 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.46-7.44 (m, 2H), 7.35-7.31 (m, 3H), 7.28-7.23 (m, 2H), 7.19 (d, *J* = 16.3 Hz, 1H) superimposed to 7.18-7.16 (m, 1H), 7.08 (d, *J* = 16.3 Hz, 1H), 3.62 (sept, *J* = 6.8 Hz, 1H), 3.51 (sept, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H) superimposed to 1.02 (d, *J* = 6.7 Hz, 3H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.4, 138.1, 137.3, 133.5, 130.7, 128.9, 128.5, 128.0, 127.8, 126.7, 125.5, 125.5, 51.1, 46.0, 20.9, 20.8, 20.7, 20.6. EI-MS *m/z* (%): 307 (M^+, 43), 264 (9), 207 (100), 178 (57).[40]

***N,N*-Diisopropyl-2-(thiophen-2-yl)benzamide (6c):** General procedure using thienylboronic acid pinacol ester **5c**. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) give **6c** as a white solid (17 mg, 30%, R_f = 0.38 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.37-7.29 (m, 4H), 7.26-

7.22 (m, 1H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H), 3.46 (sept, *J* = 6.6 Hz, 1H), 3.32 (sept, *J* = 6.6 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.41 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.53 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 170.2, 141.3, 137.8, 130.6, 129.4, 128.6, 128.0, 127.9, 127.4, 126.6, 126.0, 50.9, 45.8, 20.9, 20.7, 19.8. EI-MS *m/z* (%): 287 (M^+, 22), 244 (9), 187 (100), 115 (25).[41]

References

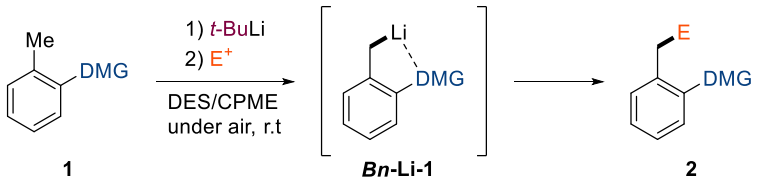
1. V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471-479.
2. C. L. Allen and J. M. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405-3415.
3. V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697-3736.
4. K. L. White and M. Movassaghi, *J. Am. Chem. Soc.*, 2016, **138**, 11383-11389.
5. V. Pace and W. Holzer, *Aust. J. Chem.*, 2013, **66**, 507-510.
6. G. Li and M. Szostak, *Chem. Rec.*, 2020, **20**, 649-659.
7. M. Blangetti, A. Deagostino, C. Prandi, C. Zavattaro and P. Venturello, *Chem. Commun.*, 2008, 1689-1691.
8. M. Blangetti, A. Deagostino, C. Prandi, S. Tabasso and P. Venturello, *Org. Lett.*, 2009, **11**, 3914-3917.
9. M. Blangetti, P. Fleming and D. F. O'Shea, *J. Org. Chem.*, 2012, **77**, 2870-2877.
10. M. Blangetti, H. Müller-Bunz and D. F. O'Shea, *Chem. Commun.*, 2013, **49**, 6125-6127.
11. A. Deagostino, V. Farina, C. Prandi, C. Zavattaro and P. Venturello, *Eur. J. Org. Chem.*, 2006, 3451-3456.
12. P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34-46.
13. V. Snieckus, *Chem. Rev.*, 1990, **90**, 879-933.
14. P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306-312.
15. S. E. García-Garrido, A. Presa Soto, E. Hevia and J. García-Álvarez, *Eur. J. Inorg. Chem.*, 2021, **2021**, 3116-3130.
16. L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salomone, S. Florio and V. Capriati, *Chem. Sci.*, 2016, **7**, 1192-1199.
17. G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati and F. M. Perna, *Angew. Chem. Int. Ed.*, 2017, **56**, 10200-10203.
18. G. Dilauro, S. M. García, D. Tagarelli, P. Vitale, F. M. Perna and V. Capriati, *ChemSusChem*, 2018, **11**, 3495-3501.
19. F. Messa, G. Dilauro, F. M. Perna, P. Vitale, V. Capriati and A. Salomone, *ChemCatChem*, 2020, **12**, 1979-1984.
20. A. F. Quivelli, P. Vitale, F. M. Perna and V. Capriati, *Front. Chem.*, 2019, **7**, 723.
21. X. Marset, A. Khoshnood, L. Sotorríos, E. Gómez Bengoa, D. A. Alonso and D. J. Ramón, *ChemCatChem*, 2017, **9**, 1269-1275.
22. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879-1880.
23. L. Wang and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1083-1085.
24. E. Bisz and M. Szostak, *Adv. Synth. Catal.*, 2019, **361**, 85-95.
25. S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti and C. Prandi, *Chem. Commun.*, 2019, **55**, 7741-7744.
26. J. Clayden, C. C. Stimson and M. Keenan, *Chem. Commun.*, 2006, 1393-1394.
27. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70-71.
28. S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley and M. Uchiyama, *J. Am. Chem. Soc.*, 2007, **129**, 15102-15103.
29. C. W. Chen and P. Beak, *J. Org. Chem.*, 1986, **51**, 3325-3334.
30. M. Uchiyama, H. Naka, Y. Matsumoto and T. Ohwada, *J. Am. Chem. Soc.*, 2004, **126**, 10526-10527.
31. A. Ueno, M. Takimoto, W. W. N. O, M. Nishiura, T. Ikariya and Z. Hou, *Chem. Asian J.*, 2015, **10**, 1010-1016.
32. G. Yang and W. Zhang, *Org. Lett.*, 2012, **14**, 268-271.

33. W. C. Wertjes, L. C. Wolfe, P. J. Waller and D. Kalyani, *Org. Lett.*, 2013, **15**, 5986-5989.
34. F. Faigl, A. Thurner, B. Molnár, G. Simig and B. Volk, *Org. Process Res. Dev.*, 2010, **14**, 617-622.
35. W.-B. Sheng, Q. Jiang, W.-P. Luo and C.-C. Guo, *J. Org. Chem.*, 2013, **78**, 5691-5693.
36. K. Moriyama, M. Takemura and H. Togo, *Org. Lett.*, 2012, **14**, 2414-2417.
37. W. Kong, C. Yu, H. An and Q. Song, *Org. Lett.*, 2018, **20**, 349-352.
38. Y. Xia, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2018, **140**, 5347-5351.
39. J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **126**, 8556-8560.
40. X.-F. Bai, L.-W. Xu, L.-S. Zheng, J.-X. Jiang, G.-Q. Lai and J.-Y. Shang, *Chem. Eur. J.*, 2012, **18**, 8174-8179.
41. M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, 1985, **26**, 5997-6000.

CHAPTER 4: Lateral lithiation in DESs: regioselective functionalization of substituted toluenes

Part of the results presented in this chapter are published in *Chem. Commun*. **2020**, *56*, 2391-2394.

In the previous chapter the first systematic study on the directed *ortho* metalation reaction of hindered benzamides using DESs as unconventional eco-friendly reaction media has been described. In strong relationship with the D*o*M strategies, of equal synthetic utility is the development of methodologies for the lateral lithiation (LL) of benzylic alkyl groups promoted by the same heteroatom-containing substituents (see section 1.2.3). As a further extension of the previous described methodology, and on the basis of our outstanding results on the basic reactivity of organolithium reagents in protic reaction media, a systematic investigation on the usefulness of these sustainable media to promote the regioselective lateral lithiation (LL) of substituted toluenes (Scheme 4.1) has been undertaken. The results of this study are presented in the following chapter.



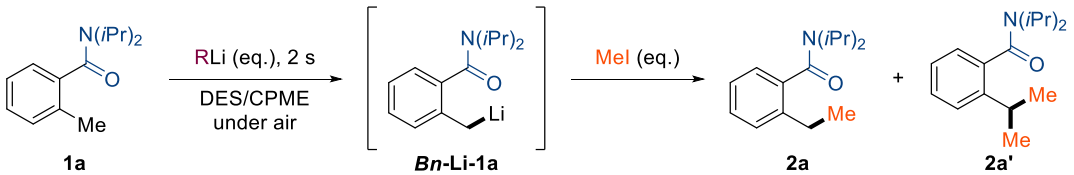
Scheme 4.1. Regioselective lateral lithiation of substituted toluene derivatives in eco-friendly eutectic mixtures.

4.1 Optimization of the reaction conditions

We started our investigations using the *N,N*-diisopropyl-2-methylbenzamide **1a** as a model substrate, since (a) we have already demonstrated that this directing group can efficiently promote the *ortho*-lithiation in CPME/DES heterogeneous mixtures (see Chapter 3) and (b) the LL of tertiary *ortho*-alkylbenzamides is generally performed using LDA or *s*-BuLi/TMEDA in VOCs at low temperatures in order to avoid self-condensation of the lithiated species (see section 1.2.3).[1-5] Based on the previously described experimental method explored for the D*o*M reaction, a vigorously stirred suspension of amide **1a** (0.2 mmol), preliminary dissolved in CPME (0.2 mL, 1 M), in ChCl/Gly 1:2 was treated with a commercial solution of *t*-BuLi (2 eq.) at room temperature under air. Quenching the reaction mixture after 2 seconds with MeI (5 eq.) afforded the corresponding *N,N*-diisopropyl-2-ethylbenzamide **2a** in 62% yield (Table 4.1, entry 1) alongside with 6% of α,α-dimethylated byproduct

2a'. Without pre-solubilization of **1a** in CPME, no lithiation occurred and the starting material **1a** was quantitatively recovered after workup (Table 4.1, entry 2). No improvements were observed when the reaction was performed at 0 °C (Table 4.1, entry 3) or using ChCl/urea 1:2 (Table 4.1, entry 4), whereas the use of water as the hydrogen bond donor was ineffective (Table 4.1, entry 5). Lowering the equivalents of electrophile (Table 4.1, entry 6 and 7) led to a decrease of conversion, while reducing the amount of lithiating agent to 1.5 eq. gave the best results in terms of yield and suppression of byproduct (Table 4.1, entry 10), as also confirmed by ^{1}H and ^{2}H NMR analysis of the corresponding deuterated product ***Bn*-D-1a** (*vide infra*). Notably, other organolithiums such as *n*-BuLi and *s*-BuLi were considerably less effective in promoting the lateral metalation under these conditions (Table 4.1, entries 11 and 12), anyway the possibility to perform the LL also with less basic alkyllithiums clearly indicates how mesomeric effects are crucial to stabilize ***Bn*-Li-1a** also under these protic thermodynamic conditions, as well as under classical kinetic conditions.

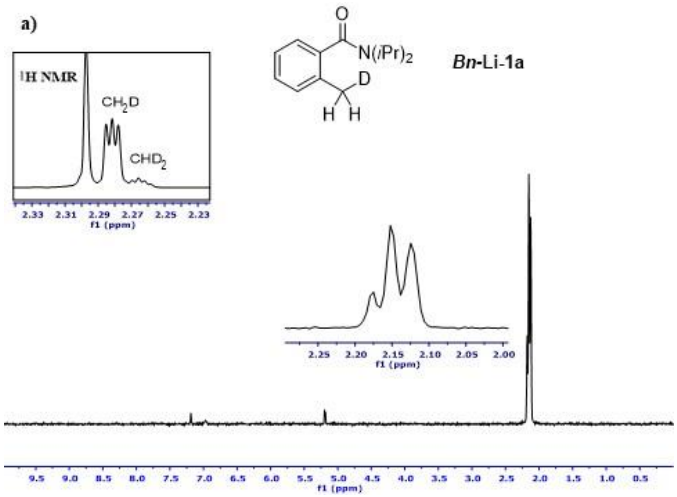
Table 4.1. Metalation reaction of **1a** under different conditions.[a]



Entry	DES	RLi (eq.)	E^{+} (eq.)	**2a** (yield %)[b]	**2a'** (yield %)[b]
1	ChCl/Gly 1:2	*t*-Bu (2)	MeI (5)	**2a** (62)	**2a'** (6)
2	ChCl/Gly 1:2[c]	*t*-Bu (2)	MeI (5)	**-**	**-**
3	ChCl/Gly 1:2[d]	*t*-Bu (2)	MeI (5)	**2a** (52)	**2a'** (9)
4	ChCl/urea 1:2	*t*-Bu (2)	MeI (5)	**2a** (59)	**2a'** (7)
5	ChCl/H_2O 1:2	*t*-Bu (2)	MeI (5)	-	-
6	ChCl/Gly 1:2	*t*-Bu (2)	MeI (2)	**2a** (44)	**2a'** (5)
7	ChCl/Gly 1:2	*t*-Bu (2)	MeI (3)	**2a** (41)	**2a'** (6)
8	ChCl/Gly 1:2	*t*-Bu (1)	MeI (5)	**2a** (50)	-
9	ChCl/Gly 1:2	*t*-Bu (1.2)	MeI (5)	**2a** (58)	-
10	ChCl/Gly 1:2	*t*-Bu (1.5)	MeI (5)	**2a** (70)	**2a'** (2)
11	ChCl/Gly 1:2	*n*-Bu (1.5)	MeI (5)	**2a** (26)	-
12	ChCl/Gly 1:2	*s*-Bu (1.5)	MeI (5)	**2a** (38)	-

[a] Reaction conditions: 1.0 g DES per 0.2 mmol of **1a**, CPME (0.2 mL); DES: ChCl/Gly 1:2; ChCl/urea 1:2; ChCl/H_2O 1:2. [b] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [c] No CPME was used. [d] T = 0 °C.

The regioselectivity of the process was evaluated by deuteration of ***Bn*-Li-1a** with CD_3OD as electrophile and ^2H NMR analysis of the reaction crude. Using 1.5 eq. of *t*-BuLi no evidence of *ortho*-incorporation was observed by ^2H NMR and ***Bn*-D-1a** was recovered with 80% yield, after column chromatography, with an excellent 80% of deuterium incorporation on the benzylic position. On the contrary, using a slightly higher amount of base (2 eq.) the regioselectivity for the benzylic position remained unchanged, however with evidence of a bis-benzylic deuterated byproduct as detected from ^1H and ^2H NMR analyses (Figure 4.1). More in details, as shown in Figure 4.1a, the mixture of mono- (CH_2D) and bis- (CHD_2) lateral deuterated **1a** is clearly detectable both in the ^1H NMR spectrum, owing to the presence of a 1:1:1 triplet ($C\underline{H}_2D$ group) close to a 1:2:3:2:1 quintuplet correlated to the $C\underline{H}D_2$ group, and in the ^2H NMR spectrum by the presence of a 1:2:1 triplet ($CH_2\underline{D}$ group) superimposed with the 1:1 doublet associated the $CH\underline{D}_2$ group. On the opposite, using 1.5 eq. of *t*-BuLi, ^1H NMR and ^2H NMR (showed in Figure 4.1b) showed only the clean signals associated to the sole ***Bn*-D-1a**, a 1:1:1 triplet for $C\underline{H}_2D$ group in ^1H NMR and a 1:2:1 triplet for $CH_2\underline{D}$ group in the ^2H NMR.



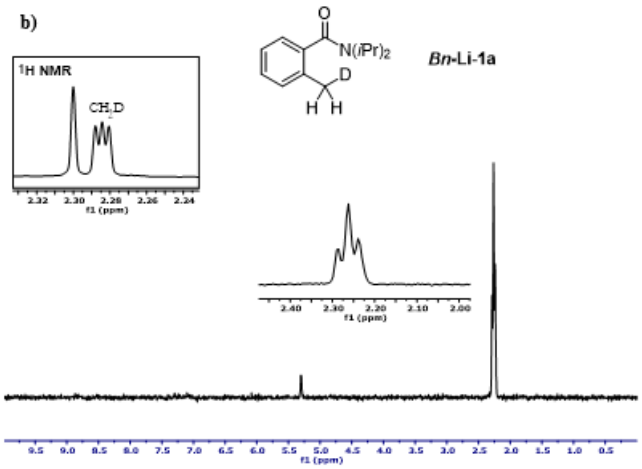
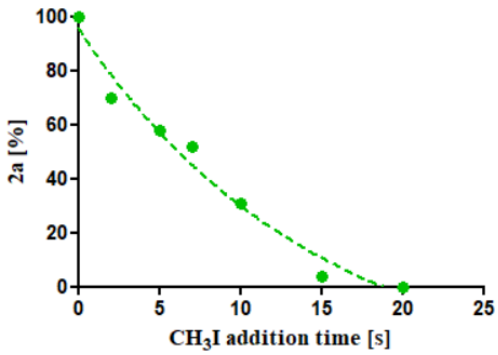


Figure 4.1. ^{2}H NMR spectra of ***Bn*-D-1a** obtained by LL-electrophilic trapping with CD_3OD in CPME/DES with **a)** 2 eq. and **b)** 1.5 eq. of *t*-BuLi. Inset: ^{1}H NMR spectra expansion of benzylic CH_3 region. The corresponding multiplets for the bis-deuterated benzylic species has been observed only using 2 eq. of *t*-BuLi in the ^{1}H NMR, while total regioselectivity for benzylic deuteration is independent from the amount of base used. *: residual CD_2Cl_2 solvent peak.

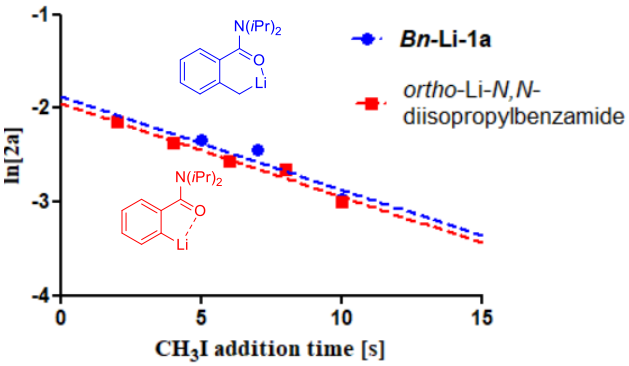
The half-life of ***Bn*-Li-1a** in CPME/ChCl/Gly 1:2 was then evaluated by quenching multiple reaction samples with MeI at different times. The estimated half-life for ***Bn*-Li-1a** from the first-order plot obtained is 6.57 seconds, which is consistent with the previous studied *ortho*-Li-*N,N*-diisopropylbenzamide in the same heterogeneous solvent system (Figure 4.2). As a result, the presence of a stabilizing conjugative effect has no effects on the half-life of the ***Bn*-Li-1a**.

a)



CH_3I addition time (s)	**2a**, yield %
2	70
5	58
7	52
10	31
15	4
20	0

b)



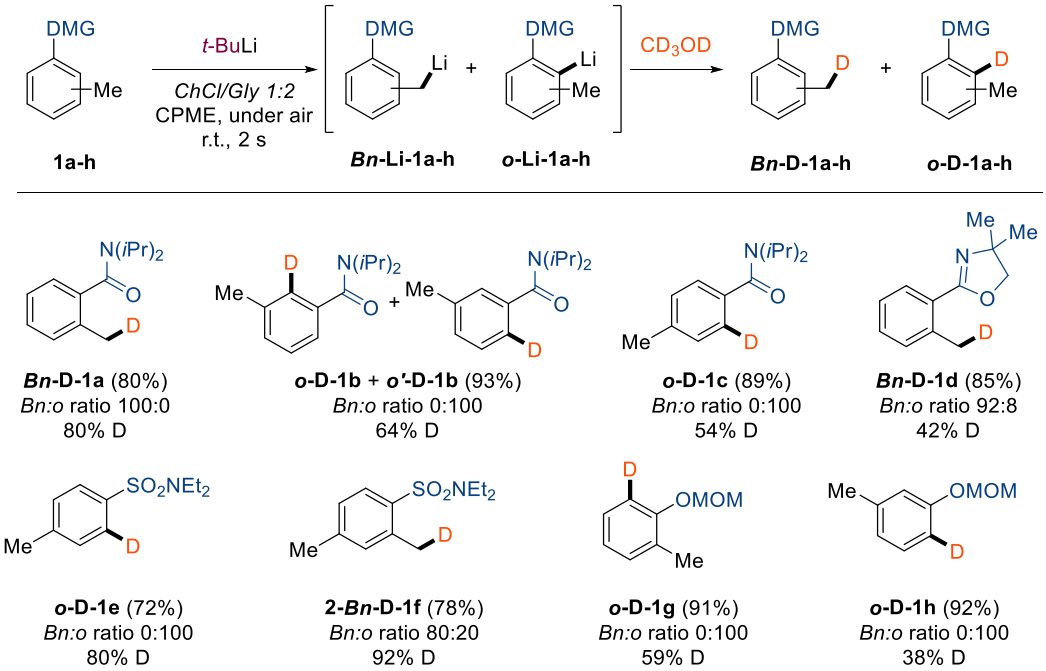
CH_3I addition time (s)	ln [**2a**]
2	-2.15
5	-2.33
7	-2.45
10	-2.96

Figure 4.2. a) Kinetic analysis of lateral metalation of **1a**. **b)** First-order kinetic plot of *o*-Li-*N,N*-diisopropylbenzamide under the same reaction conditions was added for comparison.

4.2 Comparative analysis of different substituted toluenes: role of DMGs

Whit the optimized conditions in hands, we next evaluated the possibility to extend this protocol to other toluenes bearing different DMGs in other to analyze the impact of different DMGs on the regioselectivity of the reaction. The substrates studied were treated with *t*-BuLi (1.5 eq.) in CPME (0.2 mL, 1 M) and ChCl/Gly 1:2 mixture, at room temperature and under air, followed by quenching with CD_3OD after 2 seconds, and subsequently analyzed by ^1H and ^2H NMR (Scheme 4.2 and Figure 4.3). The strongest DMG of the series, namely the tertiary amide group, efficiently promoted the sole *ortho*-lithiation of both *meta*- and *para*-substituted derivatives (Scheme 4.2, ***o*-D-1b** and ***o*-D-1c**). The latter experiments clearly indicated that under these conditions the *meta*-methyl group behaves as onlooker during the metalation event (to the best of our knowledge a regioselective LL of **1b** has been never reported using 'pure' alkyllithium reagents), while the *para*-stabilization by mesomeric effect is less important compared to the *ortho*-directing ability of the amide when an alkyllithium is chosen as base. These results are coherent with those reported for the same reactions run under conventional metalation conditions (see section 1.2.3).[6] On the other hand, the oxazolinyl moiety is a versatile coordinating DMG able to efficiently promote both D*o*M of benzene derivatives and benzylic lithiation of tolyl methyl group (see section 1.2.2).[7] Pleasingly, treatment of the *ortho*-tolyl oxazoline **1d** under the aforementioned optimized conditions gave almost complete regioselective benzylic metalation (Scheme 4.2, ***Bn*-D-1d**) with an overall 42% D incorporation. Tertiary sulfonamides also represent one of the most powerful DMG for D*o*M and LL processes (see

sections 1.2.2 and 1.2.3).[8-10] Under these conditions, lithiation of the *para*-methyl tertiary sulfonamide **1e** afforded the sole *ortho*-lithiation ***o*-D-1e** product, while treatment of the 2,4-dimethyl derivative **1f** gave almost quantitative deuterium incorporation in the benzylic position proximal to the DMG. The weaker DMG of the series, methoxymethoxy (OMOM) DMG, which offers a remarkable regiocontrol of the lithiation reaction under conventional conditions with high selectivity for D*o*M over LL,[11, 12] was finally investigated. Analogously to the results reported under classical Schlenk conditions, full *ortho*-selectivity was observed for the lithiation/deuteration of both *ortho*- (**1g**) and *meta*-(**1h**) OMOM-protected cresols in CPME/DES, indicating that the DMG strength is the predominant parameter operating at room temperature in presence of air, however with a significantly lower deuterium incorporation (up to 59%) (Scheme 4.2, ***o*-D-1g** and ***o*-D-1h**).



Scheme 4.2. Metalation reaction of substituted toluenes **1a-h** (0.2 mmol, 1.0 eq.) using *t*-BuLi (1.7 M in pentane, 0.3 mmol, 1.5 eq.) in CPME (0.2 mL, 1 M) ChCl/Gly 1:2 (1 g), at room temperature, under air, reaction time 2 s. Ratios and deuterium incorporation are based on ^{1}H NMR integration and confirmed with ^{2}H NMR (reported below). Yields in brackets refer to products isolated after flash column chromatography.

Due to the notorious efficiency of lithium amides-promoted regioselective LL of substituted toluenes[13] (see section 1.2.3), all substrates **1a-h** were treated with both LiTMP and LDA as metalating agents under the optimized reaction conditions, and, subsequently, trapped with CD_3OD but with negligible results in term of

conversion and deuterium incorporation. The use of lithium amides as base under our bench conditions will be discussed in detail in the next chapter.

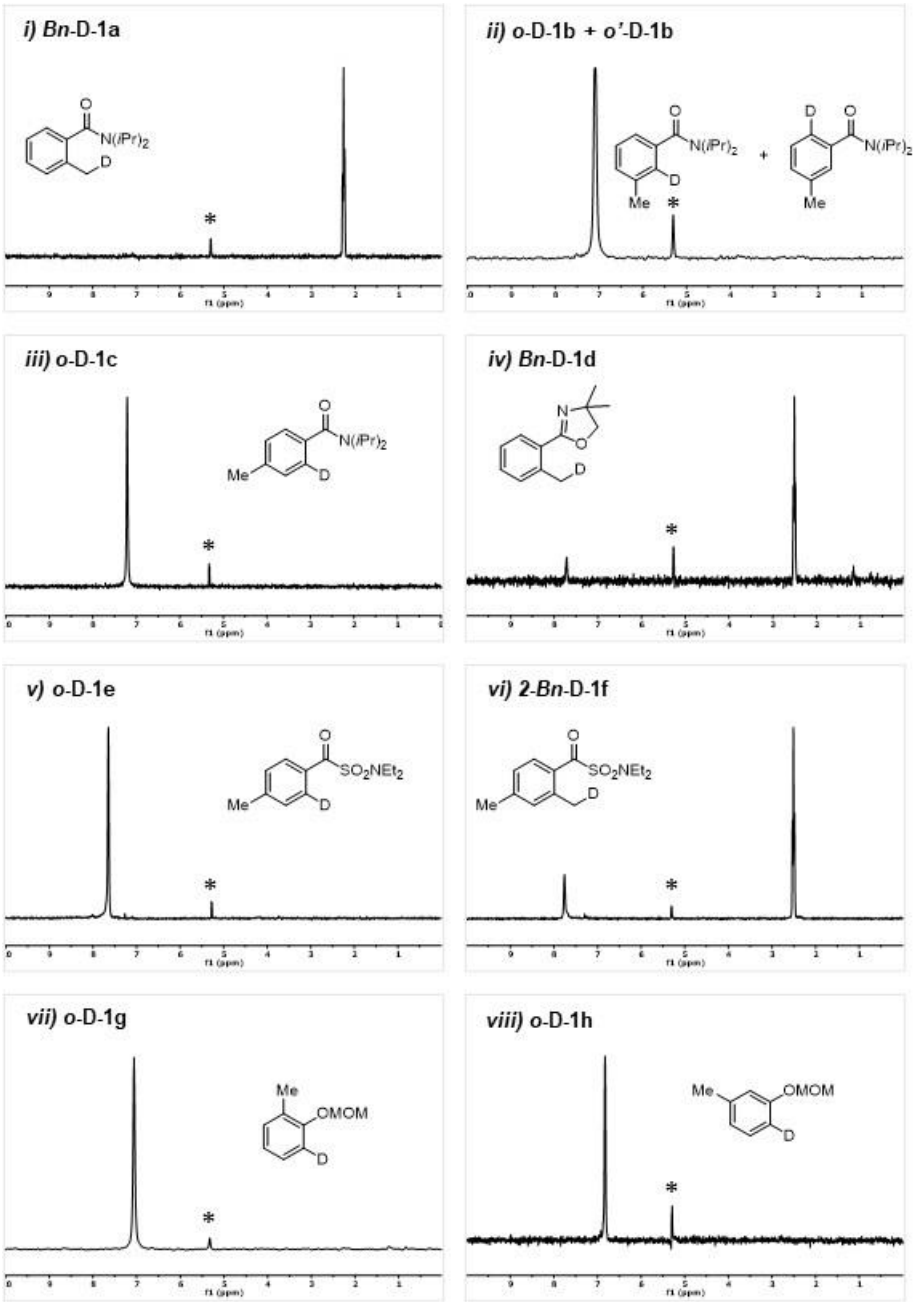


Figure 4.3. ^{2}H NMR spectra of deuteration labelling experiments: lithiation/deuteration of substituted toluenes **1a-h** using *t*-BuLi in CPME/DES at room temperature, under air. *: residual CD_2Cl_2 solvent peak.

4.3 Reaction substrate scope

With the DMGs feasible for LL in hands, and based on our previous results on the electrophilic-trapping of *ortho*-lithiated *N,N*-diisopropylbenzamides (see section 3.2), derivatives of substrates **1a**, **1d** and **1f** were then selected to evaluate the generality of this transformation (Scheme 4.3). Carbonyl electrophiles such as aldehydes and imines reacted smoothly with anion ***Bn*-Li-1a**, thereby providing the expected lateral functionalized adducts **2b** and **2c** in good yields (66% and 53% respectively). The benzylic anion ***Bn*-Li-1a** promoted the regioselective ring opening of 1,2-propylene oxide affording the corresponding homologation adduct **2d** in 56% yield. Acylation of ***Bn*-Li-1a** successfully proceeded using CO_2 and the aromatic Weinreb amide (*N*-methoxy-*N*-methylbenzamide) as electrophiles, affording the corresponding substituted phenylacetic acid **2e** and ketone **2g** in 50% and 59% yield respectively. The same ketone **2g** was also prepared using ethyl benzoate as electrophilic platform but with lower yield indicating the strong acylating power of Weinreb amides compared to esters analogues.[14] The quenching reaction of ***Bn*-Li-1a** with less electrophilic and base sensitive functional groups (*e.g.*, isothiocyanates and diphenyl phosphoryl chloride) was less favorable and furnished the corresponding thioamide **2f** and the phosphonate derivative **2h** in lower yields (34% and 26%). Unfortunately, halogenation of ***Bn*-Li-1a** with 1,2-dibromoethane, iodine and hexachloroethane promoted the formation of desired benzylic halide alongside with an important amount of homo-coupling byproduct. On the contrary, DMF and S_2Me_2 reacted strongly with ***Bn*-Li-1a** affording the desired benzylic aldehyde and sulfide respectively but with and important number of byproducts derived from a double benzylic deprotonation.

The directing ability of the tertiary amide group was then exploited for the regioselective lateral lithiation of substituted xylenes **1i-k** (Figure 4.4).

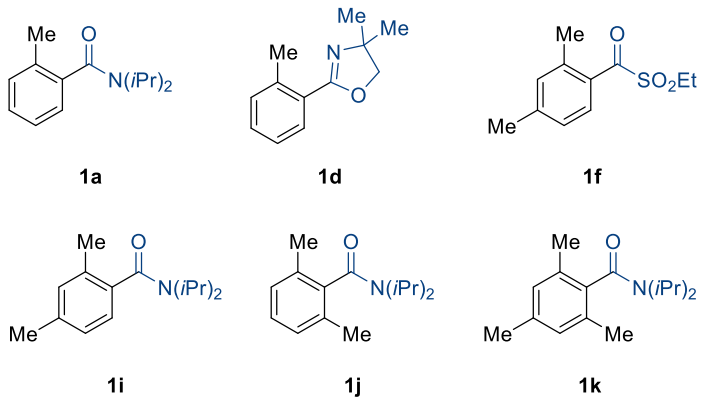
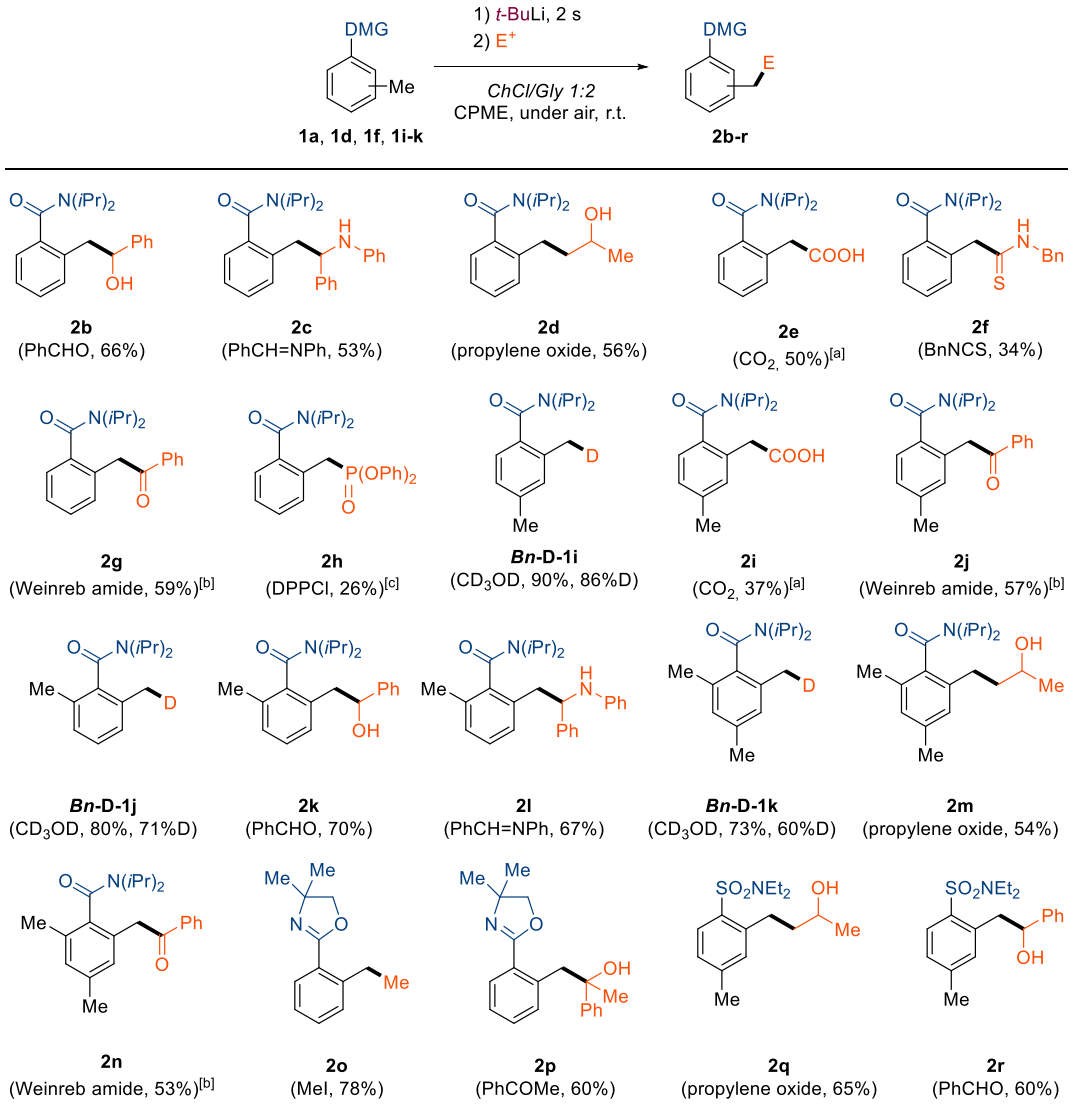


Figure 4.4. *o*-substituted toluenes **1a**, **1d**, **1f**, **1i-k** used for the scope analysis.



Scheme 4.3. Scope of the lateral lithiation reaction of substituted toluenes **1a**, **1d**, **1f**, and **1i-k** in CPME/DES (ChCl/Gly 1:2) mixture. Reaction conditions: **1a**, **1d**, **1f**, **1i-k** (0.2 mmol, 1.0 eq.), *t*-BuLi (1.7 M in pentane, 0.3 mmol, 1.5 eq.), CPME (0.2 mL, 1 M), ChCl/Gly 1:2 (1.0 g), electrophile (1 mmol, 5 eq. unless otherwise stated). The yields reported are for products isolated after flash column chromatography on silica gel. [a] CO_2 was bubbled for 15 seconds. [b] Weinreb amide. *N*-methoxy-*N*-methylbenzamide. [c] DPPCl: diphenyl phosphoryl chloride.

Deuterium labelling experiments (metalation followed by deuteration of ***Bn*-Li-1i-k** and ^{2}H NMR analysis) showed high benzylic selectivity with no detectable deuterium incorporation at the *para*-position for 2,4-dimethyl and mesityl derivatives **1i** and **1k**, while notably no bis-deuterated products were observed

upon lithiation of substrates **1k** and **1j**. Hence electrophilic quench of ***Bn*-Li-1i-k** with aldehydes, imines, amides and epoxides provided the corresponding products **2j-n** with good overall yields (53-70%). On the other hand, acylation of ***Bn*-Li-1i** with CO_2 proceeded with lower yield, affording the substituted phenylacetic acid **2i** in 37% yield. The scope of this transformation was also extended to the other previously investigated DMGs, such as *ortho*-tolyl oxazoline **1d** and *ortho,para*-dimethyl sulfonamide **1f**. The lithiation efficiently occurred in the benzylic position proximal to the DMGs moiety and led to the formation of adducts **2o-r** in good yields (60-78%) upon quenching of the corresponding ***Bn*-Li-1d** and ***Bn*-Li-1f** anions with alkylating agents, such as iodomethane and propylene oxide, and carbonyl electrophiles.

4.4 Conclusion

In summary, the directed lateral lithiation on functionalized toluene derivatives has been efficiently led under air, at room temperature, within a reaction time of 2 seconds and using environmentally friendly deep eutectic mixtures in combination with CPME, without competitive protonolysis. The reaction conditions are exceedingly mild, reaction times very fast and work-up straightforward. The most widely used DMGs in *ortho*- and lateral lithiation reactions (tertiary amides, sulfonamides and oxazolines) preserve their relative directing abilities and efficiently promote the LL under these conditions. The scope has been extended to various substrates and electrophiles, thus providing rapid access to functionalized aromatic derivatives suitable for further synthetic transformations. Together with the previously acquired results for the D*o*M metalation (see Chapter 3), this work constitutes another fundamental step for the development of new organolithium-promoted C-H functionalizations in protic reaction media. Further analyses will be focused on a generalization of this protocol in order to deepen the knowledge on the mechanistic aspects involved in these fascinating transformations.

4.5 Experimental section

4.5.1 General informations

Materials and methods. Unless specified, all reagents were used as received without further purifications. Ethyl benzoate and benzaldehyde were distilled under vacuum prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Chromatographic separations were carried out under pressure on silica gel (40-63 µm, 230-400 mesh) using flash-column techniques. The

following solutions of organolithium reagents were furnished by Sigma-Aldrich and used with the following concentration: *n*-BuLi 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane. The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[15] *N,N*-diisopropylbenzamides **1a-c**[16-18] and **1i-k**,[19, 20] oxazoline **1d**,[21] *N,N*-diethylbenzenesulfonamides **1e-f**,[22, 23] and OMOM-substituted toluenes **1g-h**[24, 25] were synthesized according to the procedures reported in the literature. Deep Eutectic Solvents (ChCl/urea 1:2; ChCl/Gly 1:2, ChCl/H_2O 1:2) were prepared by heating under stirring at 60-80 °C for 10-30 min the corresponding individual components until a clear solution was obtained.[26] Full characterization data have been reported for both the newly synthesized compounds and the known compounds.

Instrumentation. ^{1}H NMR (600 MHz) and ^{13}C{^{1}H} (150 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. ^{2}H NMR (92.07 MHz) spectra were obtained in DCM using residual CD_2Cl_2 as an internal reference. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad). Low-resolution MS spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI). GC analyses were performed on a PerkinElmer Autosystem XL chromatographic system equipped with a methyl silicone capillary column. The MS flow-injection analyses were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an a ESI ion source. The samples were analyzed in acetonitrile solution using a syringe pump at a flow rate of 5 μL/min. The tuning parameters adopted for the ESI source were: source voltage 4.0 kV. The heated capillary temperature was maintained at 275 °C. The mass accuracy of the recorded ions (vs. the calculated ones) was ± 2.5 mmu (milli-mass units). Analyses were run using both full MS (150-2000 m/z range) and MS/MS acquisition, at 500000 resolutions (200 m/z).

Nitromethane was used as internal standard for quantitative NMR analyses on crude reaction mixtures.

For each ^{1}H NMR the amount of product was determined by applying the following equation (Eq. 1):

$$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)}\ \cdot\ f\ \cdot\ 100$$

where:

- *x* is the value of integral/number of protons;
- *n* is the amount of starting material or CH_3NO_2 in mmol;
- *f* the diluting factor used for the preparation of the sample.

*4.5.2 Synthesis of N,N-diisopropylcarboxamides **1a-c, 1i-k**: general procedure*

The appropriate carboxylic acid (10.0-50.0 mmol, 1.0 eq.) was dissolved in thionyl chloride (10 eq.) and the solution was heated at reflux (80 °C) overnight. The solution was cooled to room temperature and the excess of thionyl chloride was removed under vacuum. The resulting acyl chloride was dissolved in dichloromethane (10-40 mL) then triethylamine (1.5 eq.) and diisopropylamine (1.2 eq.) were sequentially added dropwise at 0 °C. The mixture was warmed at room temperature and stirred until the reaction was completed (TLC, 4-5 hours). The mixture was washed with 1 M aq. HCl (2 x 10-30 mL), then with an aqueous saturated solution of Na_2CO_3 (2 x 10-30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure to give the corresponding amides **1a-c**, **1i-k** that were purified by flash column chromatography and/or by recrystallization.

*4.5.3 Synthesis of 4,4-dimethyl-2-(o-tolyl)-4,5-dihydrooxazole **1d***

2-Methyl-2-amino-1-propanol (20 mmol, 2.0 eq., 1.8 g) was added to benzoyl chloride (10 mmol, 1.0 eq., 1.16 mL) in dichloromethane (20 mL, 0.5 M) at 0 °C and the mixture was stirred at room temperature for 18 h. The mixture was filtered to remove the ammonium salt, washed with dichloromethane (10 ml) and then cooled to 0 °C. Thionyl chloride (30 mmol, 3.0 eq., 2.18 mL) was added dropwise and the mixture was warmed at room temperature and stirred for 3 hours. Water and 40% aq. NaOH were added slowly until the solution reached pH 11 and the organic layer was separated, washed with saturated ammonium chloride solution (2 x 10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash chromatography to give the oxazoline **1d**.

*4.5.4 Synthesis of N,N-diethylsulfonamides **1e, f**: general procedure*

To a solution of the appropriate benzoyl sulfonyl chloride (10 mmol, 1.0 eq.) in DCM (20 mL, 0.5 M) at 0 °C, diethylamine (13 mmol, 1.3 eq., 1.24 mL) and triethylamine (30 mmol, 3.0 eq., 4.2 mL) were sequentially slowly added. The reaction mixture was stirred for 1 h at room temperature, then diluted with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude solid was purified by flash chromatography to give the corresponding sulfonamides **1e, 1f**.

*4.5.5 Synthesis of OMOM protected cresols **1g, h**: general procedure*

In a Schlenk tube under nitrogen, to the appropriate phenol (10 mmol, 1.0 eq.) in anhydrous DMF (20 mL, 0.5 M), sodium hydride (13 mmol, 1.3 eq., 312 mg) and bromomethyl methyl ether (12 mmol, 1.2 eq., 0.98 mL) were slowly sequentially added at 0 °C. The mixture was warmed at room temperature and reacted for 2 h, then cooled again to 0 °C and quenched with water. The mixture was extracted with DEE (3 × 30 mL). The

combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was purified by flash chromatography to give the corresponding OMOM-protected cresols **1g, 1h**.

*4.5.6. Deuteration labelling experiments of substituted toluenes **1a**-**h**: synthesis and analysis*

Reactions were performed under air at room temperature. In an open screw cap vial, substrates **1a-h** (0.2 mmol, 1 eq.) were dissolved in CPME (0.2 mL, 1 M), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.3 mmol, 1.5 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of CD_3OD (1 mmol, 5 eq.) after 2 seconds. The mixture was diluted with water (5 mL) and extracted with DEE (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

2-(Deuteriomethyl)-*N,N*-diisopropylbenzamide (*Bn*-D-1a): general procedure starting from **1a**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave ***Bn*-D-1a** (80% D incorporation) as a white solid (35 mg, 80%, R_f = 0.16 PE/EtOAc 9/1 v/v), mp 98.6-99.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (td, *J* = 7.4, 1.5 Hz, 1H), 7.20-7.14 (m, 2H), 7.08 (dd, *J* = 7.7, 1.4 Hz, 1H), 3.66 (sept, *J* = 6.7 Hz, 1H), 3.51 (sept, *J* = 6.9 Hz, 1H), 2.30 (m, 2H), 1.57 (dd, *J* = 6.6, 1.6 Hz, 6H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.8, 138.7, 133.7, 130.5, 128.2, 125.9, 124.8, 50.9, 45.9, 21.0, 20.9, 20.8, 20.7, 18.6 (t, *J* = 19.5 Hz, 1C). ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 2.28 (t, *J* = 2.4 Hz). EI-MS *m/z* (%): 220 (M^+, 12), 120 (100), 119 (43), 92 (27). ESI-HRMS $[M+Na]^+$: *m/z* 243.1572, $C_{14}H_{20}DNONa^+$ requires 243.1578.

2-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (*o*-D-1b) and **6-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (*o'*-D-1b)**: general procedure starting from **1b**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave an inseparable mixture of ***o*-D-1b** (30% D incorporation) and ***o'*-D-1b** (34% D incorporation) as a white solid (41 mg, 93%, R_f = 0.20 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26-7.23 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H, 30%D), 7.08 (d, *J* = 7.6 Hz, 1H, 34%D), 3.95-3.38 (br m, 2H), 2.35 (s, 3H), 1.77-0.94 (br m, 12H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 171.3, 139.1, 139.0, 138.4, 138.3, 129.4, 128.4, 128.3, 126.4, 122.3 (t, *J* = 23.8 Hz, 1C), 50.9, 45.9, 21.5, 21.5, 20.8. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.11 (s). EI-MS *m/z* (%): 220 (M^+, 17), 176 (24), 177 (22), 120 (86), 119 (100), 91 (27).

2-Deuterio-*N,N*-diisopropyl-4-methylbenzamide (*o*-D-1c): general procedure starting from **1c**. Purification by flash column chromatography (PE/EtOAc 85/15 v/v) gave ***o*-D-1c** (54% D incorporation) as a white solid (39 mg, 89%, R_f = 0.38 PE/EtOAc 85/15 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22-7.19 (m, 2H), 7.19-7.16 (m, 2H), 4.10-3.31 (m, 2H),

2.36 (s, 3H), 1.67-0.95 (m, 12H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.4, 138.6, 136.2, 136.1, 129.1, 129.0, 125.8, 125.5 (t, *J* = 24.3 Hz, 1C), 50.9, 45.9, 21.4, 20.9. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.19 (s). EI-MS *m/z* (%): 220 (M^+, 14), 219 (17), 177 (21), 176 (23), 120 (90), 119 (100), 92 (17), 91 (20).[6]

2-(Deuteriomethyl)-4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (*Bn*-D-1d): General procedure starting from **1d**. Purification by flash column chromatography (9/1 PE/EtOAc v/v) gave ***Bn*-D-1d** (42% D incorporation) as yellow oil (32.3 mg, 85%, R_f = 0.45 9/1 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 7.6, 1.4 Hz, 1H), 7.22-7.19 (m, 2H), 4.07 (s, 2H), 2.56-2.54 (m, 2H), 1.39 (s, 6H).$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 162.9, 138.6, 131.2, 130.5, 129.9, 127.8, 125.6, 78.8, 67.9, 28.6, 21.2 (t, *J* = 19.5 Hz, 1C). ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 2.55 (t, *J* = 2.3 Hz). EI-MS *m/z* (%): 190 (M^+, 51), 189 (100), 174 (78), 158 (25), 146 (38), 118 (65). ESI-HRMS $[M+Na]^+$: *m/z* 213.1105, $C_{12}H_{14}DNONa^+$ requires 213.1109.

2-Deuterio-*N,N*-diethyl-4-methylbenzenesulfonamide (*o*-D-1e): general procedure starting from **1e**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave ***o*-D-1e** (80% D incorporation) as a white solid (33 mg, 72%, R_f= 0.23 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70-7.66 (m, 1H), 7.30-7.24 (m, 2H), 3.21 (q, *J* = 7.2 Hz, 4H), 2.40 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 143.0, 137.5, 137.4, 129.7, 129.6, 126.9 (t, *J* = 25.3 Hz, 1C), 42.1, 21.6, 14.2. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.69 (s). EI-MS *m/z* (%): 228 (M^+, 14), 213 (100), 212 (47), 156 (90), 92 (81).[23]

2-(Deuteriomethyl)-*N,N*-diethyl-4-methylbenzenesulfonamide (2-*Bn*-D-1f): general procedure starting from **1f**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2-*Bn*-D-1f** (92% D incorporation, 4:1 mixture of **2-*Bn*-D-1f** and ***o*-D-1f**) as a colourless oil (38 mg, 78%, R_f= 0.32 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.10-7.04 (m, 2H), 3.28 (q, *J* = 7.1 Hz, 4H), 2.53-2.51 (m, 2H), 2.35 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 143.1, 137.6, 135.6, 133.4, 129.9, 126.6, 40.7, 21.3, 20.0 (t, *J* = 19.7 Hz, 1C), 13.7. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 2.53 (t, *J* = 2.3 Hz). EI-MS *m/z* (%): 242 (M^+, 24), 227 (73), 170 (78), 106 (100), 105 (40). ESI-HRMS $[M+Na]^+$: *m/z* 265.1086, $C_{12}H_{18}DNO_2SNa^+$ requires 265.1091.

6-Deuterio-1-(methoxymethoxy)-2-methylbenzene (*o*-D-1g): general procedure starting from **1g**. Purification by flash column chromatography (PE/EtOAc 95/5 v/v) gave ***o*-D-1g** (59% D incorporation) as a colourless oil (28 mg, 91%, R_f = 0.54 PE/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18-7.14 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 5.22 (s, 2H), 3.51 (s, 3H), 2.28 (s, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 155.5, 155.5, 130.9, 127.5, 127.0, 126.9, 121.7, 121.7, 114.0, 113.7 (t, *J* = 24.4 Hz, 1C), 94.6, 56.1, 16.4. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.03 (s). EI-MS *m/z* (%): 153 (M^+, 34), 152 (20), 123 (11), 122 (12), 92 (14), 91 (10), 45 (100).[27]

6-Deuterio-1-(methoxymethoxy)-3-methylbenzene (*o*-D-1h): general procedure starting from **1h**. Purification by flash column chromatography (PE/EtOAc 95/5 v/v) gave ***o*-D-1h** (38% D incorporation) as a colourless oil (28 mg, 92%, R_f = 0.58 PE/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19-7.16 (m, 1H), 6.87 (s, 1H), 6.86-6.92 (m, 2H), 5.17 (s, 2H), 3.48 (s, 3H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 157.4, 139.7, 129.4, 129.3, 122.9, 117.1, 113.4, 113.1 (t, *J* = 24.6 Hz, 1C), 94.5, 56.1, 26.4. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 6.84 (s). EI-MS *m/z* (%): 153 (M^+, 32), 152 (40), 123 (17), 122 (26), 92 (15), 91 (19), 45 (100).[27]

*4.5.7. Lateral-lithiation in DESs: general procedure, synthesis and analysis of compounds **2a-r***

Reactions were performed under air at room temperature. In an open screw cap vial, substituted toluenes **1a**, **1d**, **1f** or **1i-k** (0.2 mmol, 1 eq.) were dissolved in CPME (0.2 mL, 1 M), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. *t*-BuLi (0.3 mmol, 1.5 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of a selected electrophile (1 mmol, 5 eq.) after 2 seconds. The mixture was diluted with water (5 mL) and extracted with DEE (3 x 5 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated under vacuum. The crude products **2** were purified by flash column chromatography on silica gel.

***N,N*-diisopropyl-2-ethylbenzamide (2a):** general procedure starting from **1a** and iodomethane. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2a** as a white solid (30 mg, 64%, R_f = 0.21 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30-7.23 (m, 2H), 7.17 (td, *J* = 7.2, 1.7 Hz, 1H), 7.10-7.08 (dd, *J* = 7.1, 1.2 Hz, 1H), 3.67 (sept, *J* = 6.8 Hz, 1H), 3.50 (sept, *J* = 6.8 Hz, 1H), 2.65 (m, 2H), 1.57 (d, *J* = 6.8 Hz , 6H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 170.8, 140.0, 138.1, 128.7, 128.4, 125.8, 124.9, 50.8, 45.8, 25.8, 20.9, 20.8, 20.8, 20.7, 15.3. EI-MS *m/z* (%): 233 (M^+, 20), 190 (17), 133 (100), 132 (26), 105 (11).[28]

2-(2-hydroxy-2-phenylethyl)-*N,N*-diisopropylbenzamide (2b): general procedure starting from **1a** and benzaldehyde. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2b** as a white semi-solid (43 mg, 66%, R_f = 0.22 PE/EtOAc 8/2 v/v). Minor and major diastereoisomers (d_r = 5:1) were not separated by chromatography. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.52-6.71 (m, 9H, major + 9H, minor), 5.19 (dd, *J* = 6.4, 4.0 Hz, 1H, minor), 4.81 (dd, *J* = 11.0, 3.5 Hz, 1H, major), 4.31 (br s, 1H, major + 1H, minor), 3.81 (sept, *J* = 6.7 Hz, 1H, major), 3.71 (sept, *J* = 6.8 Hz, 1H, minor), 3.56 (m, 1H, major + 1H, minor), 3.11 (dd, *J* = 13.8, 4.0 Hz, 1H, minor), 2.99 (dd, *J* = 13.8, 3.5 Hz, 1H, major), 2.92 (dd, *J* = 13.9, 6.4 Hz, 1H, minor), 2.77 (dd, *J* = 13.8, 11.0 Hz, 1H, major), 1.64 (d, *J* = 6.7 Hz, 3H, major) superimposed to 1.63 (d, *J* = 6.8 Hz, 3H, minor), 1.59 (d, *J* = 6.8 Hz, 3H, major) superimposed to 1.59 (d, *J* = 6.9 Hz, 3H, minor), 1.18 (d, *J*

= 6.7 Hz, 3H, major), 1.13 (d, *J* = 6.6 Hz, 3H, minor), 1.08 (d, *J* = 6.7 Hz, 3H, minor), 1.03 (d, *J* = 6.8 Hz, 3H, major). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 172.2 (major), 171.7 (minor), 146.6, 144.6, 138.5, 138.0, 136.2, 133.9, 131.9, 130.5, 129.4, 128.5, 128.1, 128.0, 127.1, 127.0, 126.6, 126.5, 126.2, 125.7, 124.9, 124.8, 75.7 (major), 72.9 (minor), 51.6 (major), 51.3 (minor), 46.5 (major), 46.2 (minor), 44.3 (major), 43.0 (minor), 21.3 (major), 21.2 (minor), 20.9 (minor), 20.8 (major), 20.6, 20.5. EI-MS *m/z* (%): 325 (M^+, 4), 219 (70), 207 (62), 178 (41), 176 (100), 119 (86).[29]

***N,N*-diisopropyl-2-(2-phenyl-2-(phenylamino)ethyl)benzamide (2c):** general procedure starting from **1a** and *N*-benzylidene aniline. Purification by flash column chromatography (*n*-hexane/EtOAc 9/1 v/v) gave **2c** as a white solid (43 mg, 53%, R_f = 0.24 *n*-hexane/EtOAc 9/1 v/v), mp 168-169 °C (MeOH). Minor and major diastereoisomers (d_r = 8:1) were not separated by chromatography. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.52 (d, *J* = 7.4 Hz, 2H, major), 7.45 (d, *J* = 7.6 Hz, 1H, major), 7.39-7.14 (m, 6H, major + 7H, minor), 7.07-7.02 (m, 4H, minor), 6.97 (t, *J* = 7.8 Hz, 2H, major), 6.60 (t, *J* = 7.3 Hz, 1H, minor), 6.56 (d, *J* = 8.0 Hz, 2H, minor), 6.50 (t, *J* = 7.3 Hz, 1H, major) superimposed to 6.47 (d, *J* = 8.0 Hz, 2H, major), 4.78 (dd, *J* = 6.3, 4.1 Hz, 1H, minor), 4.46 (dd, *J* = 11.4, 3.6 Hz, 1H, major), 3.71-3.61 (m, 1H, major + 1H, minor), 3.54 (sept, *J* = 6.6 Hz, 1H, major + 1H, minor), 3.19 (dd, *J* = 14.0, 4.1 Hz, 1H, minor), 3.08 (dd, *J* = 14.0, 6.2 Hz, 1H, minor), 3.01 (dd, *J* = 13.9, 3.6 Hz, 1H, major), 2.82 (dd, *J* = 13.9, 11.2 Hz, 1H, major), 1.65 (dd, *J* = 6.8, 1.5 Hz, 6H, major), 1.61 (dd, *J* = 9.5, 6.8 Hz, 6H, minor), 1.14-1.09 (m, 3H, major + 6H, minor), 0.99 (d, *J* = 6.7 Hz, 3H, major). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 171.5 (major), 171.4 (minor), 148.0 (major), 145.2 (major), 139.0 (minor), 138.6 (major), 135.4 (minor), 135.2 (major), 133.1 (minor), 133.0 (minor), 131.5 (minor), 129.8 (major), 129.4 (minor), 129.0 (major), 128.9 (minor), 128.9 (major), 128.8 (major), 128.5 (minor), 127.7 (minor), 127.2 (minor), 127.0 (major), 126.8 (minor), 126.8 (major), 126.3 (major), 125.9 (minor), 124.7 (major), 115.9 (major), 115.7 (minor), 113.7 (minor), 113.0 (major), 60.8 (major), 60.5 (minor), 51.2 (major), 51.1 (minor), 46.2 (major), 46.2 (minor), 42.6 (major), 41.3 (minor), 21.1 (minor), 21.0 (major + minor), 20.8 (major), 20.6 (major + minor + minor), 20.5 (major). EI-MS *m/z* (%): 400 (M^+, 7), 182 (100). ESI-HRMS $[M+Na]^+$: *m/z* 423.2412, $C_{27}H_{32}NO_2Na^+$ requires 423.2407.

2-(3-hydroxybutyl)-*N,N*-diisopropylbenzamide (2d): general procedure starting from **1a** and propylene oxide. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2d** as a colourless oil (31 mg, 56%, R_f = 0.15 PE/EtOAc 8/2 v/v). Minor and major diastereoisomers (d_r = 4:1) were not separated by chromatography. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.33-7.25 (m, 2H, major + 2H, minor), 7.21-7.15 (m, 1H, major + 1H, minor), 7.08-7.04 (m, 1H, major + 1H, minor), 3.86-3.80 (m, 1H, minor), 3.71 (sept, *J* = 6.6 Hz, 1H, minor) superimposed to 3.66 (sept, *J* = 6.7 Hz, 1H, major), 3.52 (sept, *J* = 6.8 Hz, 1H, minor) superimposed to 3.51 (sept, *J* = 7.0 Hz, 1H, major), 3.46 (dqd, *J* = 12.6, 6.3, 2.5 Hz, 1H major), 3.27 (br s, 1H, major + 1H, minor), 2.74-2.60 (m, 2H, major + 2H, minor), 1.85-1.67 (m, 2H, major + 2H, minor), 1.60-1.52 (m, 6H, major + 6H,

minor), 1.16-1.06 (m, 9H, major + 9H, minor). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 172.2 (major), 171.5 (minor), 139.0 (minor), 138.4 (major), 137.9 (major), 137.4 (minor), 129.8 (minor), 129.7 (major), 128.7 (major), 128.7 (minor), 126.1 (major), 125.9 (minor), 124.8 (minor), 124.6 (major), 68.3 (minor), 63.7 (major), 51.4 (major), 51.1 (minor), 46.3 (major), 46.0 (minor), 41.0 (minor), 40.8 (major), 29.9 (minor), 28.1 (major), 23.7 (minor), 23.2 (major), 20.9 (minor), 20.8 (major), 20.8 (major), 20.7 (minor), 20.7 (minor), 20.6 (minor), 20.5 (major), 20.4 (major). EI-MS *m/z* (%): 277 (M^+, 5), 159 (54), 135 (55), 133 (39), 131, (100), 86 (72). ESI-HRMS $[M+Na]^+$: *m/z* 300.1936, $C_{17}H_{27}NO_2Na^+$ requires 300.1934.

2-(2-(diisopropylcarbamoyl)phenyl)acetic acid (2e): general procedure starting from **1a** and CO_2 (bubbled for 15 seconds). The crude acid was dissolved in 1 N NaOH (5 mL) and washed with DEE (2 x 5 mL). The aqueous layer was then acidified with 1M hydrochloric acid (6 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts were washed with water (2 x 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **2e** as a white solid (26 mg, 50%, R_f = 0.14 PE/EtOAc 7/3 v/v + HCOOH 1%) mp 147.3-148.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.40 (td, *J* = 7.7, 1.5 Hz, 1H), 7.32 (td, *J* = 7.5, 1.3 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.5 Hz, 1H), 3.95 (sept, *J* = 6.8 Hz, 1H), 3.65-3.52 (m, 3H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 172.5, 171.1, 136.0, 132.2, 131.3, 130.4, 127.5, 125.8, 52.1, 47.2, 41.9, 21.5, 21.0, 20.4, 20.2. ESI-HRMS $[M+Na]^+$: *m/z* 286.1422, $C_{15}H_{21}NNaO_3^+$ requires 286.1414.

2-(2-(Benzylamino)-2-thioxoethyl)-*N,N*-diisopropylbenzamide (2f): General procedure starting from **1a** and benzyl isothiocyanate. Purification by flash column chromatography (95/5 Toluene/EtOAc v/v) gave **2f** as yellow oil (25 mg, 34%, R_f = 0.45 95/5 Toluene/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.51 (br s, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.36 (td, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.28 (td, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.24-7.17 (m, 3H), 7.14 (dd, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.11-7.10 (m, 2H), 4.86 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.72 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.18 (d, *J* = 13.1 Hz, 1H), 3.89 (d, *J* = 13.8 Hz, 1H), 3.80 (sept, *J* = 6.8 Hz, 1H), 3.55 (sept, *J* = 6.8 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 201.2, 171.8, 137.1, 136.8, 133.9, 130.3, 129.5, 128.5, 127.4, 127.3, 127.2, 124.9, 51.7, 50.0, 49.9, 46.5, 21.3, 20.8, 20.5. EI-MS *m/z* (%): 368 (M^+, 60), 335 (3), 291 (12), 268 (16), 234 (20), 176 (28), 91 (100). ESI-HRMS $[M+H]^+$: *m/z* 369.1986, $C_{22}H_{29}N_2OS^+$ requires 369.1995.

***N,N*-diisopropyl-2-(2-oxo-2-phenylethyl)benzamide (2g):** general procedure starting from **1a** and *N*-methoxy-*N*-methylbenzamide. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2g** as a white solid (38 mg, 59%, R_f = 0.14 PE/EtOAc 8/2 v/v), mp 101.2-102.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 8.3, 1.2, 2H), 7.58-7.53 (m, 1H), 7.48-7.43 (m, 2H), 7.32 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29-7.25 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.61 (d, *J* = 17.2 Hz, 1H), 4.25

(d, *J* = 17.2 Hz, 1H), 3.82 (sept, *J* = 6.6 Hz, 1H), 3.41 (sept, *J* = 6.8 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 197.7, 170.4, 138.6, 136.6, 133.4, 131.8, 131.5, 128.8, 128.6 (2C), 126.9, 125.1, 51.1, 45.9, 42.6, 21.0, 20.7, 20.6, 20.5. EI-MS *m/z* (%): 323 (M^+, 35), 322 (50), 223 (86), 195 (99), 105 (100), 86 (47), 77 (52). ESI-HRMS $[M+Na]^+$: *m/z* 346.1783, $C_{21}H_{25}NO_2Na^+$ requires 346.1778.

Diphenyl (2-(diisopropylcarbamoyl)benzyl)phosphonate (2h): general procedure starting from **1a** and diphenyl phosphoryl chloride. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2h** as a white solid (23.5 mg, 26% yield, R_f = 0.08 PE/EtOAc 8/2 v/v), mp 105-107 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 7.8, 2.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.31-7.25 (m, 5H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 3.81 (sept, *J* = 6.6 Hz, 1H), 3.73 (dd, *J* = 20.4, 15.7 Hz, 1H), 3.56 (dd, *J* = 22.8, 15.7 Hz, 1H), 3.48 (sept, *J* = 6.7 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.04 (dd, *J* = 6.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 169.8, 150.4 (d, *J* = 9.7 Hz, 1C), 150.3 (d, *J* = 8.9 Hz, 1C), 131.1 (d, *J* = 5.2 Hz, 1C), 129.9, 129.8, 128.8, 127.7 (d, *J* = 8.5 Hz, 1C), 127.2, 125.7, 125.4, 125.3, 120.9 (d, *J* = 4.0 Hz, 1C), 120.8 (d, *J* = 4.6 Hz, 1C), 51.2, 46.1, 30.1 (d, *J* = 140.6 Hz, 1C), 21.0, 20.9, 20.8, 20.5. ^{31}P NMR (242 MHz, $CDCl_3$): δ 20.60 (t, *J* = 21.8 Hz). ESI-HRMS $[M+Na]^+$: *m/z* 474.1816, $C_{26}H_{30}NO_4PNa^+$ requires 474.1805.

2-(Deuteriomethyl)-*N,N*-diisopropyl-4-methylbenzamide (*Bn*-D-1i): General procedure starting from **1i** and CD_3OD. Purification by flash column chromatography (9/1 PE/EtOAc v/v) gave ***Bn*-D-1i** (86% D incorporation) as white solid (42 mg, 90%, R_f = 0.25 9/1 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.00-6.94 (m, 3H), 3.68 (sept, *J* = 6.7 Hz, 1H), 3.49 (sept, *J* = 6.8 Hz, 1H), 2.31 (s, 3H), 2.27-2.23 (m, 2H), 1.56 (d, *J* = 6.9 Hz, 6H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 171.1, 137.8, 135.9, 133.5, 131.1, 126.5, 124.7, 50.9, 45.8, 21.3, 21.0, 20.9, 20.8, 20.7, 18.6 (t, *J* = 18.9 Hz, 1C). ^{2}H NMR (92.07 MHz, CH_2Cl_2): 2.24 (t, *J* = 2.4 Hz). EI-MS *m/z* (%): 234 (M^+, 13), 218 (12), 191 (13), 134 (100), 133 (41), 233 (10). ESI-HRMS $[M+H]^+$: *m/z* 235.1908, $C_{15}H_{23}DNO^+$ requires 235.1915.

2-(2-(Diisopropylcarbamoyl)-5-methylphenyl)acetic acid (2i): general procedure starting from **1i** and CO_2 (bubbled for 15 seconds). The crude acid was dissolved in 1 N NaOH (5 mL) and washed with DEE (2 x 5 mL). The aqueous layer was then acidified with HCl 1M (6 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts were washed with water (2 x 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **2i** (20.5 mg, 37% yield) as a white semi-solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 13.31 (br s, 1H), 7.27 (br s, 1H), 7.12-7.09 (m, 2H), 3.98 (sept, *J* = 6.7 Hz, 1H), 3.60 (sept, *J* = 6.7 Hz, 1H) superimposed to 3.56 (d, *J* = 12.7 Hz, 1H), 3.53 (d, *J* = 12.7 Hz, 1H), 2.35 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H). EI-MS *m/z* (%): 277 (M^+, 13), 276 (22), 177 (21), 149 (100), 133 (38), 86 (37). $^{13}C\{^{1}H\}$

NMR (150 MHz, $CDCl_3$): δ 172.8, 171.4, 140.7, 133.1, 132.3, 131.9, 128.2, 125.8, 52.1, 47.1, 41.9, 21.5, 21.3, 21.0, 20.5, 20.1. EI-MS *m/z* (%): 277 (M^+, 14), 276 (23), 177 (21), 149 (100), 133 (39), 86 (3). ESI-HRMS $[M+Na]^+$: *m/z* 300.1573, $C_{16}H_{23}NO_3Na^+$ requires 300.1570.

***N,N*-Diisopropyl-4-methyl-2-(2-oxo-2-phenylethyl)benzamide (2j):** general procedure starting from **1i** and *N*-methoxy-*N*-methylbenzamide. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2j** as a white solid (38.5 mg, 57% yield, R_f = 0.26 PE/EtOAc 8/2 v/v), mp 91-93 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.07 (s, 2H), 7.04 (s, 1H), 4.59 (d, *J* = 17.1 Hz, 1H), 4.19 (d, *J* = 17.0 Hz, 1H), 3.84 (sept, *J* = 6.5 Hz, 1H), 3.39 (sept, *J* = 6.7 Hz, 1H), 2.32 (s, 3H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 197.9, 170.7, 138.4, 136.7, 135.9, 133.3, 132.1, 131.7, 128.8, 128.6, 127.6, 125.1, 51.1, 45.8, 42.5, 21.4, 21.0, 20.7, 20.6, 20.5. EI-MS *m/z* (%): 337 (M^+, 37), 336 (52), 237 (100), 236 (47), 209 (96), 194 (43), 133 (26), 105 (92), 86 (41), 77 (53). ESI-HRMS $[M+Na]^+$: *m/z* 360.1939, $C_{22}H_{27}NO_2Na^+$ requires 360.1934.

6-(Deuteriomethyl)-*N,N*-diisopropyl-2-methylbenzamide (*Bn*-D-1j): General procedure starting from **1j** and CD_3OD. Purification by flash column chromatography (9/1 PE/EtOAc v/v) gave ***Bn*-D-1j** (71% D incorporation) as white solid (37.6 mg, 80%, R*f* = 0.35 9/1 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 3.61 (sept, *J* = 6.7 Hz, 1H), 3.51 (sept, *J* = 6.8 Hz, 1H), 2.30-2.24 (m, 5H) 1.60 (d, *J* = 6.9 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 6H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.3, 138.2, 133.4, 133.4, 127.6, 127.6, 50.9, 46.0, 21.2, 20.7, 18.85 (*t*, *J* = 19.1 Hz, 1C). ^{2}H NMR (92.07 MHz, CH_2Cl_2): 2.22 (t, *J* = 2.3 Hz). EI-MS *m/z* (%): 234 (M^+, 4), 218 (27), 191 (10), 134 (100), 133 (75). ESI-HRMS $[M+Na]^+$: *m/z* 257.1736, $C_{15}H_{22}DNONa^+$ requires 257.1735.

2-(2-Hydroxy-2-phenylethyl)-*N,N*-diisopropyl-6-methylbenzamide (2k): General procedure starting from **1j** and benzaldehyde. Purification by flash column chromatography (85/15 PE/EtOAc v/v) gave **2k** as colourless semi-solid (48 mg, 70%, R_f = 0.33 85/15 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 6.9 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.29-7.21 (m, 3H), 7.10 (d, *J* = 7.6 Hz, 1H), 4.76 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.65-3.54 (m, 3H), 2.96 (dd, *J* = 13.8, 3.4 Hz, 1H), 2.72 (dd, *J* = 13.8, 10.5 Hz, 1H), 2.33 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.2 Hz, 3H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 172.3, 146.4, 137.8, 135.3, 133.2, 128.9, 128.5, 128.5, 127.4, 127.1, 125.7, 76.1, 51.5, 46.6, 44.5, 21.5, 20.7, 20.5, 19.3. EI-MS *m/z* (%): 339 (M^+, 2), 233 (61), 218 (100), 190 (46), 133 (75). ESI-HRMS $[M+Na]^+$: *m/z* 362.2094, $C_{22}H_{29}NO_2Na^+$ requires 362.2091.

***N,N*-diisopropyl-2-methyl-6-(2-phenyl-2-(phenylamino)ethyl)benzamide (2l)**: General procedure starting from **1j** and *N*-benzylidene aniline. Purification by flash column chromatography (9/1 PE/EE v/v) gave **2l** as white semi-solid (55.5 mg, 67%, R_f = 0.25 9/1

PE/EE v/v). The two diastereoisomers (d_r = 1:1) were not separated by chromatography. ^{1}H NMR (600 MHz, $CDCl_3$, mixture of diastereoisomers): δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30-7.16 (m, 8H), 7.06-7.00 (m, 4H), 6.97-6.93 (m, 3H), 6.57-6.45 (m, 6H), 6.31-6.30 (m, 1H), 4.75-4.73 (m, 1H), 4.40-4.38 (m, 1H), 3.61-3.49 (m, 4H), 3.19 (dd, *J* = 13.9, 3.5 Hz, 1H), 3.03-2.95 (m, 2H), 2.82-2.82 (m, 1H), 2.34 (s, 3H) superimposed to 2.44 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H) superimposed to 1.67 (d, *J* = 6.8 Hz, 3H) superimposed to 1.64 (d, *J* = 6.8 Hz, 3H) superimposed to 1.63 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.7 Hz, 3H) superimposed to 1.13 (d, *J* = 6.7 Hz, 3H) 1.08 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, mixture of diastereoisomers): δ 171.4, 171.1, 148.4, 145.4, 138.5, 138.3, 134.8, 133.4, 133.3, 132.5, 128.9, 128.8, 128.7, 128.7, 128.5, 128.5, 128.4, 127.2, 127.0, 126.9, 126.3, 116.7, 115.8, 113.7, 113.0, 61.1, 58.6, 51.2, 51.1, 46.3, 46.3, 42.9, 41.4, 21.3, 21.2, 21.1, 21.0, 20.8, 20.6, 20.5, 19.3, 19.3. EI-MS *m/z* (%): 414 (M^+, 5), 298 (23), 233 (15), 190 (10), 182 (100). ESI-HRMS $[M+Na]^+$: *m/z* 437.2561, $C_{28}H_{34}N_2ONa^+$ requires 437.2563.

2-(Deuteriomethyl)-*N,N*-diisopropyl-4,6-dimethylbenzamide (*Bn*-D-1k): general procedure starting from **1k** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave ***Bn*-D-1k** (60% D incorporation) as a white solid (36 mg, 73%, R_f = 0.38 PE/EtOAc 8/2 v/v), mp 115.3-116.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (s, 2H), 3.63 (sept, *J* = 6.6 Hz, 1H), 3.49 (sept, *J* = 6.8 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.23-2.21 (m, 2H), 1.59 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.7, 137.2, 135.6, 133.3, 133.3, 128.3 (2C), 50.9, 45.9, 21.2, 21.2, 20.7, 19.0, 18.8 (t, *J* = 19.5 Hz). ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 2.20 (t, *J* = 2.3 Hz). EI-MS *m/z* (%): 248 (M^+, 3), 233 (23), 232 (27), 148 (100), 147 (49). ESI-HRMS $[M+Na]^+$: *m/z* 271.1893, $C_{16}H_{24}DNONa^+$ requires 271.1891.

2-(3-Hydroxybutyl)-*N,N*-diisopropyl-4,6-dimethylbenzamide (2m): general procedure starting from **1k** and propylene oxide. Purification by flash column chromatography (PE/EtOAc 7/3 v/v) gave **2m** as a colourless oil (33 mg, 54% yield, R_f = 0.36 PE/EtOAc 7/3 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.84 (s, 1H), 3.60 (sept, *J* = 6.6 Hz,, 1H), 3.52 (sept, *J* = 6.8 Hz, 1H), 3.45-3.39 (m, 1H), 2.61 (dd, *J* = 8.0, 4.7 Hz, 2H), 2.29 (s, 3H), 2.23 (s, 3H), 1.74-1.65 (m, 2H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 172.4, 137.8, 137.4, 135.4, 132.9, 128.7, 127.3, 63.5, 51.4, 46.4, 41.0, 28.4, 23.3, 21.4, 21.0, 21.0, 20.8, 20.4, 19.1. EI-MS *m/z* (%): 305 (M^+, 2), 290 (37), 288 (27), 272 (38), 232 (38), 205 (24), 187 (29), 186 (35), 163 (56), 161 (54), 159 (100), 145 (29), 119 (65), 84 (58), 43 (35). ESI-HRMS $[M+Na]^+$: *m/z* 328.2251, $C_{19}H_{31}NO_2Na^+$ requires 328.2247.

***N,N*-diisopropyl-2,4-dimethyl-6-(2-oxo-2-phenylethyl)benzamide (2n):** general procedure starting from **1k** and *N*-methoxy-*N*-methylbenzamide. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2n** as a white solid (37 mg, 53%, R_f = 0.25 PE/EtOAc 8/2 v/v), mp 147.6-148.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08-8.04 (m,

2H), 7.55-7.50 (m, 1H), 7.47-7.41 (m, 2H), 6.90 (s, 1H), 6.83 (s, 1H), 4.41 (d, *J* = 16.2 Hz, 1H), 4.03 (d, *J* = 16.2 Hz, 1H), 3.67 (sept, *J* = 6.7 Hz, 1H), 3.47 (sept, *J* = 6.9 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H). 0.98 (d, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 197.9, 170.3, 137.6, 136.4, 135.4, 133.7, 133.3, 130.2, 129.8, 128.9, 128.8, 128.2, 51.0, 46.1, 42.7, 21.4, 21.3, 21.1, 20.8, 20.4, 19.3. EI-MS *m/z* (%): 351 (M^+, 3), 336 (100), 251 (58), 223 (45), 105 (63). ESI-HRMS $[M+Na]^+$: *m/z* 374.2078, $C_{23}H_{29}NO_2Na^+$ requires 374.2091.

2-(2-Ethylphenyl)-4,4-dimethyl-4,5-dihydrooxazole (2o): General procedure starting from **1d** and iodomethane. Purification by flash column chromatography (96/4 PE/EtOAc v/v) gave **2o** as colourless oil (32 mg, 78%, R_f = 0.33 96/4 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 4.09 (s, 2H), 2.96 (q, *J* = 7.5 Hz, 2H), 1.40 (s, 6H), 1.21 (t, *J* = 7.4 Hz, 3H).$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 163.2, 144.6, 130.8, 130.2, 129.6, 127.3, 125.7, 79.0, 67.8, 28.5, 27.4, 15.8. EI-MS *m/z* (%): 203 (M^+, 100), 188 (30), 160 (19), 148 (95), 132 (35), 117 (45), 104 (21).[30]

1-(2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl)-2-phenylpropan-2-ol (2p): General procedure starting from **1d** and acetophenone. Purification by flash column chromatography (9/1 PE/EtOAc v/v) gave **2p** as colourless oil (37 mg, 60%, R_f = 0.30 9/1 PE/EtOAc v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.77-7.73 (m, 1H), 7.56-7.52 (m, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28-7.23 (m, 3H), 6.87-6.85 (m, 1H), 4.16 (d, *J* = 8.3 Hz, 1H), 4.13 (d, *J* = 8.3 Hz, 1H), 3.39 (d, *J* = 13.4 Hz, 1H), 3.33 (d, *J* = 13.4 Hz, 1H), 1.64 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H) .$^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 163.5, 149.8, 138.8, 132.9, 130.3, 129.6, 127.9, 126.3, 126.2, 125.3, 79.3, 74.8, 68.1, 47.8, 29.9, 28.7, 28.7. EI-MS *m/z* (%): 309 (M^+, 1), 276 (5), 189 (100), 174 (41). ESI-HRMS $[M+H]^+$: *m/z* 310.1805, $C_{20}H_{24}NO_2^+$ requires 310.1802.

***N,N*-Diethyl-2-(3-hydroxybutyl)-4-methylbenzenesulfonamide (2q):** general procedure starting from **1f** and propylene oxide. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2q** as a colourless semi-solid (39 mg, 65% yield, R_f = 0.10 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.16 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 3.83-3.77 (m, 1H), 3.30 (q, *J* = 7.2 Hz, 2H) superimposed to 3.29 (q, *J* = 7.1 Hz, 2H), 3.08-2.96 (m, 2H), 2.37 (s, 3H), 2.13 (br s, 1H), 1.88-1.75 (m, 2H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 143.3, 142.0, 135.6, 132.7, 129.7, 126.8, 67.1, 41.2, 41.1, 28.8, 23.6, 21.4, 13.9. EI-MS *m/z* (%): 299 (M^+, 8), 284 (15), 254 (27), 209 (22), 185 (25), 129 (27), 119 (30), 117 (33), 115 (26), 105 (31), 91 (36), 74 (47), 73 (37), 72 (60), 58 (100). ESI-HRMS $[M+Na]^+$: *m/z* 322.1451, $C_{15}H_{22}NO_3SNa^+$ requires 322.1447.

***N,N*-Diethyl-2-(2-hydroxy-2-phenylethyl)-4-methylbenzenesulfonamide (2r):** general procedure starting from **1f** and benzaldehyde. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2r** as a colourless semi-solid (29 mg, 60% yield,

R_f = 0.13 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.16 (s, 2H), 7.14 (s, 1H), 5.01 (dd, *J* = 8.3, 5.1 Hz 1H), 3.35-3.27 (m, 6H), 2.37 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 145.0, 143.3, 138.0, 136.2, 134.0, 129.3, 128.5, 127.5, 127.5, 125.8, 75.1, 43.1, 41.4, 21.4, 13.9. ESI-HRMS $[M+Na]^+$: *m/z* 370.1453, $C_{19}H_{25}NO_3SNa^+$ requires 370.1447.

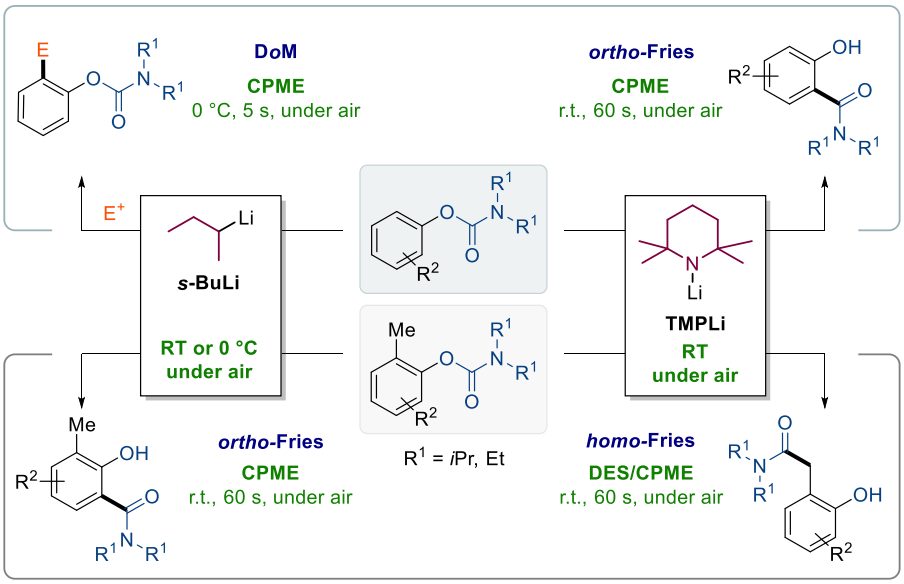
References

1. R. E. Ludt, J. S. Griffiths, K. N. McGrath and C. Hauser, *J. Org. Chem.*, 1973, **38**, 1668-1674.
2. P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2607-2616.
3. D. J. Hlasta and J. J. Court, *Tetrahedron Lett.*, 1989, **30**, 1773-1776.
4. M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R. Billedeau and V. Snieckus, *J. Org. Chem.*, 1984, **49**, 742-747.
5. J. Clayden and J. H. Pink, *Tetrahedron Lett.*, 1997, **38**, 2561-2564.
6. P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34-46.
7. H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, 1975, **40**, 2008-2009.
8. H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis and D. Slocum, *Can. J. Chem.*, 1969, **47**, 1543-1546.
9. H. Watanabe and C. R. Hauser, *J. Org. Chem.*, 1968, **33**, 4278-4279.
10. S. L. MacNeil, O. Familoni and V. Snieckus, *J. Org. Chem.*, 2001, **66**, 3662-3670.
11. M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, 1982, **47**, 2101-2108.
12. R. C. Ronald and M. R. Winkle, *Tetrahedron*, 1983, **39**, 2031-2042.
13. J. Clayden, *Organolithiums: selectivity for synthesis*, Elsevier, 2002.
14. R. Senatore, L. Ielo, S. Monticelli, L. Castoldi and V. Pace, *Synthesis*, 2019, **51**, 2792-2808.
15. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879-1880.
16. S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley and M. Uchiyama, *J. Am. Chem. Soc.*, 2007, **129**, 15102-15103.
17. L. Wang and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1083-1085.
18. G. Yang and W. Zhang, *Org. Lett.*, 2012, **14**, 268-271.
19. J. Clayden, P. Johnson and J. H. Pink, *J. Chem. Soc., Perkin Trans. 1*, 2001, 371-375.
20. D. Arnodo, S. Ghinato, S. Nejrotti, M. Blangetti and C. Prandi, *Chem. Commun.*, 2020, **56**, 2391-2394.
21. J. Clayden, C. C. Stimson and M. Keenan, *Chem. Commun.*, 2006, 1393-1394.
22. S. Okumura and Y. Nakao, *Org. Lett.*, 2017, **19**, 584-587.
23. S. L. MacNeil, O. B. Familoni and V. Snieckus, *J. Org. Chem.*, 2001, **66**, 3662-3670.
24. Z. Cai, S. Li, Y. Gao and G. Li, *Adv. Synth. Catal.*, 2018, **360**, 4005-4011.
25. I. De Silvestro, S. L. Drew, G. S. Nichol, F. Duarte and A. L. Lawrence, *Angew. Chem. Int. Ed.*, 2017, **56**, 6813-6817.
26. A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70-71.
27. P. Fleming and D. F. O'Shea, *J. Am. Chem. Soc.*, 2011, **133**, 1698-1701.
28. J. Clayden, P. Johnson, J. H. Pink and M. Helliwell, *J. Org. Chem.*, 2000, **65**, 7033-7040.
29. D. Ach, V. Reboul and P. Metzner, *Eur. J. Org. Chem.*, 2003, **2003**, 3398-3406.
30. X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78-79.

CHAPTER 5: Ultrafast regio- chemoselective anionic Fries rearrangement promoted by polar organometallic reagents in sustainable reaction media

The results presented in this chapter are not published yet.

Among the wide number of functional groups which have been extensively exploited as DMGs, the *O*-aryl carbamate moiety represent one of the strongest D*o*M directors. Aromatic carbamates are cleanly metalated at their *ortho*-position at low temperatures, allowing synthetically useful functionalizations upon electrophilic quench. Furthermore, in the absence of an external electrophile the aryl anion undergoes a rapid intramolecular carbamoyl transfer upon slow warming to room temperature (anionic *ortho*-Fries rearrangement, A*o*F), leading to the formation of functionalized salicylamides which can be further subjected to D*o*M chemistry manipulations (see section 1.2.3). Based on our promising results on D*o*M and LL of arenes bearing a DMG under protic-tolerated reaction conditions in presence of air and moisture at room temperature, in this chapter our systematic study on the usefulness of both DESs and CPME as sustainable reaction media for the organolithium-promoted anionic *ortho*-and *homo*-Fries rearrangement on aromatic carbamates will be discussed (Scheme 5.1).



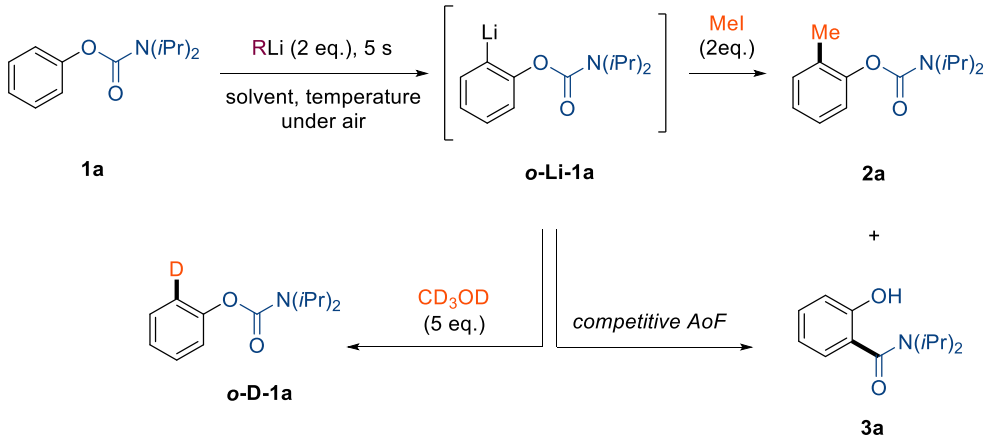
Scheme 5.1. Organolithiums promoted synthetic manipulations of *O*-arylcarbamates in sustainable solvents under air: D*o*M/electrophilic trapping (top left), A*o*F (top right), regioselective A*o*F (bottom left) and *homo*-Fries rearrangement on *ortho*-methyl analogues (bottom right).

5.1 Directed *ortho*-metalation of *O*-arylcarbamates

We started our investigation using phenyl *N,N*-diisopropylcarbamate **1a** as a model substrate since: a) bulky isopropyl groups prevent the competitive nucleophilic addition of the organolithium reagent to the electrophilic carboxylic group; b) these bulky carbamates are easy metalated under classical kinetics conditions (-78 °C) using alkyllithiums or lithium amides and c) the corresponding *ortho*-Li species is stable at -78 °C and does not undergo competitive anionic Fries rearrangement at low temperatures.[1] In a preliminary experiment, a solution of **1a** (0.2 mmol, 0.7 M in CPME) was suspended in ChCl/Gly 1:2 (1 g), under vigorous stirring in order to create an emulsion, and then reacted at 0 °C under air with commercially available *n*-BuLi (2 eq). Quenching the reaction mixture with MeI (2 eq.) after 5 seconds led to the exclusive formation of the corresponding *ortho*-methyl analogue **2a** (59%) alongside with a not negligible amount of unreacted **1a** (Table 5.1, entry 1) Notably, under these conditions neither salicylamide **3a** arising from a competitive A*o*F reaction nor nucleophilic substitution byproducts were detected by GC-MS and ^{1}H NMR analysis of the reaction crude. In comparison with our previous studies on the metalation of hindered benzamides, the *O*-carbamate DMG shows a stronger directing ability than the amide group, as experimental evidence even the less basic *n*-BuLi is able to promote the D*o*M of **1a** in a satisfactory yield. Furthermore, this preliminary result also suggests, as expected, a minor tendency of the carbamate group to undergo acyl nucleophilic substitution in the presence of organolithium reagents. Homogeneous conditions using only the environmentally friendly CPME (1 mL, 0.2 M) as reaction media led to the full conversion of **1a** and, consequently, significantly improved the yield of **2a** (81%) (Table 5.1, entry 1). As expected, when *n*-BuLi was replaced with stronger organolithiums such as *s*-BuLi (Table 5.1, entry 2) and *t*-BuLi (Table 5.1, entry 3) a general increase of the metalation performance was observed, and the highest yield of **2a** (90%) was obtained using *s*-BuLi in CPME (Table 5.1, entry 2 and Figure 5.1). On the other hand, under heterogeneous conditions (CPME/DES mixture) yields are generally slightly lower, with the best recovery of **2a** (80%) obtained using the strongest metalating agent of the series (*t*-BuLi, Table 5.1 entry 3). Among the panorama of metalating agents, the use of lithium amides for promoting the directed *ortho*-metalation of *O*-arylcarbamates under strictly controlled anhydrous conditions and at low temperatures is a well-established methodology,[2] and their reactivity as bases under unconventional conditions still remains unexplored. In order to evaluate the possibility to use lithium amides as metalating agents, **1a** was reacted with a freshly prepared solution of LiTMP (2 eq.) in 2-MeTHF (1 M), at 0 °C, under air. Quenching with MeI (2 eq.) after 5 seconds led to the formation of **2a** in

good yield both using CPME (80%) and CPME/DES (78%) as reaction media (Table 5.1, entry 4), as a mixture of *ortho*-methyl **2a** and *ortho*-ethyl functionalized arenes. The latter was formed upon the consecutive *in situ* LiTMP-promoted LL of **2a**; this result opens the door to the possibility to perform a 1,4-*homo*-Fries rearrangement *via* LL of *ortho*-methyl carbamates (*vide infra*).

Table 5.1. Metalation reaction of phenyl *N,N*-diisopropylcarbamate **1a** under different conditions. [a] [b]



Entry	RLi (2 eq.)	T (°C)	E^+ (eq.)	DES/CPME[b]		CPME[c]	
				2a (%)	**3a** (%)	**2a** (%)	**3a** (%)
1	*n*-BuLi	0	MeI (2)	59	0	81	0
2	*s*-BuLi	0	MeI (2)	55	22	90	0
3	*t*-BuLi	0	MeI (2)	80	0	86	0
4	LiTMP	0	MeI (2)	78[d]	0	80[d]	0
5	*s*-BuLi	0	CD_3OD (5)	[e]	0	[e]	0
6	*n*-BuLi	25	MeI (2)	6	54	26	70
7	*s*-BuLi	25	MeI (2)	0	52	14	59
8	*t*-BuLi	25	MeI (2)	35	44	29	59

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), solvent, 0.4 mmol of *n*-BuLi (2.5 M in hexanes), *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane), LiTMP (1 M in 2-MeTHF) under vigorous stirring, iodomethane (0.4 mmol, 2 eq.). Yields were determined by ^1H NMR using CH_3NO_2 as the internal standard. [b] ChCl/Gly 1:2 (1 g), CPME (0.3 mL). [c] CPME: 1 mL. [d] Yield of metalation products reported as sum of **2a** and 2-ethyl-*N,N*-diisopropyl-*O*-phenylcarbamate. [e] ***o*-D-1a**: 45% isolated yield, 54% deuterium incorporation in DES/CPME, 92% isolated yield, 99% deuterium incorporation in CPME. Deuterium incorporations are based on ^1H NMR integration and confirmed with ^2H NMR.

When the reactions were run at room temperature (Table 5.1, entries 6-8) the intermediate aryllithium ***o*-Li-1a** became unstable, and the main product observed in the reaction mixture was the salicylamide derivative **3a** arising from the intramolecular 1,3-O-C carbomoyl transfer process. Notably, the competitive A*o*F migration occurred independently from both the metalating agent and the reaction media. Finally, the regioselectivity of the metalation reaction was assessed by metalation of **1a** with *s*-BuLi in CPME at 0 °C, followed by quenching of the corresponding anion ***o*-Li-1a** with CD_3OD after 5 seconds. The ^1H and ^2H NMR (Figure 5.2) analysis of the rection crude reveled the high regioselective formation of the expected ***o*-D-1a** in quantitative yield (92%) with total deuterium incorporation (99%) at the *ortho*-position (Table 5.1 entry 5).

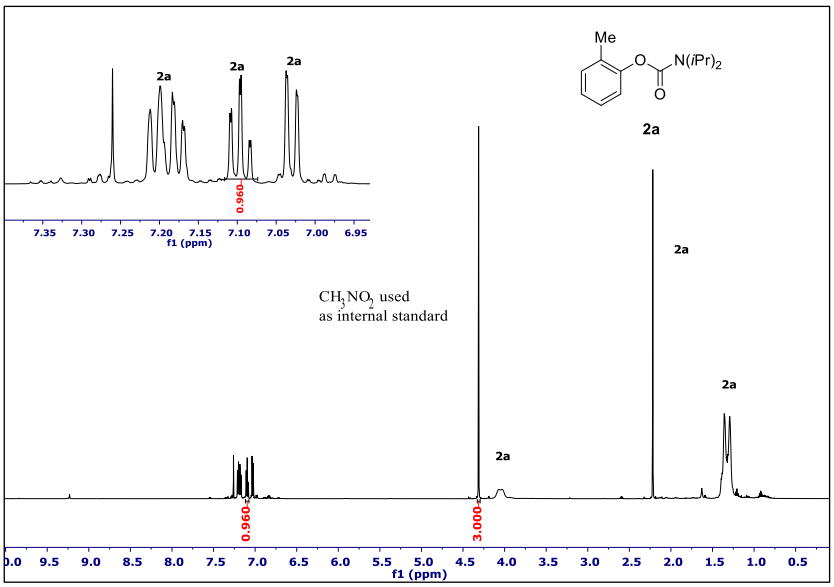


Figure 5.1. ^1H NMR of D*o*M crude reaction mixture reported in Table 5.1, entry 2: only signals of **2a** were observed. Inset: expansion of the aromatic region with integration of the reference signal of **2a** used for ^1H NMR SI yield analysis.

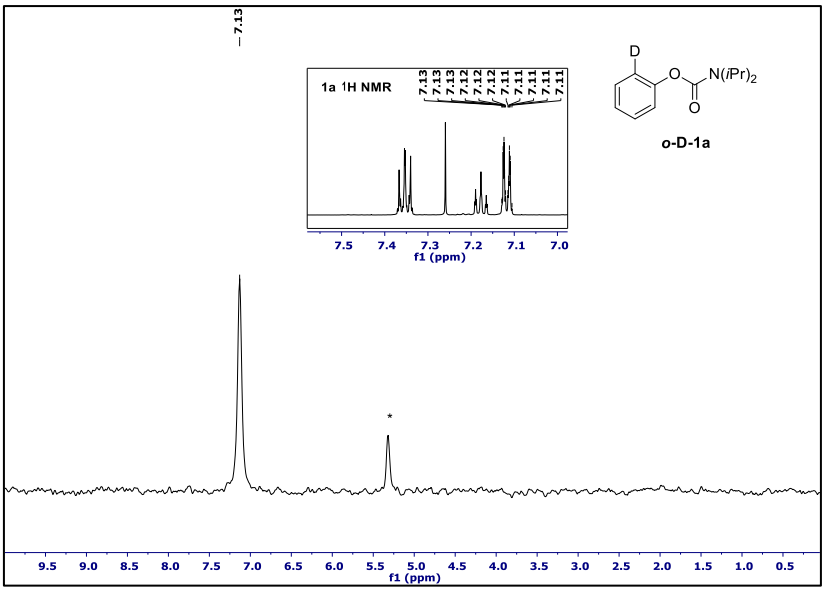
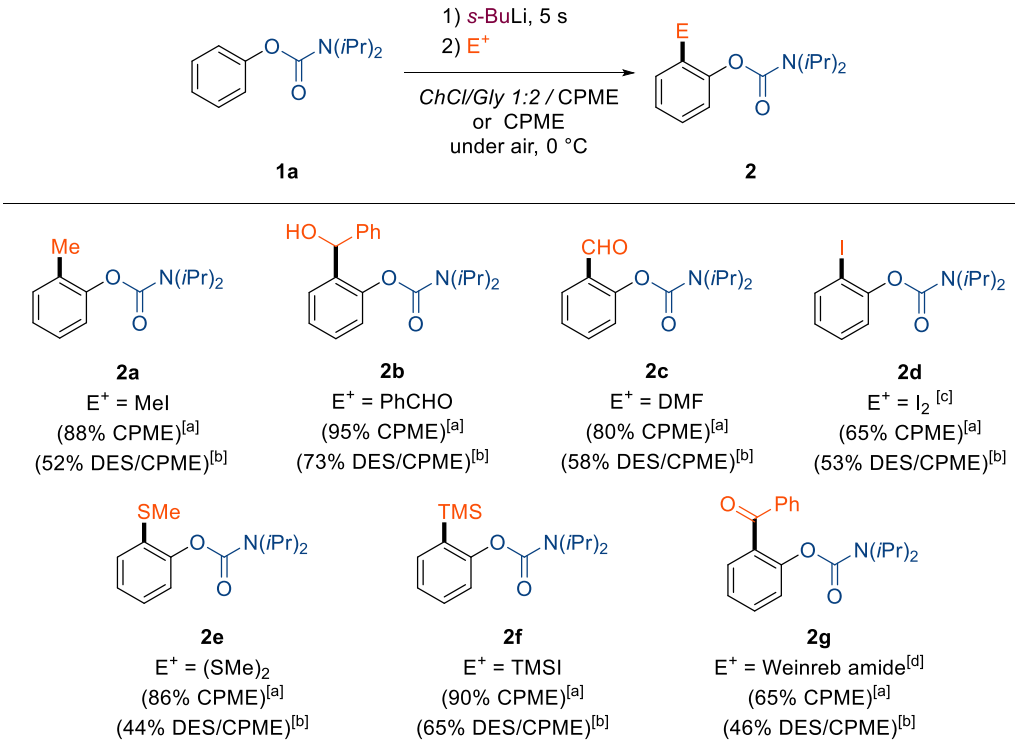


Figure 5.2. ^{2}H-NMR of ***o*-D-1a**: regioselective D incorporation at the *ortho*-position. Inset: ^{1}H NMR spectra expansion of aromatic region of **1a**. *: residual CD_2Cl_2 solvent peak.

We next evaluated the possibility to synthesize different *ortho*-functionalized carbamates potentially useful for further synthetic manipulations (*vide infra*) under both homogeneous and heterogeneous conditions (Scheme 5.2). Strong electrophiles such as benzaldehyde and DMF reacted smoothly with anion ***o*-Li-1a** in CPME, thereby providing the expected *ortho*-functionalized adducts **2b**,**c** in quantitative yields (95% and 80% respectively). Slightly lower yields were however obtained under heterogeneous conditions using the CPME/DES mixture (73% and 58% respectively). An analogous trend was observed using sulfurylating (S_2Me_2) and silylating (TMSI) agents, which provided the corresponding functionalized adducts **2e**,**f** in quantitative yields (86% and 90%) using CPME, with less satisfactory results under heterogeneous conditions. Other electrophiles, such as I_2 (2 M solution in 2-MeTHF) and the powerful acylating agent *N*-methoxy-*N*-methylbenzamide (Weinreb amide) gave access to the synthetically useful *ortho*-iodo derivative **2d** and *ortho*-acyl carbamate **2g** in good yields (up to 65%) in both reaction media.



Scheme 5.2. Scope of the *ortho*-lithiation reaction of phenyl *N,N*-diisopropylcarbamate **1a** in pure CPME and CPME/DES (ChCl/Gly 1:2) mixture under air. [a] Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2.0 eq.), CPME (1 mL, 0.2 M), electrophile (0.4 mmol., 2 eq.) at 0 °C. Quench after 5 seconds. The yields reported are for products isolated after flash column chromatography on silica gel. [b] same reaction conditions but using CPME (0.3 mL, 0.7 M)/ChCl/Gly 1:2 (1.0 g) per 0.2 mmol of **1a**. [c] I_2 was added as a 2 M solution in 2-MeTHF. [d] Weinreb amide: *N*-methoxy-*N*-methylbenzamide.

5.2 A*o*F: optimization of the reaction conditions

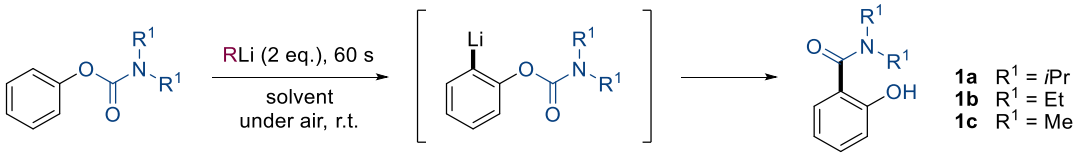
As mentioned above, when the metalation of **1a** occurs at room temperature the *ortho*-lithiated ***o*-Li-1a** species spontaneously undergoes an A*o*F rearrangement affording the salicylamide **3a** as the main reaction product (Table 5.1 entries 6-8). Motivated by these preliminary results, a **1a** (0.2 mmol) solution in CPME (0.3 mL, 0.7 M) was suspended in ChCl/Gly 1:2 (1 g) under vigorous stirring, and then reacted at room temperature under air with commercially available *n*-BuLi (2 eq). Quenching the reaction mixture with water after 60 seconds yielded the corresponding salicylamide **3a** (71%) after work up (Table 5.2, entry 1). No significant changes in terms of yield were observed using other alkyllithiums, such as *s*-BuLi (2 eq.) or *t*-BuLi (2 eq.) (Table 5.2, entries 2, 3). Whereas the use of

LiTMP (1 M solution in 2-MeTHF, 2 eq.) as metalating agent led to a significant decrease of **3a** yield (30%) (Table 5.2, entry 5), LDA (1 M solution in 2-MeTHF, 2 eq.) was completely ineffective (Table 5.2, entry 4) to promote the A*o*F reaction. Replacing Gly with other HBD-component of the DES mixture led to different results: urea and ethylene glycol caused a decrease of **3a** yield (30% and 10%) (Table 5.2 entries 6-7), while the use of ChCl/Xyl 1:1 and ChCl/Fru 2:1 deep eutectic systems gave similar results (**3a** yield up to 60%) as ChCl/Gly 1:2 eutectic mixture (Table 5.2 entries 8-9). Nevertheless, the use of DESs as reaction media prevents a total conversion of **1a** due to the competitive protonolysis of the organometallic reagents, the yield of **3a** was thus maximized to 71% (Table 5.2, entry 1). When the DES was replaced with pure CPME (1 mL, 0.2 M) as solvent, metalation of **1a** with *n*-BuLi (2 eq.) lead to full conversion of the starting material and promoted the formation of the A*o*F product **3a** in good yield (77%), alongside with the undesired formation of *N,N*-diisopropylpentanamide byproduct arising from the nucleophilic addition of the organolithium to **1a** (Table 5.2, entry 10). Remarkably, the replacing of *n*-BuLi with the more sterically hindered *s*-BuLi (2 eq.) was crucial to obtain a quantitative yield of **3a** (98%) (Table 5.2, entry 11) without any byproducts, as detected by GC-MS and ^{1}H NMR (Figure 5.3) analysis of the crude reaction mixture. Unexpectedly, the use of a more sterically hindered organolithium reagent, such as *t*-BuLi (2 eq.), resulted in a loss of selectivity due to the formation of dearomatization products (Table 5.2, entry 12).[3] Furthermore, the use of lithium amides as metalating agents in pure CPME resulted more efficient than under heterogeneous conditions. LDA (1 M in 2-MeTHF, 2 eq.) was able to promote the A*o*F rearrangement of **1a** with a moderate 34% yield of **3a** (Table 5.2, entry 13), while LiTMP (1 M in 2-MeTHF, 2 eq.) delightfully led to the quantitative recovery of the migration product **3a** (98%) without the formation of any byproduct (Table 5.2, entry 14 and Figure 5.4).

We next analyzed the reactivity of less hindered phenyl *N,N*-diethyl carbamate **1b** and phenyl *N,N*-dimethyl carbamate **1c**. Unsurprisingly, when **1b** (0.2 mmol, 1.0 eq.) was reacted both with *n*-BuLi (2 eq.) and *s*-BuLi (2 eq.) in CPME (1 mL, 0.2 M) only nucleophilic addition products were detected in the reaction crude, while *t*-BuLi was able to promote the formation of **3a** in a moderate 56% yield (Table 5.2, entries 15-17). Noteworthy, when LiTMP (1 M in 2-MeTHF, 2 eq.) was used, the reaction proceeded in a totally chemoselective fashion and the A*o*F product **3a** was recovered in good yield (85%) after workup (Table 5.2, entry 18). This remarkable result makes the use of LiTMP crucial in view of the extension of the reaction scope, since it potentially allows the metalation reaction even in the presence of other organolithiums-sensitive functionalities on the aromatic ring (see next section). However, when phenyl *N,N*-dimethyl carbamate **1c** was chosen as substrate the A*o*F rearrangement turned out to be ineffective with both *t*-BuLi and

LiTMP (Table 5.2, entries 19-20), as a consequence of the lower steric hindrance around the carbonyl moiety which privileges the progress of nucleophilic pathways.

Table 5.2. D*o*M/Fries-rearrangement of *N,N*-dialkyl-*O*-phenylcarbamates **1a-c** under different conditions.[a]



1a-c ***o*-Li-1a-c** **3a-c**

Entry	Substrate	Solvent[b]	RLi (2 eq.)	Product (yield %)[c]
1	**1a**	ChCl/Gly 1:2	*n*-BuLi	**3a** (71)
2	**1a**	ChCl/Gly 1:2	*s*-BuLi	**3a** (62)
3	**1a**	ChCl/Gly 1:2	*t*-BuLi	**3a** (61)
4	**1a**	ChCl/Gly 1:2	LDA	**-**
5	**1a**	ChCl/Gly 1:2	LiTMP	**3a** (30)
6	**1a**	ChCl/urea 1:2	*n*-BuLi	**3a** (38)
7	**1a**	ChCl/EG 1:2	*n*-BuLi	**3a** (10)
8	**1a**	ChCl/Xyl 1:1	*n*-BuLi	**3a** (54)
9	**1a**	ChCl/Fru 2:1	*n*-BuLi	**3a** (60)
10	**1a**	CPME	*n*-BuLi	**3a** (77)
11	**1a**	CPME	*s*-BuLi	**3a** (98)
12	**1a**	CPME	*t*-BuLi	**3a** (61)
13	**1a**	CPME	LDA	**3a** (34)
14	**1a**	CPME	LiTMP	**3a** (98)
15	**1b**	CPME	*n*-BuLi	- [d]
16	**1b**	CPME	*s*-BuLi	- [d]
17	**1b**	CPME	*t*-BuLi	**3b** (56)
18	**1b**	CPME	LiTMP	**3b** (85)
19	**1c**	CPME	*t*-BuLi	- [d]
20	**1c**	CPME	LiTMP	- [d]

[a] Reaction conditions: 0.2 mmol of **1a-c**, 0.4 mmol of *n*-BuLi (2.5 M in hexanes), *s*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane), LDA (1 M in 2-MeTHF), LiTMP (1 M in 2-MeTHF) under vigorous stirring. [b] 1 g of DES and 0.3 mL of CPME per 0.2 mmol of **1a-c** (entries 1-9) *or* 1 mL of CPME per 0.2 mmol of **1a-c** (entries 10-20). DES: ChCl/Gly 1:2; ChCl/urea 1:2; ChCl/EG 1:2, EG = ethylene glycol, ChCl/Xyl 1:1, Xyl = xylitol, ChCl/Fru 2:1, Fru = fructose. [c] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [d] Only S_NAc-derived products were detected.

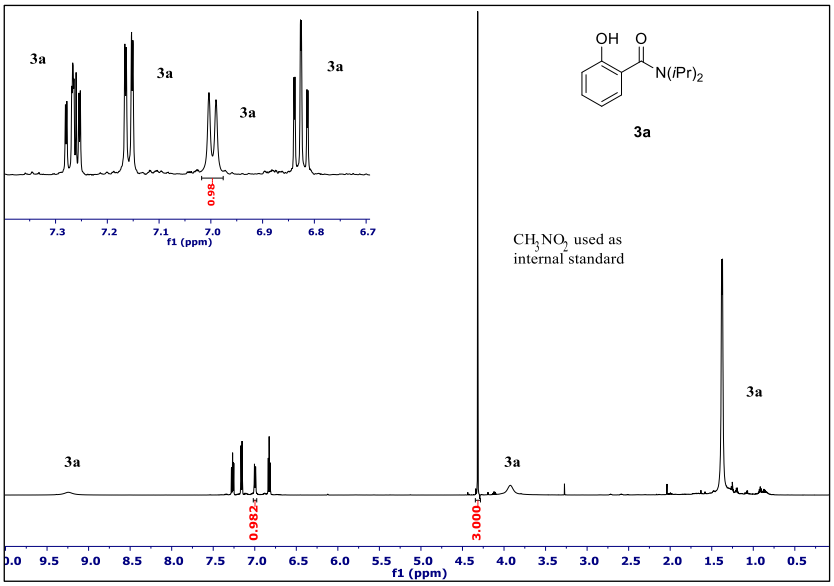


Figure 5.3. ^{1}H NMR of A*o*F crude reaction mixture reported in Table 5.2, entry 11: only signals of **3a** were observed. Inset: expansion of the aromatic region with integration of the reference signal of **3a** used for ^{1}H NMR SI yield analysis.

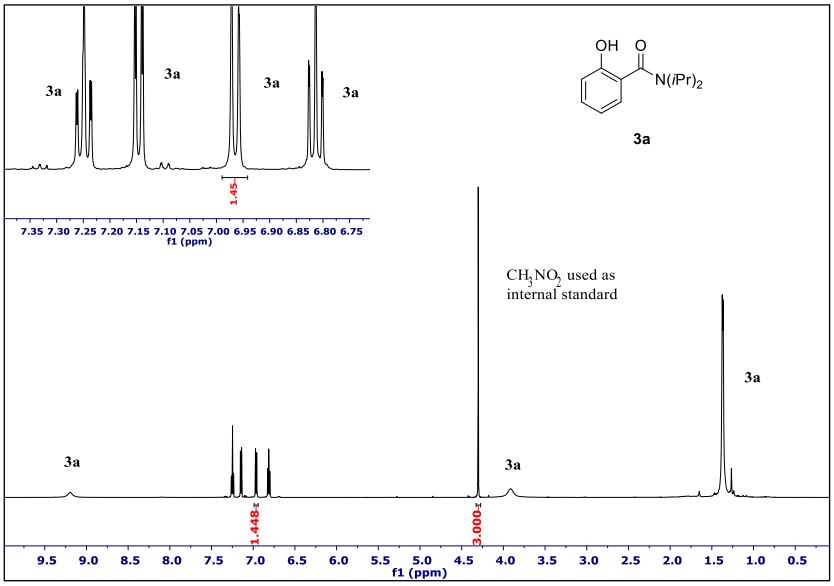


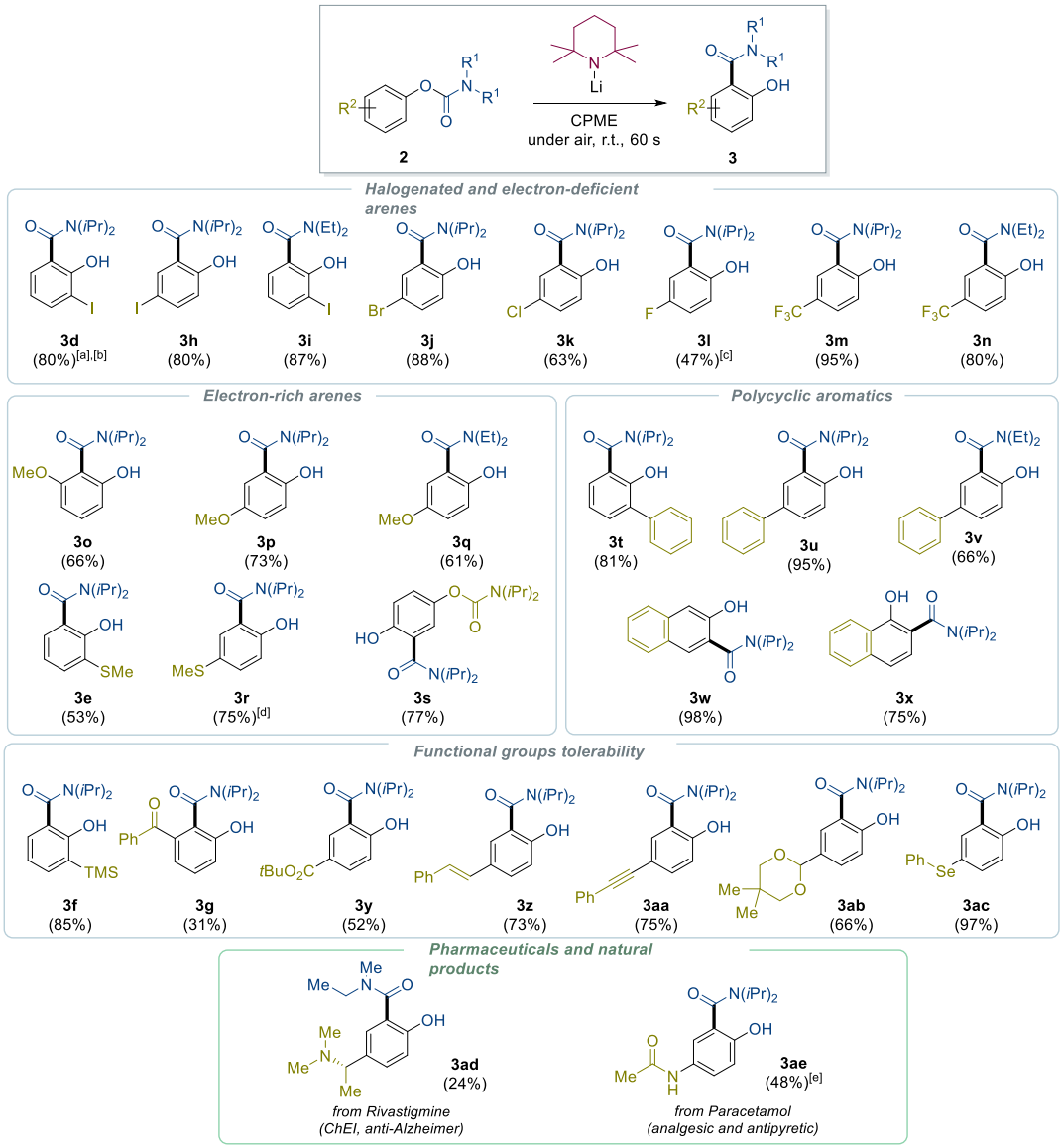
Figure 5.4. ^{1}H NMR of A*o*F crude reaction mixture reported in Table 5.2, entry 14: only signals of **3a** were observed. Inset: expansion of the aromatic region with integration of the reference signal of **3a** used for ^{1}H NMR SI yield analysis

5.3 Scope of the reaction

With the optimized reaction conditions in hand, scope and limitations of this transformation were evaluated for a series of phenyl *N,N*-diisopropyl and *N,N*-diethyl carbamates **2** decorated with different functionalities on the aromatic ring (Scheme 5.3). All the reactions were performed using CPME as solvent, under air and at room temperature, using a freshly prepared solution of LiTMP (1 M in 2-MeTHF) as privileged metalating agent. We started our investigations with the challenging *ortho*-iodo derivative **2d**, which suffer of chemoselectivity issues due to the presence of the sensitive iodine atom on the aromatic ring. Pleasingly, treatment of **1d** with LiTMP under our optimized conditions led to the recovery of the corresponding salicylamide **3d** in good yield (80%) without affecting the iodide functionality. On the opposite, when the same reaction was run using *s*-BuLi (2 eq.) as metalating agent only salicylamide **3a** was recovered due to the extremely fast competitive halogen-lithium exchange. This result observed with LiTMP further corroborates our initial choice of this commodity reagent as privileged metalating agent to promote the A*o*F rearrangement on substituted *O*-aryl carbamates. The reaction has been easily scaled-up to 5 mmol scale (1.7 g) of **2d** with comparable efficiencies in terms of yield and chemoselectivity (no Li/I exchange products were detected). Remarkably, *o*-iodosalicylamide **3d** and tetramethylpiperidine (TMP) were recovered by a simple acid-base workup procedure (**3d** 83% yield, 78% of TMP recovery), without the necessity of further purification steps and the use of VOCs. These aspects make this methodology of potential interest for nonacademic audiences.

The methodology was successfully extended to other halogenated *N,N*-diisopropyl and *N,N*-diethylcarbamates **2h-n**. The reaction proceeded smoothly with iodinated (**2h**,**i**), brominated (**2j**) and chlorinated (**2k**) derivatives without competitive halogen-lithium exchange, and with highly reactive trifluoromethylated derivatives (**2m**,**n**). The corresponding salicylamides **3h-k** and **3m**,**n** were recovered in good overall yields (63-95%). On the opposite, when the *para*-fluorophenyl *N,N*-diisopropylcarbamate **2l** was reacted with LiTMP only nucleophilic aromatic substitution products were detected in the reaction crude. Using *s*-BuLi as metalating agent, the desired product **3l** was obtained however in a moderate yield (47%). Electron-rich arenes decorated with a methoxy group in *meta*- (**2o**) and *para*- (**2p**,**q**) positions or bearing a thiomethyl group (**2e**,**r**) were regioselective metalated by LiTMP proximal to the carbamate moiety, (a) exclusively at the 2-position in the case of **2o** and b) not in competition with α-lithiation to sulphur (for **2e**,**r**), as assessed by metalation-deuteration experiments on **2r** and ^{2}H NMR analysis of the corresponding deuterated derivative (95% D incorporation). The

corresponding salicylamides **3e**, **3o-r** were recovered in moderate to good yields (53-65%), and the lower yields observed were attributed to a deactivating effect of the electron donating functionality on the aromatic ring. Interestingly, when the 1,4-bis(carbamate) **2s** was treated with LiTMP (2 eq.) only the product arising from a single carbamoyl transfer **3s** was recovered in good yield (77%), while the double migrated product has never been observed even increasing the amount of metalating agent up to 3 eq. The A*o*F migration reaction proceed with satisfactory results even for a series of polyaromatic derivatives **2t-x**, among them biphenyl derivatives **2t-v** afforded the corresponding salicylamides **3t-v** in good yield (66-95%), while α- (**2x**) and β- (**2w**) napthylcarbamates were metalated by LiTMP with excellent regioselectivity leading to the formation of salicylamides **3x** and **3w** in remarkable yields (75% and 98% respectively). We next investigated the chemoselectivity of the reaction and the tolerance of different organolithium-sensitive functional groups toward our thermodynamic metalation conditions. The previously synthesized carbamates **2b** and **2c**, bearing a benzylic alcohol (**2b**) and the highly electrophilic formyl group (**2c**) in the *ortho*-position, were ineffective to undergo a LiTMP-promoted carbamoyl migration, and only complex mixtures of products were obtained with no evidence of privileged A*o*F products. Notwithstanding these preliminary negative results, our methodology tolerates the presence of several functional groups, such as silyl (**2f**), ketone (**2g**), ester (**2y**), olefin (**2z**) and alkyne (**2aa**), acetal (**2ab**) and selenide (**2ac**). LiTMP was able to promote the A*o*F rearrangement with high chemoselectivity, and the corresponding salicylamides **3f**,**g** and **3y-ac** were obtained in moderate to good yields (31-97%) with total preservation of the sensitive functional group. Remarkably, no competitive nucleophilic addition (**2g**,**y**), carbolithiation (**2z**,**aa**), α-lithiation (**2ab**) or transmetalation (**2ac**) products were detected in the crude reaction mixtures. However, the incorporation of nitro, ciano and boronate groups on the aromatic ring made the procedure ineffective, and the corresponding desired salicylamides have not been isolated due to the prevalence of alternative reaction pathways. Finally, the potential of our methodology in drug derivatization has been illustrated with the organolithium-promoted A*o*F rearrangement of Rivastigmine **2ad**,[4, 5] an acetylcholinesterase inhibitor (AChEI) used for the treatment of Alzheimer's disease, and the well-known acetaminophen (Paracetamol) drug.[6] Rivastigmine, an aryl *N*-ethyl-*N*-methyl-carbamate, represents a quite challenging substrate due to the reduced steric hindrance of the amide moiety, which might be less efficient than *N*,*N*-diethyl (however higher than *N*,*N*-dimethyl) derivatives to prevent the formation of nucleophilic addition products.



Scheme 5.3. Scope of the A*o*F rearrangement of *O*-arylcarbamates **2** in CPME at room temperature under air. [a] Reaction conditions: **2** (0.2 mmol, 1.0 eq.), LiTMP (1 M in 2-MeTHF, 0.4 mmol, 2.0 eq.), CPME (1 mL, 0.2 M). Quench after 60 seconds with water. The yields reported are for products isolated after flash column chromatography on silica gel. [a] Using *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) only **3a** was obtained. [b] 5 mmol scale: **3d** yield 85%. [c] *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was used as base. [d] Regioselectivity of the metalation was assessed by ^{2}H NMR analyses of the corresponding deuterated compounds. [e] Reaction conditions: **2ae** (0.2 mmol, 1 eq.) in 2-MeTHF (1 mL, 0.2 M), *s*-BuLi (1.4 M in cyclohexane, 0.6 mmol, 3 eq.).

Treatment of commercially available (*S*)-Rivastigmine **2ad** with 2 eq. of LiTMP gave access to the corresponding salicylamide **3ad**, however in low yield due to the prevailing nucleophilic addition pathway. On the other hand, Paracetamol drug (a phenol) needs a preliminary derivatization into the corresponding carbamate **2ae**, and its metalation may suffer of the competitive NH-lithiation due to the presence of the acetylamino group on the aromatic ring (another potential DMG). Owing to the complete insolubility of **2ae** in CPME, the metalation/A*o*F sequence was performed using the environmentally friendly 2-MeTHF as solvent (1 mL, 0.2 M). When reacted in the presence of LiTMP (2 eq.), no products were observed in the crude reaction mixture, and only the starting material was recovered unreacted. When an additional equivalent of metalating agent was employed, comparable results were obtained. Replacing LiTMP with the more basic *s*-BuLi (2 eq.), a small amount of migration product was detected in the crude, while the use of 3 eq. of base led to the formation of the desired adduct **3ae** in a satisfactory 48% yield after column chromatography.

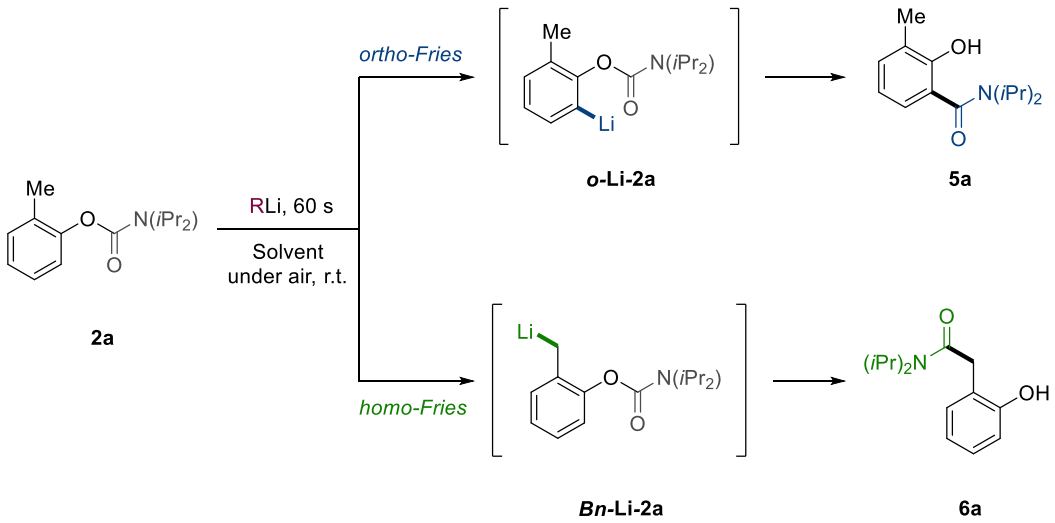
5.4 Regioselectivity issues: *ortho*- vs *homo*-Fries rearrangement

The *ortho*-tolyl *N,N*-diisopropylcarbamate **2a**, previously synthesized by D*o*M of carbamate **1a** followed by quench with iodomethane, represents a fascinating substrate since it can be subjected to further metalation studies. In fact, two metalation sites are present on the aromatic ring: a) the *ortho* position, susceptible to the directed *ortho*-metalation process and consequent *ortho*-Fries (1,3-O-C) rearrangement, and b) the benzylic position, which can be subjected to lateral lithiation and sequential *homo*-Fries (1,4-O-C) rearrangement. In order to evaluate the possibility to regioselectively direct the metalation and, as a consequence, the carbamoyl transfer into the *o*-arylic or benzylic position, we designed a series of experiments in order to discriminate these two competitive pathways (Table 5.3).

Pleasingly, metalation of **2a** with *s*-BuLi (2 eq.) in CPME, at room temperature and under air, afforded the sole *ortho*-Fries product **5a** in a remarkable 88% yield, as a consequence of the thermodynamic control of the migration (Table 5.3, entry 1). Although the reaction outcome is presumably driven by the relative stabilities of the corresponding phenoxide leaving groups,[7] treatment of **2a** with *s*-BuLi in the presence of a heterogeneous mixture of CPME/ChCl/Gly (1:2 mol mol-1) led to an unexpected 1:1 mixture of *ortho*- (**5a**) and *homo*-Fries (**6a**) products (Table 5.3, entry 2). At a glance, this result suggests a putative stabilizing effect of the eutectic mixture upon the *homo*-Fries phenolate anion, as a matter of fact lithiation of **2a** with LiTMP (1 M in 2-MeTHF, 2 eq.) proceeded smoothly, with high efficiency and in a total regioselective fashion only under heterogeneous conditions

(80% of α-arylacetamide **6a,** Table 5.3, entry 3), whereas only an unresolved complex mixtures of products was recovered in the absence of DES (Table 5.3, entry 4).

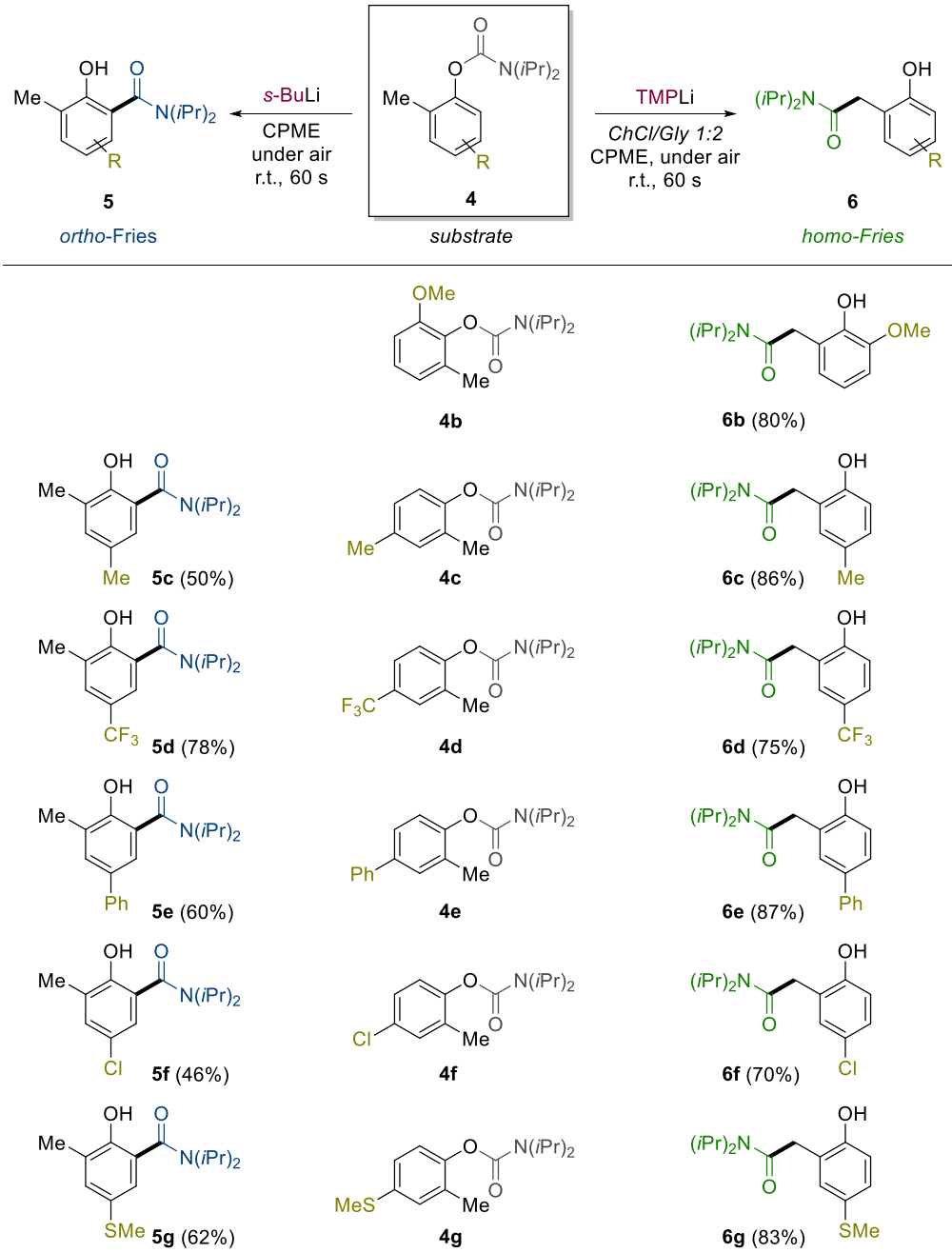
Table 5.3. Regioselective metalation-Fries rearrangement of **2a** under air, at room temperature.



Entry	RLi (2 eq.)	Solvent	*ortho*-Fries (1,3) **5a** yield%[c]	*homo*-Fries (1,4) **6a** yield%[c]
1	*s*-BuLi	CPME[a]	88	0
2	*s*-BuLi	ChCl/Gly 1:2/ CPME[b]	54	46
3	LiTMP	ChCl/Gly 1:2/ CPME[b]	0	80
4	LiTMP	CPME[a]	0	10

[a] Reaction conditions: 0.2 mL of CPME per 0.2 mmol of **2a** (entries 1,3), *s*-BuLi (1.4 M in cyclohexane) *or* LiTMP (1 M in 2-MeTHF, 2 eq.). Quench after 60 seconds with water, open air, room temperature. [b] 1 g of ChCl/Gly 1:2 and 0.3 mL of CPME per 0.2 mmol of **2a** (entries 2,4), *s*-BuLi (1.4 M in cyclohexane) *or* LiTMP (1 M in 2-MeTHF, 2 eq.). Quench after 60 seconds with water, open air, room temperature. [c] isolated yields.

Finally, a series of *ortho*-tolyl carbamates **4** decorated with different EDG (methoxy **4b**, thiomethyl **4g**), neutral (methyl **4c**), EWG (trifluoromethyl, **4d**), phenyl (**4e**) and chloro (**4f**) substituents on the aromatic ring were synthesized and subjected to optimized metalation conditions to generate the corresponding salicylamide derivatives **5c-g** (*s*-BuLi in CPME, 46-78% yield) and their homologous α-arylacetamide derivatives **6b-c** (LiTMP in CPME/DES mixture, 70-86% yield) with high regioselectivity (Scheme 5.4).



Scheme 5.4. Regioselective *ortho- vs homo*-Fries rearrangement on **4c-g.** *Ortho*-Fries, reaction conditions: **4c-g** (0.2 mmol, 1.0 eq.), *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) in CPME (1 mL, 0.2 M), under air, at room temperature. *Homo-Fries*, reaction conditions: **4b-g** (0.2 mmol, 1.0 eq.), LiTMP (1 M in 2-MeTHF, 0.4 mmol, 2.0 eq.), CPME (0.3 mL, 0.7 M), ChCl/Gly 1:2 (1 g). The yields reported are for products isolated after flash column chromatography on silica gel.

5.5 Conclusions

In summary, the reactivity of *O*-arylcarbamates with polar organolithium reagents could be conveniently controlled by changing the reaction conditions in the presence of air and moisture using eco-friendly unconventional solvents. The *ortho*-Li species can be successfully generated by D*o*M reaction both at room temperature and at 0 °C using alternatively CPME or CPME/DES as solvents. However, the electrophilic quenching of the *o*-aryllithium is feasible only at 0 °C due to the competitive *ortho*-Fries rearrangement occurring at room temperature. Nevertheless, the use of appropriated electrophiles give access to the corresponding *ortho*-functionalized species that could be used for further synthetic manipulations. Moreover, we have developed an efficient protocol, using for the first time the highly hindered lithium amide LiTMP as metalating agent at room temperature in the eco-friendly solvent CPME, under air, to access a wide variety of salicylamide derivatives arising from the 1,3-O-C anionic Fries rearrangement in good to quantitative yield, with an unprecedent level of chemoselectivity and functional groups tolerance under non-classical Schlenk conditions. The possibility to perform the reaction on gram scale, and the feasibility to recover the 2,2,6,6,-tetramethylpiperidine which can be reused to generate the lithium amide by simple acid-base workup, makes this protocol even more suitable for industrial development. Finally, regioselective *ortho* vs lateral manipulation of *ortho*-tolyl carbamates has been successfully achieved using *s*-BuLi in CPME to promote the D*o*M/A*o*F migration sequence, and for the first time the lithium amide LiTMP as metalating agent in eutectic mixtures to promote the benzylic metalation-migration sequence, at room temperature in presence of air and moisture.

Future progresses will be focused on understanding the solvent- and base-dependent behaviour of the regioselectivity, and on the development of total synthesis of small molecules of biological-pharmaceutical interest using the portfolio of organolithium-promoted nucleophilic and basic transformations under sustainable bench conditions.

5.6 Experimental Section

5.6.1 General information

Materials and methods. Unless specified, all reagents were used as received without further purifications. Anhydrous tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF) and cyclopentyl methyl ether (CPME) were distilled under nitrogen over Na/benzophenone ketyl prior to use. Reactions were monitored by GC-MS analysis and/or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Chromatographic

separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. The following solutions of organolithium reagents were furnished by Merck-Aldrich and Acros Organics and were used with the following concentration: *n*-BuLi 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane. The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[8] 2,2,6,6-Tetramethylpiperidine (TMP) was dried over CaH_2, distilled under reduced pressure prior to use, and stored under inert atmosphere. Full characterisation data, including copies of ^1H and ^{13}C NMR spectra, have been reported for both the newly synthesized compounds and the known compounds. *O*-arylcarbamates **1a-c**,[9, 10] **2b-ae**[7, 11-17] were synthesized according to the procedures reported in the literature.

Instrumentation. ^1H NMR (600 MHz), $^{13}C\{^1H\}$ (150 MHz), ^2H NMR (92.07 MHz), ^{19}F (564 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad). Low-resolution MS spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI). GC analyses were performed on a PerkinElmer Autosystem XL chromatographic system equipped with a methyl silicone capillary column. The MS flow-injection analyses were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an a ESI ion source. The samples were analysed in acetonitrile solution using a syringe pump at a flow rate of 5 μL/min. The tuning parameters adopted for the ESI source were: source voltage 4.0 kV. The heated capillary temperature was maintained at 275 °C. The mass accuracy of the recorded ions (vs. the calculated ones) was ± 2.5 mmu (milli-mass units). Analyses were run using both full MS (150-2000 m/z range) and MS/MS acquisition, at 500000 resolutions (200 m/z).

Nitromethane was used as the internal standard for quantitative NMR analysis of the crude reaction mixture. The amount of product was determined by applying the following equation (Eq. 1):

$$(1) \qquad yield\ (\%) = \frac{x\ (product) \cdot n\ (MeNO2)}{n(starting\ material)} \cdot f \cdot 100$$

where:

- *x* is the value of integral/number of protons;
- *n* is the amount of starting material or nitromethane in mmol;
- *f* the diluting factor used for the preparation of the sample.

5.6.2 Preparation of lithium 2,2,6,6-tetramethylpiperidine (LiTMP) solution in 2-MeTHF

In a Schlenk tube under a positive nitrogen pressure, *n*-BuLi (2.5 M in hexanes, 4.0 mmol, 1.0 eq.) was added to a precooled (0 °C) stirred solution of 2,2,6,6-

tetramethylpiperidine (TMP) (4.4 mmol, 1.1 eq., 0.75 mL) in anhydrous 2-MeTHF (1.51 mL). The mixture was stirred at 0 °C for 10 minutes to yield a clear solution of LiTMP that was used without further purifications.[18]

*5.6.3 Synthesis of carbamates **1a-c, 2h-ae, 4b-c** by carbamoylation*

To a stirred solution of the appropriate phenol (10 mmol, 1.0 eq.) in anhydrous pyridine (10 mL, 1 M) under nitrogen, the appropriate carbamoyl chloride (10 mmol, 1.0 eq.) was added. The resulting reaction mixture was stirred overnight at reflux. The mixture was allowed to cool to room temperature and then quenched with 20 mL of aqueous 1 M HCl at 0 °C. After extraction with DEE or EtOAc, the organic layer was washed with aqueous 1 M HCl (3 x 20 mL) and aqueous 1 M NaOH (2 x 20 mL), dried over Na2SO4 and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel or by crystallization. Characterization of ^{1}H and ^{13}C NMR of unknown compounds are reported below.

4-Iodophenyl-*N,N*-diisopropylcarbamate (2h): General procedure starting from 4-iodophenol and *N,N*-diisopropylcarbamoyl chloride gave **2h** as a white solid (2.30 g, 66%), mp 55.0-57.5 °C, which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67-7.63 (m, 2H), 6.91-6.88 (m, 2H), 4.08 (br s, 1H) superimposed to 3.93 (br s, 1H), 1.32 (br s, 6H) superimposed to 1.28 (br s, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 153.4, 151.4, 138.3, 124.2, 88.8, 47.1, 46.3, 21.7, 20.5. EI-MS *m/z* (%): 347 (M^+, 5), 220 (57), 128 (100), 86 (80), 43 (48).

4-Bromophenyl-*N,N*-diisopropylcarbamate (2j): General procedure starting from 4-bromophenol and *N,N*-diisopropylcarbamoyl chloride gave **2j** as a white solid (2.30 g, 77%), mp 54.3-56.5 °C, which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.08 (br s, 1H) superimposed to 3.94 (br s, 1H), 1.32 (br s, 6H) superimposed to 1.28 (br s, 6H). $^{13}C\{1H\}$ NMR (150 MHz, CDCl3): δ 153.5, 150.6, 132.3, 123.8, 118.0, 47.1, 46.3, 21.7, 20.5. EI-MS *m/z* (%): 301 (M^+, 1), 299 (M+, 1), 174 (42), 172 (43), 128 (100), 86 (97), 43 (53).

4-Chlorophenyl-*N,N*-diisopropylcarbamate (2k): General procedure starting from 4-chlorophenol and *N,N*-diisopropylcarbamoyl chloride gave **2k** as a pale-yellow liquid (1.94 g, 76%), which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.09 (br s, 1H) superimposed to 3.94 (br s, 1H), 1.33 (br s, 6H) superimposed to 1.28 (br s, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 153.6, 150.1, 130.4, 129.3, 123.3, 47.1, 46.3, 21.7, 20.5. EI-MS *m/z* (%): 255 (M^+, 1), 128 (100), 86 (64), 43 (34).

4-Fluorophenyl-*N,N*-diisopropylcarbamate (2l): General procedure starting from 4-fluorophenol and *N,N*-diisopropylcarbamoyl chloride gave **2l** as an orange liquid (1.78 g,

75%), which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09-7.05 (m, 2H), 7.05-7.01 (m, 2H), 4.09 (br s, 1H) superimposed to 3.95 (br s, 1H), 1.33 (br s, 6H) superimposed to 1.28 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 159.9 (d, *J* = 243.0 Hz, 1C), 153.9, 147.4 (d, *J* = 2.7 Hz, 1C), 123.3 (d, *J* = 8.6 Hz, 1C), 115.9 (d, *J* = 23.2 Hz, 1C), 47.1, 46.2, 21.7, 20.6. ^{19}F NMR (564 MHz, $CDCl_3$): δ -118.34 (tt, *J* = 8.6, 4.9 Hz). EI-MS *m/z* (%): 239 (M^+, 1), 128 (85), 112 (100), 86 (94), 43 (66).

4-(Methylthio)phenyl-*N,N*-diisopropylcarbamate (2r): General procedure starting from 4-(methylthio)phenol and *N,N*-diisopropylcarbamoyl chloride gave **2r** as a colourless solid (1.82 g, 68%), mp 38.2-40.0 °C, which was used without any further purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.07-7.03 (m, 2H), 4.09 (br s, 1H) superimposed to 3.94 (br s, 1H), 2.46 (s, 3H), 1.32 (br s, 6H) superimposed to 1.28 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.9, 149.5, 134.5, 128.5, 122.5, 47.1, 46.2, 21.7, 20.6, 17.1. EI-MS *m/z* (%): 267 (M^+, 21), 140 (94), 128 (81), 125 (35), 86 (100), 43 (57).

Naphthalen-1-yl-*N,N*-diisopropylcarbamate (2x): General procedure starting from naphthalen-1-ol and *N,N*-diisopropylcarbamoyl chloride; purification by crystallization from hexane gave **2x** as a white solid (1.81 g, 66%), mp 104.5-106.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54-7.44 (m, 3H), 7.28-7.23 (m, 1H), 4.16 (br m, 2H), 1.47 (br s, 6H) superimposed to 1.35 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 154.0, 147.5, 134.8, 128.1, 127.9, 126.3, 126.3, 125.6, 125.4, 121.6, 118.3, 47.1, 46.5, 21.8, 20.7. EI-MS *m/z* (%): 271 (M^+, 14), 144 (90), 128 (84), 115 (55), 86 (100), 43 (44).

***Tert*-butyl-4-((*N,N*-diisopropylcarbamoyl)oxy)benzoate (2y)**: General procedure starting from *tert*-butyl 4-hydroxybenzoate;[19] purification by flash column chromatography on silica gel (petroleum ether/Et_2O 9/1 v/v + Et_3N 0.5%) gave **2y** as a white solid (0.95 g, 59%, R*f* = 0.25 petroleum ether/Et_2O 9/1 v/v + Et_3N 0.5%), mp 52.0-56.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H), 7.17-7.14 (m, 2H), 4.10 (br s, 1H) superimposed to 3.95 (br s, 1H), 1.58 (s, 9H), 1.33 (br s, 6H) superimposed to 1.29 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 165.4, 155.0, 153.3, 130.9, 128.7, 121.5, 81.1, 47.2, 46.3, 28.3, 21.7, 20.5. EI-MS *m/z* (%): 138 (M^+ - 183, 39), 128 (100), 121 (20), 86 (96), 43 (35).

4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenyl-*N,N*-diisopropylcarbamate (2ab) General procedure starting from 4-(5,5-dimethyl-1,3-dioxan-2-yl)phenol;[20] purification by flash column chromatography on silica gel (petroleum ether/Et_2O 7/3 v/v + Et_3N 0.5%) gave **2ab** as a white solid (0.59 g, 35%, R*f* = 0.35 petroleum ether/Et_2O 7/3 v/v + Et_3N 0.5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53-7.44 (m, 2H), 7.16-7.08 (m, 2H), 5.38 (s, 1H), 4.12 (br s, 1H) superimposed to 3.91 (br s, 1H), 3.78-3.74 (m, 2H), 3.64 (d, *J* = 10.2 Hz, 2H), 1.31 (br s, 12H) superimposed to 1.28 (s, 3H), 0.80 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.8, 151.9, 135.4, 127.2, 121.6, 101.3, 77.7, 46.1, 30.3, 23.2, 22.0, 21.7, 20.6. EI-MS *m/z* (%): 335 (M^+, 2), 207 (18), 128 (100), 121 (17), 86 (85), 43 (34).

4-(Phenylselanyl)phenyl-*N,N*-diisopropylcarbamate (2ac): General procedure starting from 4-(phenylselanyl)phenol;[21] purification by flash column chromatography (petroleum ether/EtOAc 95/5 v/v) on silica gel gave **2ac** as colourless liquid (0.33 g, 62%, R*f* = 0.38 petroleum ether/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52-7.49 (m, 2H), 7.44-7.40 (m, 2H), 7.26-7.22 (m, 3H), 7.08-7.04 (m, 2H), 4.08 (br s, 1H) superimposed to 3.96 (br s, 1H), 1.31 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.7, 151.3, 135.0, 132.3, 132.0, 129.4, 127.2, 126.4, 123.0, 47.1, 46.3, 21.7, 20.6. EI-MS *m/z* (%): 376 (M^+, 4), 250 (13), 170 (83), 128 (91), 86 (100), 43 (53).

4-Acetamidophenyl-*N,N*-diisopropylcarbamate (2ae): General Procedure starting from 4-acetamidophenol (Paracetamol) and *N,N*-diisopropylcarbamoyl chloride; purification by flash column chromatography on silica gel (DCM/MeOH 98/2 v/v) gave **2ae** as a yellow solid (0.98 g, 36%, R*f* = 0.13, DCM/MeOH 98/2 v/v), mp 140.2-144.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (br s, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.13 (br s, 1H) superimposed to 3.93 (br s, 1H), 2.09 (s, 3H), 1.33 (br s, 6H) superimposed to 1.29 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 168.7, 154.5, 147.4, 135.4, 122.1, 121.3, 47.2, 46.2, 24.3, 21.7, 20.6. EI-MS *m/z* (%): 278 (M^+, 13), 151 (18), 128 (85), 109 (89), 86 (100), 43 (62).

2-Methoxy-6-methylphenyl-*N,N*-diisopropylcarbamate (4b): General procedure starting from 2-methoxy-6-methylphenol and *N,N*-diisopropylcarbamoyl chloride gave **4b** as a colourless solid (1.84 g, 69%), mp 50.5-54.5 °C, without any purification. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.04 (t, *J* = 7.9 Hz, 1H), 6.81-6.77 (m, 2H), 4.15 (br s, 1H) superimposed to 3.95 (br s, 1H), 3.79 (s, 3H), 2.21 (s, 3H), 1.37 (br s, 6H) superimposed to 1.28 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.6, 152.1, 139.4, 132.3, 125.4, 122.6, 110.0, 56.1, 47.0, 46.1, 21.7, 20.7, 16.3. EI-MS *m/z* (%): 265 (M^+, 10), 138 (67), 128 (77), 123 (34), 86 (100), 43 (44).

2,4-Dimethylphenyl-*N,N*-diisopropylcarbamate (4c): General procedure starting from 2,4-dimethylphenol and *N,N*-diisopropylcarbamoyl chloride; purification by flash column chromatography on silica gel (petroleum ether/Et_2O 9/1 v/v) gave **4c** as a colourless liquid (1.68 g, 68%, R*f* = 0.38 petroleum ether/Et_2O 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.01 (d, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 4.08 (br s, 1H) superimposed to 4.00 (br s, 1H), 3.17 (s, 3H), 2.29 (s, 3H), 1.35 (br s, 6H) superimposed to 1.28 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.9, 147.9, 134.9, 131.7, 130.3, 127.4, 122.1, 46.9, 46.2, 21.7, 20.9, 20.7, 16.5. EI-MS *m/z* (%): 249 (M^+, 5), 128 (73), 122 (74), 107 (23), 86 (100), 43 (48).

*5.6.4 Synthesis of N,N-diisopropylcarbamates **4d-g** by directed ortho-metalation*

To a stirred solution of the appropriate *N,N*-diisopropylcarbamate (2.0 mmol, 1.0 eq.) in anhydrous THF (10 mL, 0.2 M) under nitrogen at -78 °C, *t*-BuLi (1.6 M in pentane, 2.0 eq.) was added dropwise. After 1 h at -78 °C, iodometane (5 mmol, 2.5 eq., 0.32 mL)

was added, the reaction was warmed to room temperature and stirred overnight. The mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The crude was purified by flash column chromatography or by crystallization.

2-Methyl-4-(trifluoromethyl)phenyl-*N,N*-diisopropylcarbamate (4d): General procedure starting from **2m**; purification by flash column chromatography on silica gel (petroleum ether/Et_2O 9/1 v/v) gave **4d** as a colourless liquid (0.52 g, 86%, R*f* = 0.5 petroleum ether/Et_2O 9/1 v/v).^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.05 (sept, *J* = 6.2 Hz, 2H), 2.27 (s, 3H), 1.36 (brd, *J* = 6.9 Hz, 6H) superimposed to 1.31 (brd, *J* = 7.1 Hz 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 152.9, 152.7, 131.7, 128.2 (q, *J* = 3.6 Hz, 1C), 127.6 (q, *J* = 32.2 Hz, 1C), 124.2 (q, *J* = 272.0 Hz, 1C), 124.1 (d, *J* = 4.3 Hz, 1C), 122.9, 47.1, 46.6, 21.7, 20.6, 16.7. ^{19}F NMR (564 MHz, $CDCl_3$): δ -62.01 (s). EI-MS *m/z* (%): 176 (M^+ - 127, 44), 128 (85), 86 (100), 43 (55).

3-Methyl-[1,1'-biphenyl]-4-yl-*N,N*-diisopropylcarbamate (4e): General procedure starting from **2u**; purification by flash column chromatography on silica gel (petroleum ether/Et_2O 9/1 v/v) gave **4e** as a yellow solid (0.58 g, 93%, R*f* = 0.25 petroleum ether/Et_2O 9/1 v/v), mp 84.0-85.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.45-7.39 (m, 4H), 7.35-7.31 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 4.08 (br s, 2H), 2.29 (s, 3H), 1.38 (br s, 6H) superimposed to 1.32 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.7, 149.6, 141.0, 138.6, 131.0, 130.0, 128.8, 127.3, 127.2, 125.7, 122.7, 47.0, 46.4, 21.7, 20.7, 16.8. EI-MS *m/z* (%): 311 (M^+, 10), 184 (85), 128 (95), 86 (100), 43 (42).

4-Chloro-2-methylphenyl-*N,N*-diisopropylcarbamate (4f): General procedure starting from **2k**; purification by flash column chromatography on silica gel (petroleum ether/Et_2O 9/1 v/v) gave **4f** as a yellow liquid (0.22 g, 41%, R*f* = 0.35 petroleum ether/Et_2O 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.19 (d, *J* = 2.6 Hz, 1H), 7.14 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.04 (br s, 2H), 2.19 (s, 3H), 1.34 (br s, 6H) superimposed to 1.29 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.3, 148.7, 132.7, 130.8, 130.4, 126.8, 123.7, 47.0, 46.4, 21.7, 20.6, 16.6. EI-MS *m/z* (%): 269 (M^+, 1), 142 (46), 128 (84), 107 (19), 86 (100), 43 (48).

2-Methyl-4-(methylthio)phenyl-*N,N*-diisopropylcarbamate (4g): General procedure starting from **2r**; purification by flash column chromatography on silica gel (petroleum ether/Et_2O 8/2 v/v) gave **4g** as a yellow liquid (0.58 g, 98%, R*f* = 0.32 petroleum ether/Et_2O 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.1 Hz, 1H), 7.10 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.04 (br s, 2H), 2.45 (s, 3H), 2.19 (s, 3H), 1.34 (br s, 6H) superimposed to 1.29 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.6, 148.1, 134.6, 131.4, 130.2, 126.0, 122.9, 47.0, 46.3, 21.7, 20.6, 17.0, 16.6. EI-MS *m/z* (%): 281 (M^+, 23), 154 (81), 139 (28), 128 (79), 86 (100), 43 (49).

*5.6.5 Directed ortho-metalation of phenyl-N,N-diisopropylcarbamate **1a** under homogeneous and heterogeneous reaction conditions: synthesis and analysis of compounds **2a-g***

Homogeneous conditions (CPME): reactions were performed under air at 0 °C. In an open screw cap vial, phenyl-*N,N*-diisopropylcarbamate **1a** (0.2 mmol, 1 eq., 35 mg) was dissolved in CPME (1 mL, 0.2 M), and the mixture was vigorously stirred for 5 min at 0 °C. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 5 seconds, then quenched with the selected electrophile (0.4 mmol, 2 eq.). The mixture was diluted with water then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na2SO4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

Heterogeneous conditions (CPME/DES): reactions were performed under air at 0 °C. In an open screw cap vial, phenyl-*N,N*-diisopropylcarbamate **1a** (0.2 mmol, 1 eq., 35 mg) was dissolved in CPME (0.3 mL), then ChCl/Gly 1:2 (1 g) was added and the mixture was vigorously stirred for 5 minutes at 0 °C. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 5 seconds, then quenched with the selected electrophile (0.4 mmol, 2 eq.). The mixture was diluted with water then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na2SO4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

***o*-Tolyl-*N,N*-diisopropylcarbamate (2a)**: General procedure starting from **1a** and iodomethane; purification by flash column chromatography on silica gel (PE/DEE 9/1 v/v) gave **2a** as a white solid (R*f* = 0.29 PE/DEE 9/1 v/v, 41 mg, 88% in CPME; 24 mg, 52% in DES/CPME), mp 54.5-55.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.10 (td, *J* = 7.4, 1.3 Hz, 1H), 7.04 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.08 (br s, 1H) superimposed to 4.03 (br s, 1H), 2.22 (s, 3H), 1.36 (br s, 6H) superimposed to 1.30 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.7, 150.1, 131.1, 130.8, 126.9, 125.4, 122.4, 46.9, 46.3, 21.7, 20.6, 16.6. EI-MS *m/z* (%): 235 (M^+, 3), 128 (83), 108 (72), 86 (100), 43 (52).

2-(Hydroxy(phenyl)methyl)phenyl-*N,N*-diisopropylcarbamate (2b): General procedure starting from **1a** and benzaldehyde; purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **2b** as a white semisolid (R*f* = 0.55 PE/EtOAc 8/2 v/v, 62 mg, 95% in CPME; 48 mg, 73% in DES/CPME). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2H), 7.35-7.23 (m, 5H), 7.19 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.98 (s, 2H), 3.99 (sept, *J* = 6.7 Hz, 2H), 3.52 (br s, 1H), 1.31-1.26 (br m, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 154.5, 149.0, 142.7, 137.1, 129.6, 129.0, 128.3, 127.2, 126.5, 126.3, 122.6, 70.4, 47.0, 46.7, 21.5, 21.4, 20.5, 20.5. EI-MS *m/z* (%): 182 (M^+ - 145, 57), 181 (85), 128 (61), 86 (100).

2-Formylphenyl-*N,N*-diisopropylcarbamate (2c): General procedure starting from **1a** and dry DMF; purification by flash column chromatography on silica gel (PE/EtOAc 9/1 v/v) gave **2c** as a colourless liquid (R*f* = 0.34 PE/EtOAc 9/1 v/v, 40 mg, 80% in CPME; 29 mg, 58% in DES/CPME). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.19 (s, 1H), 7.89 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.60 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.12 (br s, 1H), 4.00 (br s, 1H), 1.36 (d, *J* = 6.5 Hz, 6H) superimposed to (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 188.9, 153.3, 153.1, 135.3, 129.5, 128.9, 125.7, 123.7, 47.1, 46.9, 21.6, 20.5. EI-MS *m/z* (%): 249 (M^+,1), 128 (100), 122 (50), 121 (48), 86 (96), 43 (60).[22]

2-Iodophenyl-*N,N*-diisopropylcarbamate (2d): General procedure starting from **1a** and a 2 M solution of iodine in 2-MeTHF; purification by flash column chromatography on silica gel (PE/DEE) gave **2d** as a yellow solid (R*f* = 0.29 PE/DEE, 45 mg, 65% in CPME; 37 mg, 53% DES/CPME), mp 56.0-58.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.34 (td, *J* = 7.8, 1.6 Hz, 1H), 7.14 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.93 (td, *J* = 7.7, 1.5 Hz, 1H), 4.25 (br m, 1H), 3.92 (br m, 1H), 1.37 (d, *J* = 6.9 Hz, 6H) superimposed to 1.34 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 152.3, 151.9, 139.3, 129.3, 127.0, 123.7, 91.4, 47.1, 46.7, 21.6, 20.6. EI-MS *m/z* (%): 247 (M^+, 1), 220 (71), 128 (100), 86 (72), 43 (37).

2-(Methylthio)phenyl-*N,N*-diisopropylcarbamate (2e): General procedure starting from **1a** and dimethyldisulfide; purification by flash column chromatography on silica gel (*n*-hexane /DEE 8/2 v/v) gave **2e** as a white solid (R*f* = 0.35 *n*-hexane /DEE 8/2 v/v, 46 mg, 86 % in CPME; 25 mg, 44% in DES/CPME), mp 83.0-86.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.18 (td, *J* = 7.3, 1.6 Hz, 1H) superimposed to 7.16 (td, *J* = 7.4, 1.8 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.7 Hz, 1H), 4.14 (br s, 1H) superimposed to 3.99 (br s, 1H), 2.43 (s, 3H), 1.41-1.34 (br m, 6H) superimposed to 1.34-1.27 (br m, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 153.0, 148.6, 132.1, 126.6, 126.0, 125.8, 123.0, 46.8, 21.6, 20.6, 15.2. EI-MS *m/z* (%): 267 (M^+, 18), 140 (85), 128 (89), 86 (100), 43 (52).

2-(Trimethylsilyl)phenyl-*N,N*-diisopropylcarbamate (2f): General procedure starting from **1a** and iodotrimethylsilane; purification by flash column chromatography on neutral alumina (Brockmann grade III, *n*-hexane /DEE 9/1 v/v) gave **2f** as a white solid (R*f* = 0.22 *n*-hexane /DEE 9/1 v/v, 47 mg, 90% in CPME; 38 mg, 65% in DES/CPME), mp 96.2-98.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 7.17 (td, *J* = 7.3, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.36 (sept, *J* = 6.6 Hz, 1H), 3.74 (sept, *J* = 6.7 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.30 (d, *J* = 6.8 Hz, 6H), 0.20 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 156.4, 153.4, 135.0, 131.9, 130.5, 124.8, 122.5, 47.3, 46.0, 21.4, 20.7, -0.7. EI-MS *m/z* (%): 278 (M^+ - 15, 8), 151 (26), 128 (199), 86 (96), 43 (40).

2-Benzoylphenyl-*N,N*-diisopropylcarbamate (2g): General procedure starting from **1a** and *N*-methoxy-*N*-methylbenzamide (Weinreb amide); purification by flash column chromatography on neutral alumina (Brockmann grade III, PE/EtOAc 9/1 v/v) gave **2g** as a colourless liquid (R*f* = 0.34 PE/EtOAc 9/1 v/v, 42 mg, 65% in CPME; 42 mg, 46% DES/CPME). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85-7.81 (m, 2H), 7.55-7.47 (m, 3H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 3.85-3.73 (br m, 1H), 3.71-3.58 (br m, 1H), 1.13 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 195.4, 152.2, 149.1, 137.7, 133.0, 132.5, 131.7, 130.1, 129.9, 128.5, 125.1, 123.5, 46.8, 46.4, 21.0, 20.4. EI-MS *m/z* (%): 197 (M^+ - 198, 100), 128 (89), 86 (74), 43 (39).

*5.6.6 AoF rearrangement in CPME: synthesis and analysis of compounds **3a-b, 3d-ae***

Reactions were performed under air at room temperature. In an open screw cap vial, the appropriate carbamate **1a**, **2d-ae** (0.2 mmol, 1 eq.) was dissolved in CPME (1 mL, 0.2 M) and the mixture was vigorously stirred for 5 minutes. Unless otherwise stated, LiTMP (1 M in 2-MeTHF, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 1 minute and finally quenched with water or 1 M HCl. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na2SO4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

2-Hydroxy-*N,N*-diisopropylbenzamide (3a): General procedure starting from **1a**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3a** as a white solid (42 mg, 95%, R*f* = 0.47 PE/EtOAc 8/2 v/v), mp 159.1-163.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 7.30-7.26 (m, 1H), 7.17 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.01-6.97 (m, 1H), 6.83 (tt, *J* = 7.4, 1.1 Hz, 1H), 3.94 (br s, 2H), 1.40 (s, 6H) superimposed to 1.39 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.2, 158.2, 131.7, 126.9, 120.4, 118.7, 118.1, 49.1, 21.1. EI-MS *m/z* (%): 221(M^+, 37), 178 (44), 121 (100), 86 (95), 65 (17), 58 (27).[23]

***N,N*-Diethyl-2-hydroxybenzamide (3b)**: General procedure starting from **1b**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3b** as a white solid (33 mg, 85%, R*f* = 0.27 PE /EtOAc 8/2 v/v), mp 100.2-102.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 7.33-7.28 (m, 1H), 7.28-7.24 (m, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.5, 158.7, 132.3, 127.4, 118.5, 118.3, 118.1, 42.2, 13.5. EI-MS *m/z* (%): 193 (M^+, 40), 192 (61), 121 (100), 72 (31), 58 (33), 28 (45).[24]

2-Hydroxy-3-iodo-*N,N*-diisopropylbenzamide (3d): General procedure starting from **2d**. Purification by flash column chromatography on silica gel (PE/EtOAc 95/5 v/v) gave **3d** as a white solid (56 mg, 80 %, R*f* = 0.23 PE/EtOAc 95/5 v/v), mp 71.2-74.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.54 (br s, 1H), 7.74 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.2

Hz, 1H), 6.63 (t, *J* = 7.7 Hz, 1H), 3.87 (br s, 2H), 1.38 (s, 6H) superimposed to 1.37 (s, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 170.0, 156.3, 140.8, 127.0, 121.2, 120.7, 86.5, 49.2, 21.0. EI-MS *m/z* (%): 347 (M^+, 40), 304 (67), 247 (100), 119 (13), 92 (27), 86 (65).

2-Hydroxy-*N,N*-diisopropyl-3-(methylthio)benzamide (3e): General procedure starting from **2e**. Purification by flash column chromatography on silica gel (PE/EtOAc 85/15 v/v) gave **3e** as a white solid (28 mg, 53 %, R*f* = 0.35 PE /EtOAc 85/15 v/v), mp 53.8-57.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.32 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.06 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.86 (t, *J* = 7.7 Hz, 1H), 3.80 (br s, 2H), 2.40 (s, 3H), 1.37 (br s, 12H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 170.0, 154.1, 131.6, 125.7, 125.0, 122.3, 119.8, 48.9, 21.0, 17.3. EI-MS *m/z* (%): 267 (M^+, 91), 224 (17), 167 (100), 166 (98), 138 (75), 86 (71), 58 (22).

2-Hydroxy-*N,N*-diisopropyl-3-(trimethylsilyl)benzamide (3f): General procedure starting from **2f**. Purification by flash column chromatography on neutral alumina (Brockmann grade III, *n*-hexane/DEE 9/1 v/v) gave **3f** as a white solid (50 mg, 85%, R*f* = 0.38 *n*-hexane/DEE 9/1 v/v), mp 97.1-102.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.39 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.18 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 3.96 (br s, 2H), 1.40 (s, 6H) superimposed to 1.39 (s, 6H), 0.31 (s, 9H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 171.8, 163.2, 137.3, 128.6, 128.1, 118.8, 118.2, 49.1, 21.2, -0.9. EI-MS *m/z* (%): 293 (M^+ - 4, 23), 250 (19), 177 (100), 149 (29), 86 (35).

3-Benzoyl-2-hydroxy-*N,N*-diisopropylbenzamide (3g): General procedure starting from **2g**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3g** as a colourless liquid (20 mg, 31 %, R*f* = 0.25 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.92 (s, 1H), 7.54-7.41 (m, 5H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.84 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 1H), 3.87 (sept, *J* = 6.6 Hz, 1H), 3.45 (sept, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.7 Hz, 6H), 1.19 (d, *J* = 6.7 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 202.0, 169.3, 163.2, 139.3, 136.7, 136.5, 134.2, 130.6, 129.3, 127.7, 126.3, 119.8, 119.1, 118.2, 51.5, 46.0, 20.6, 20.3. EI-MS *m/z* (%): 325 (M^+, 33), 226 (53), 225 (100), 100 (37), 86 (23), 28 (30).

2-Hydroxy-5-iodo-*N,N*-diisopropylbenzamide (3h): General procedure starting from **2h**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3h** as a white solid (55 mg, 80%, R*f* = 0.20 PE/EtOAc 8/2 v/v), mp 186.2-188.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.48 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 3.85 (br s, 2H), 1.37 (s, 6H) superimposed to 1.36 (s, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 169.5, 156.8, 139.8, 135.1, 124.1, 120.4, 80.1, 49.2, 20.9. EI-MS *m/z* (%): 347 (M^+, 72), 304 (77), 24 (91), 246 (68), 86 (100), 58 (35), 28 (69).

***N,N*-Diethyl-2-hydroxy-3-iodobenzamide (3i)**: General procedure starting from **2i**. Purification by flash column chromatography on silica gel (PE/EtOAc 9/1 v/v) gave **3i** as a white solid (55 mg, 87%, R*f* = 0.23 PE/EtOAc 9/1 v/v), mp 78.0-82.1 °C. ^{1}H NMR (600

MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.81-7.76 (m, 1H), 7.25 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.64 (t, *J* = 7.7 Hz, 1H), 3.50 (q, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3): δ 170.7, 157.4, 141.7, 127.6, 120.4, 118.7, 86.3, 42.3, 13.5. EI-MS *m/z* (%): 319 (M^+, 75), 318 (93), 302 (18), 247 (100), 119 (14), 92 (28), 72 (23), 58 (40).[25]

5-Bromo-2-hydroxy-*N,N*-diisopropylbenzamide (3j): General procedure starting from **2j**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3j** as a white solid (53 mg, 88%, R*f* = 0.38 PE/EtOAc 8/2 v/v), mp 194.8-199.1 °C with dec. ^1H NMR (600 MHz, $CDCl_3$): δ 9.18 (br s, 1H), 7.36-7.30 (m, 1H), 7.26-7.22 (m, 1H), 6.91-6.80 (m, 1H), 3.87 (br s, 2H), 1.38 (s, 6H) superimposed to 1.37 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3): δ 169.7, 156.6, 134.2, 129.3, 122.6, 120.0, 110.6, 49.3, 21.0. EI-MS *m/z* (%): 301 (M^+, 29), 299 (M^+, 30), 258 (32), 256 (32), 201 (48), 199 (58), 86 (100), 58 (34).

5-Chloro-2-hydroxy-*N,N*-diisopropylbenzamide (3k): General procedure starting from **2k**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3k** as a white solid (32 mg, 63%, R*f* = 0.38 PE/EtOAc 8/2 v/v), mp 184.4-187.8 °C with dec. ^1H NMR (600 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.22 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.12 (d, *J* = 2.6 Hz, 1H), 6.96-6.90 (br m, 1H), 3.90 (br s, 2H), 1.39 (s, 6H) superimposed to 1.38 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3): δ 169.8, 156.0, 131.3, 126.4, 123.6, 122.2, 119.5, 49.4, 21.0. EI-MS *m/z* (%): 255 (M^+, 45), 212 (36),155 (79), 154 (45), 86 (100), 58 (33).

5-Fluoro-2-hydroxy-*N,N*-diisopropylbenzamide (3l): General procedure starting from **2l** with *s*-BuLi. Purification by flash column chromatography on silica gel (*n*-hexane/EtOAc 85/15 v/v) gave **3l** as a white solid (22 mg, 47%, R*f* = 0.15 *n*-hexane/EtOAc 85/15 v/v), mp 132.1-137.8 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 8.91 (br s, 1H), 7.03-6.95 (m, 2H), 6.88-6.83 (m, 1H), 3.90 (br s, 2H), 1.38 (s, 6H) superimposed to 1.37 (s, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3): δ 169.7, 155.3 (d, *J* = 238.5 Hz, 1C), 152.5, 122.4, 118.9 (d, *J* = 8.3 Hz, 1C), 117.7 (d, *J* = 22.6 Hz, 1C), 112.8 (d, *J* = 24.5 Hz, 1C), 49.2, 20.8. ^{19}F NMR (564 MHz, $CDCl_3$): δ -124.9 (s). EI-MS *m/z* (%): 239 (M^+, 49), 196 (39), 139 (100), 138 (54), 86 (90), 58 (32).

2-Hydroxy-*N,N*-diisopropyl-5-(trifluoromethyl)benzamide (3m): General procedure starting from **2m**. Purification by flash column chromatography on silica gel (PE/EtOAc 9/1 v/v) gave **3m** as a white solid (55 mg, 95%, R*f* = 0.20 PE/EtOAc 9/1 v/v), mp 184.6-186.6 °C with dec. ^1H NMR (600 MHz, $CDCl_3$): δ 9.93 (br s, 1H), 7.42 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.38 (d, *J* = 1.4 Hz, 1H), 6.98-6.90 (br m, 1H), 3.80 (br s, 2H), 1.37 (br s, 12H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl3): δ 170.0, 159.9, 128.3 (q, *J* = 3.1 Hz, 1C), 124.3 (q, *J* = 271.1 Hz, 1C), 124.2 (q, *J* = 4.3 Hz, 1C), 121.5, 121.0 (q, *J* = 32.8 Hz, 1C), 118.1, 49.4, 20.9. ^{19}F NMR (564 MHz, $CDCl_3$): δ -61.4 (s). EI-MS *m/z* (%): 289 (M^+, 25), 246 (58), 189 (100), 161 (27), 86 (100), 58 (27).

***N,N*-Diethyl-2-hydroxy-5-(trifluoromethyl)benzamide (3n)**: General procedure starting from **2n**. Purification by flash column chromatography on silica gel (PE /EtOAc 8/2

v/v) gave **3n** as a white solid (44 mg, 80%, R*f* = 0.18 PE/EtOAc 8/2 v/v), mp 122.9-125.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.31 (br s, 1H), 7.58-7.54 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 6H). ^{13}C {^{1}H} NMR (150 MHz, CDCl3): δ 170.4, 161.6, 129.3 (q, *J* = 4.5 Hz, 1C), 124.9 (q, *J* = 3.7 Hz, 1C), 123.3 (q, *J* = 252.3 Hz, 1C), 120.9 (q, *J* = 32.7 Hz, 1C), 118.7, 118.1, 42.6, 13.4. ^{19}F NMR (564 MHz, $CDCl_3$): δ -61.6 (s). EI-MS *m/z* (%): 261 (M^+, 50), 260 (61), 244 (20), 232 (15), 189 (100), 161 (28), 58 (61).[26]

2-Hydroxy-*N,N*-diisopropyl-6-methoxybenzamide (3o): General procedure starting from **2o**. Purification by flash column chromatography on silica gel (PE/EtOAc 6/4 v/v) gave **3o** as a white solid (33 mg, 66%, R*f* = 0.22 PE/EtOAc 6/4 v/v), mp 194.2-200.0 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (br s, 1H), 7.09 (t, *J* = 8.2 Hz, 1H), 6.54 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 3.91-3.45 (br m, 2H) superimposed to 3.77 (s, 3H), 1.81-0.89 (br m, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 167.7, 156.1, 155.9, 130.2, 114.1, 110.4, 102.2, 55.5, 51.1, 46.4, 20.7. EI-MS *m/z* (%): 251 (M^+, 22), 234 (15), 208 (42), 151 (100), 150 (34), 86 (56).[16]

2-Hydroxy-*N,N*-diisopropyl-5-methoxybenzamide (3p): General procedure starting from **2p**. Purification by flash column chromatography on silica gel (PE/EtOAc 6/4 v/v) gave **3p** as a white solid (37 mg, 73%, R*f* = 0.30 PE/EtOAc 6/4 v/v), mp 124.1-125.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (s, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.84 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.69 (d, *J* = 3.0 Hz, 1H), 3.92 (br s, 2H), 3.75 (s, 3H), 1.39 (br s, 6H) superimposed to 1.38 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.7, 152.0, 151.2, 121.5, 118.7, 117.4, 111.8, 56.0, 49.1, 21.1. EI-MS *m/z* (%): 251 (M^+, 49), 209 (21), 151 (39), 150 (100), 149 (30), 86 (31).[14]

***N,N*-Diethyl-2-hydroxy-5-methoxybenzamide (3q)**: General procedure starting from **2q**. Purification by flash column chromatography on silica gel (PE/EtOAc 6/4 v/v) gave **3q** as a yellow solid (27 mg, 61%, R*f* = 0.25 PE/EtOAc 6/4 v/v), mp 94.4-97.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.94 (br s, 1H), 6.94-6.89 (m, 2H), 6.79 (d, *J* = 2.8 Hz, 1H), 3.76 (s, 3H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.2, 152.3, 151.8, 118.9, 118.7, 118.4, 112.3, 56.0, 42.2, 13.5. EI-MS *m/z* (%): 223 (M^+, 67), 151 (56), 150 (100), 107 (12), 72 (37), 58 (16).[7]

2-Hydroxy-*N,N*-diisopropyl-5-(methylthio)benzamide (3r): General procedure starting from **2r**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3r** as a white solid (42 mg, 75%, R*f* = 0.28 PE/EtOAc 8/2 v/v), mp 143.1-147.5 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.25 (br s, 1H), 7.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.13-7.02 (m, 2H), 3.86 (br s, 2H), 2.43 (s, 3H), 1.34 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.6, 155.6, 132.5, 127.4, 126.9, 121.4, 118.8, 49.4, 20.9, 18.4. EI-MS *m/z* (%): 267 (M^+, 47), 225 (16), 167 (28), 166 (100), 165 (25), 86 (31).

3-(Diisopropylcarbamoyl)-4-hydroxyphenyl diisopropylcarbamate (3s): General procedure starting from **2s**. Purification by flash column chromatography on silica gel (PE/EtOAc 7/3 v/v) gave **3s** as a white solid (56 mg, 77%, R*f* = 0.25 PE/EtOAc 7/3 v/v), mp 162.1-166.3 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.14 (br s, 1H), 7.02 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.01-6.98 (m, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 4.32-3.68 (br m, 4H), 1.41-1.19 (br m, 24H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.6, 154.4, 154.1, 143.0, 125.0, 120.1, 119.9, 118.4, 49.6, 47.2, 46.1, 21.7, 20.9, 20.6. EI-MS *m/z* (%): 364 (M^+, 19), 195 (9), 135 (14), 128 (66), 86 (100), 43 (39).

2-Hydroxy-*N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (3t): General procedure starting from **2t**. Purification by flash column chromatography on silica gel (PE/EtOAc 95/5 v/v) gave **3t** as a white solid (48 mg, 81%, R*f* = 0.20 PE/EtOAc 95/5 v/v), mp 99.4-102.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.58 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.37-7.33 (m, 2H), 7.17 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.93 (t, *J* = 7.7 Hz, 1H), 3.96 (br s, 2H), 1.42 (s, 6H) superimposed to 1.40 (s, 6H). ^{13}C {^{1}H} NMR (150 MHz, CDCl3): δ 171.2, 154.5, 137.8, 132.4, 130.7, 129.5, 128.4, 127.4, 126.2, 121.4, 118.9, 49.2, 21.1. EI-MS *m/z* (%): 297 (M^+, 40), 254 (39), 197 (100), 196 (44), 168 (31), 139 (22), 115 (20), 86 (46).

4-Hydroxy-*N,N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (3u): General procedure starting from **2u**. Purification through trituration with DEE gave **3u** as a white solid (56 mg, 95%), mp 163.2-164.5 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.27 (br s, 1H), 7.53 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.52-7.48 (m, 2H), 7.46-7.39 (m, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.15-7.04 (br m, 1H), 4.00 (br s, 2H), 1.41 (br s, 12H). ^{13}C {^{1}H} NMR (150 MHz, CDCl3): δ 171.1, 157.5, 140.5, 131.9, 130.4, 129.0, 127.0, 126.6, 125.4, 120.6, 118.5, 49.3, 21.1. EI-MS *m/z* (%): 297 (M^+, 61), 254 (18), 197 (64), 196 (100), 139 (30), 86 (54).

***N,N*-Diethyl-4-hydroxy-[1,1'-biphenyl]-3-carboxamide (3v)**: General procedure starting from **2v**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3v** as a white solid (36 mg, 66%, R*f* = 0.15 PE/EtOAc 8/2 v/v), mp 151.8-155.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.72 (br s, 1H), 7.56 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.52-7.49 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.33 (tt, *J* = 7.1, 1.2 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 3.58 (q, *J* = 7.1 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.5, 158.3, 140.5, 131.9, 131.1, 129.1, 127.1, 126.7, 126.0, 118.5, 118.5, 42.4, 13.6. EI-MS *m/z* (%): 269 (M^+, 97), 268 (44), 197 (75), 196 (100), 168 (19), 139 (31), 115 (22), 72 (45).[26]

3-Hydroxy-*N,N*-diisopropyl-2-naphthamide (3w): General procedure starting from **2w**. Purification through trituration with DCM gave **3u** as a white solid (53 mg, 98%), mp 256.2-259.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.74 (br s, 1H), 7.73(d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.45 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.38 (br s, 1H), 7.32 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 3.96 (br s, 2H), 1.38 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.9, 153.4, 135.6, 128.3, 127.6, 127.2, 126.8, 126.6, 124.0, 123.2, 112.2, 49.7, 20.9, 20.8. EI-MS *m/z* (%): 271 (M^+, 60), 228 (23), 171 (69), 170 (100), 142 (37), 115 (45).

1-Hydroxy-*N,N*-diisopropyl-2-naphthamide (3x): General procedure starting from **2x**. The crude material was dissolved in EtOAc and purified by acid-base extraction with 1 M NaOH (5 x 5 mL) and 1 M HCl to give **3x** as a white solid (41 mg, 75%), mp 97.3-99.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.2 Hz, 1H), 7.75 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.56-7.48 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 3.99 (br s, 2H), 1.42 (s, 6H) superimposed to 1.41 (s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.3, 156.7, 135.2, 128.1, 127.3, 125.7, 125.7, 123.6, 123.5, 117.7, 112.4, 49.2, 21.2.

***Tert*-butyl 3-(*N,N*-diisopropylcarbamoyl)-4-hydroxybenzoate (3y)**: General procedure starting from **2y**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3y** as a white solid (33 mg, 52%, R*f* = 0.37 PE/EtOAc 8/2 v/v), mp 199.5-202.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.26 (br s, 1H), 7.92-7.89 (m, 2H), 6.98 (br d, *J* = 8.4 Hz, 1H), 3.94 (br s, 2H), 1.57 (s, 9H), 1.40 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.7, 165.2, 162.5, 133.2, 129.3, 122.4, 119.1, 117.9, 81.0, 49.5, 28.4, 21.1. EI-MS *m/z* (%): 321 (M^+, 31), 278 (29), 248 (18), 222 (46), 165 (64), 147 (27), 86 (100).

(*E*)-2-Hydroxy-*N,N*-diisopropyl-5-styrylbenzamide (3z): General procedure starting from **2z**. Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3z** as a white solid (47 mg, 73%, R*f* = 0.20 PE/EtOAc 8/2 v/v), mp 212.5-215.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.26 (br s, 1H), 7.51-7.47 (m, 2H) superimposed to 7.46 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.39-7.33 (m, 2H), 7.30 (d, *J* = 2.2 Hz, 1H), 7.25 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.01 (d, *J* = 16.3 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 16.3 Hz, 1H), 3.96 (br s, 2H), 1.43 (br s, 6H) superimposed to 1.42 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.0, 157.6, 137.5, 129.4, 128.8, 128.4, 128.0, 127.6, 127.1, 126.4, 125.2, 120.9, 118.4, 49.2, 21.1. EI-MS *m/z* (%): 323 (M^+, 26), 196 (67), 165 (26), 128 (85), 86 (100), 43 (43).

2-Hydroxy-*N,N*-diisopropyl-5-(phenylethynyl)benzamide (3aa): General procedure starting from **2aa** . Purification by flash column chromatography on silica gel (PE/EtOAc 8/2 v/v) gave **3aa** as a white solid (50 mg, 75%, R*f* = 0.28 PE/EtOAc 8/2 v/v), mp 100.6-104.7 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.55 (br s, 1H), 7.52-7.49 (m, 2H), 7.42 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.36-7.31 (m, 4H), 6.96 (d, *J* = 8.5 Hz, 1H), 3.92 (br s, 2H), 1.40 (br s, 6H) superimposed to 1.39 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.3, 157.3, 134.6, 131.6, 130.2, 128.5, 128.2, 123.5, 121.7, 118.1, 113.7, 89.1, 88.1, 49.2, 21.0. EI-MS *m/z* (%): 321 (M^+, 52), 279 (16), 220 (100), 163 (26), 86 (26).

5-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-hydroxy-*N,N*-diisopropylbenzamide (3ab): General procedure starting from **2ab**. Purification by flash column chromatography on silica gel (DEE/PE 1/1 v/v + Et_3N 0.5 %) gave **3ab** as a white solid (44 mg, 66%, R*f* = 0.10, DEE/PE 1/1 v/v + Et_3N 0.5 %), mp 197.3-202 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.47 (br s, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 3.96 (br s, 2H), 3.74 (d, *J* = 11.3 Hz, 2H), 3.63 (d, *J* = 11.1 Hz, 2H), 1.46-1.33 (br m, 12H), 1.28 (s, 3H), 0.79 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.1, 159.1,

130.0, 129.0, 125.2, 119.5, 117.9, 101.4, 77.8, 49.0, 46.2, 30.3, 23.1, 22.0, 21.1. EI-MS *m/z* (%): 335 (M^+, 37), 292 (65), 235 (79), 206 (25), 149 (37), 86 (100).

2-Hydroxy-*N,N*-diisopropyl-5-(phenylselanyl)benzamide (3ac): General procedure starting from **2ac**. Purification by trituration of the crude reaction mixture with DEE gave **3ac** as a white solid (73 mg, 97%), mp 180.5-182.5 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.49 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.38-7.32 (m, 3H), 7.25-7.18 (m, 3H), 6.94 (d, *J* = 8.6 Hz, 1H), 3.82 (br s, 2H), 1.31 (br s, 12H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.3, 158.3, 138.1, 133.6, 133.0, 131.6, 129.4, 127.0, 121.5, 119.2, 118.5, 49.3, 21.0. EI-MS *m/z* (%): 376 (M^+, 9), 335 (15), 276 (100), 220 (32), 196 (26), 86 (68).

5-(1-(Dimethylamino)ethyl)-*N*-ethyl-2-hydroxy-*N*-methylbenzamide (3ad): General procedure starting from commercially available Rivastigmine. Purification by flash column chromatography on silica gel (DCM/methanol 9/1 v/v) gave **3ad** as a colourless liquid (12 mg, 24%, R*f* = 0.17 DCM/methanol 91/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.55 (q, *J* = 7.3 Hz, 2H), 3.20 (q, *J* = 6.7 Hz, 1H), 3.11 (s, 3H), 2.20 (s, 6H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ. 171.7, 159.0, 149.2, 128.2, 117.7, 117.0, 116.6, 65.8, 44.8, 43.3, 35.8, 19.9, 12.9.

5-acetamido-2-hydroxy-*N,N*-diisopropylbenzamide (3ae): General procedure starting from **2ae** using *s*-BuLi and 2-MeTHF as solvent. Purification by flash column chromatography on silica gel (DCM/methanol 95/5 v/v) gave **3ae** as a white solid (27 mg, 48%, R*f* = 0.25 DCM/methanol 95/5 v/v), mp 235.0-239.0 °C. ^{1}H NMR (600 MHz, CD_3OD): δ 7.37-7.33 (m, 1H), 7.31-7.28 (m, 1H), 6.78 (dd, *J* = 8.7, 1.2 Hz, 1H), 3.72 (br s, 2H), 2.08 (s, 3H), 1.48 (br s, 6H) superimposed to 1.21 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CD_3OD): δ 171.4, 171.2, 151.1, 132.1, 127.1, 123.3, 120.2, 116.7, 52.9, 47.1, 23.6, 20.8. EI-MS *m/z* (%): 278 (M^+, 81), 236 (26), 178 (73), 177 (100), 135 (69), 86 (91), 58 (31), 43 (30).

*5.6.7 Regioselective 1,3-anionic migration: synthesis and analysis of compounds **5a**, **5c-g***

Reactions were performed under air at room temperature. In an open screw cap vial, the selected carbamates **2a**, **4c-g** (0.2 mmol, 1.0 eq.) were dissolved in CPME (1 mL, 0.2 M) and the mixture was vigorously stirred for 5 minutes. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 1 minute and finally quenched with water or 1 M HCl. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na2SO4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

2-Hydroxy-*N,N*-diisopropyl-3-methylbenzamide (5a): General procedure starting from **2a**. Purification by flash column chromatography on silica gel (PE/acetone 95/5 v/v) gave **5a** as a white solid (41 mg, 88%, R*f* = 0.35 PE/acetone 95/5 v/v), mp 90.8-92.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 3.95 (br s, 2H), 2.27 (s, 3H), 1.39 (br s, 6H) superimposed to 1.37 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.7, 156.3, 132.8, 127.2, 124.4, 119.6, 118.1, 49.1, 21.1, 16.2. EI-MS *m/z* (%): 235 (M^+, 50), 192 (32), 135 (100), 106 (18), 86 (88), 77 (30), 58 (26).[27]

2-Hydroxy-*N,N*-diisopropyl-3,5-dimethylbenzamide (5c): General procedure starting from **4c**. Purification by flash column chromatography on silica gel (PE /EtOAc 9/1 v/v) gave **5c** as a white solid (27 mg, 50%, R*f* = 0.43 PE /EtOAc 9/1 v/v), mp 101.5-106.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.93 (s, 1H), 6.97 (br s, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 3.94 (br s, 2H), 2.23 (s, 3H) superimposed to 2.23 (s, 3H), 1.39 (br s, 6H) superimposed to 1.38 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.7, 153.8, 133.5, 127.1, 126.8, 124.4, 119.8, 49.1, 21.1, 20.7, 16.1. EI-MS *m/z* (%): 249 (M^+, 65), 206 (21), 149 (93), 148 (100), 120 (31), 91 (30), 86 (83).

2-Hydroxy-*N,N*-diisopropyl-3-methyl-5-(trifluoromethyl)benzamide (5d): General procedure starting from **4d** . Purification by flash column chromatography on silica gel (PE /DEE 95/5 v/v) gave **5d** as a white solid (45 mg, 78%, R*f* = 0.28 PE /DEE 95/5 v/v), mp 163.4-166.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.39 (br s, 1H), 7.30 (br s, 1H), 3.91 (br s, 2H), 2.29 (s, 3H), 1.41 (br s, 6H) superimposed to 1.40 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 170.6, 159.4, 129.3 (q, *J* = 3.0 Hz, 1C), 128.3, 124.4 (q, *J* = 271.4 Hz, 1C), 121.9 (q, *J* = 4.4 Hz, 1C), 120.3 (q, *J* = 32.6 Hz, 1C), 119.0, 49.4, 21.1, 16.2. ^{19}F NMR (564 MHz, $CDCl_3$): δ -61.52 (s). EI-MS *m/z* (%): 303 (M^+, 38), 260 (46), 203 (100), 127 (21), 86 (96), 58 (28).

4-Hydroxy-*N,N*-diisopropyl-5-methyl-[1,1'-biphenyl]-3-carboxamide (5e): General procedure starting from **4e**. Purification by flash column chromatography on silica gel (PE/acetone 98/2 v/v) gave **5e** as a white solid (37 mg, 60%, R*f* = 0.15 PE/acetone 98/2 v/v), mp 153-156 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.52-7.48 (m, 2H), 7.44-7.39 (m, 3H), 7.31 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.27-7.25 (m, 1H), 4.02 (br s, 2H), 2.33 (s, 3H), 1.43 (br s, 6H) superimposed to 1.41 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.6, 156.0, 140.8, 131.5, 131.3, 129.0, 127.5, 126.9, 126.7, 123.0, 119.9, 49.2, 21.2, 16.3. EI-MS *m/z* (%): 311 (M^+, 48), 269 (13), 211 (39), 210 (100), 182 (18), 153 (18), 86 (26).

5-Chloro-2-hydroxy-*N,N*-diisopropyl-3-methylbenzamide (5f): General procedure starting from **4f**. Purification by flash column chromatography on silica gel (PE/DEE 9/1 v/v) gave **5f** as a white solid (25 mg, 46%, R*f* = 0.15 PE/DEE 9/1 v/v), mp 137.2-141.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.13-7.11 (m, 1H), 6.97 (d, *J* = 2.6 Hz, 1H), 3.91 (br s, 2H), 2.23 (s, 3H), 1.39 (br s, 6H) superimposed to 1.38 (br s, 6H). ^{13}C{^{1}H} NMR (150

MHz, CDCl3): δ 170.3, 154.9, 132.3, 129.3, 123.9, 122.9, 120.8, 49.3, 21.1, 16.1. EI-MS *m/z* (%): 269 (M^+, 67), 226 (27), 169 (80), 168 (86), 86 (100), 77 (32), 58 (30).

2-Hydroxy-*N,N*-diisopropyl-3-methyl-5-(methylthio)benzamide (5g): General procedure starting from **4g**. Purification by flash column chromatography on silica gel (PE/EtOAc 9/1 v/v) gave **5g** as a white solid (35 mg, 62%, R*f* = 0.40 PE/EtOAc 9/1 v/v), mp 131.1-132.9 °C with dec. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.17-7.16 (m, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 3.93 (br s, 2H), 2.42 (s, 3H), 2.24 (s, 3H), 1.39 (br s, 6H) superimposed to 1.38 (br s, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.0, 155.1, 133.7, 128.2, 126.1, 125.2, 120.3, 49.3, 21.1, 18.5, 16.1. EI-MS *m/z* (%): 281 (M^+, 39), 239 (10), 180 (100), 86 (14).

*5.6.8 Regioselective 1,4-anionic migration: synthesis and analysis of compounds **6a-g***

Reactions were performed under air at room temperature. In an open screw cap vial, the appropriate carbamate **2a**, **4b-g** (0.2 mmol, 1 eq.) was dissolved in CPME (0.3 mL), then ChCl/Gly 1:2 (1 g) was added and the resulting mixture was vigorously stirred for 5 minutes. LiTMP (1 M in 2-MeTHF, 2 eq., 0.4 mmol) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched with water or 1 M HCl after 1 min. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na2SO4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

2-(2-Hydroxyphenyl)-*N,N*-diisopropylacetamide (6a): General procedure starting from **2a**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6a** as a white solid (38 mg, 80%, R*f* = 0.21 PE/EtOAc 9/1 v/v), mp 159.0-162.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.92 (br s, 1H), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.81 (td, *J* = 7.4, 1.3 Hz, 1H), 4.24 (br s, 1H), 3.75 (s, 2H) superimposed to 3.59 (br s, 1H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.24 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.8, 157.4, 130.2, 129.0, 121.3, 120.0, 118.2, 46.9, 50.5, 38.9, 21.2, 20.5. EI-MS *m/z* (%): 235 (M^+, 51), 128 (18), 107 (37), 86 (100), 77 (24), 43 (48).

2-(2-Hydroxy-3-methoxyphenyl)-*N,N*-diisopropylacetamide (6b): General procedure starting from **4b**. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **6b** as a yellow solid (42 mg, 80%, R*f* = 0.22 PE/EtOAc 8/2 v/v), mp 151.5-154.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 6.80-6.77 (m, 2H), 6.74-6.70 (m, 1H), 4.20-4.08 (br m, 1H), 3.88 (s, 3H), 3.70 (s, 2H), 3.51 (br s, 1H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.16 (d, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 171.6, 148.4, 145.3, 122.1, 121.9, 119.6, 110.4, 64.5, 58.5, 56.1, 49.7, 46.4, 37.8, 25.4, 21.0, 20.6, 18.5. EI-MS *m/z* (%): 265 (M^+, 45), 164 (18), 137 (27), 86 (100), 43 (35).

2-(2-Hydroxy-5-methylphenyl)-*N,N*-diisopropylacetamide (6c): General procedure starting from **4c**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6c** as a white solid (43 mg, 86%, R*f* = 0.28 PE/EtOAc 9/1 v/v), mp 163.5-166.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.0 (br s, 1H), 6.96 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 4.24 (br s, 1H), 3.67 (s, 2H) superimposed to 3.61 (br s, 1H), 2.25 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.26 (d, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.7, 155.1, 130.7, 129.4, 129.0, 121.2, 118.0, 50.0, 46.7, 39.0, 21.3 20.5. EI-MS *m/z* (%): 249 (M^+, 53), 148 (16), 121 (30), 86 (100), 43 (33).

2-(2-Hydroxy-5-(trifluoromethyl)phenyl)-*N,N*-diisopropylacetamide (6d): General procedure starting from **4d**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6d** as a white solid (43 mg, 75%, R*f* = 0.33 PE/EtOAc 9/1 v/v), mp 150.1-152.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.01 (br s, 1H), 7.42 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.27-7.24 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 4.21 (br s, 1H), 3.75 (s, 2H) superimposed to 3.65 (br s, 1H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.1, 160.7, 127.4 (q, *J* = 3.0 Hz, 1C), 126.3 (q, *J* = 4.3 Hz, 1C), 124.6 (q, *J* = 270.7, 1C), 121.8 (q, *J* = 32.9 Hz, 1C), 121.7, 118.5, 50.4, 47.0, 38.9, 21.3, 20.5. ^{19}F NMR (564 MHz, $CDCl_3$): δ -61.12 (s). EI-MS *m/z* (%): 303 (M^+, 30), 260 (15), 175 (27), 128 (19), 86 (100), 43 (48).

2-(4-Hydroxy-[1,1'-biphenyl]-3-yl)-*N,N*-diisopropylacetamide (6e): General procedure starting from **4e**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6e** as a white solid (54 mg, 87%, R*f* = 0.18 PE/EtOAc 9/1 v/v), mp 189.3-192.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.40 (br s, 1H), 7.53-7.49 (m, 2H), 7.44-7.38 (m, 3H), 7.32-7.28 (m, 1H), 7.25-7.22 (m, 1H), 7.07-7.03 (m, 1H), 4.29 (br s, 1H), 3.79 (s, 2H) superimposed to 3.64 (br s, 1H), 1.36 (d, *J* = 6.9 Hz, 6H), 1.29 (d, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.6, 157.2, 141.1, 133.2, 129.0, 128.8, 127.8, 126.8, 126.7, 121.7, 118.6, 50.1, 46.8, 39.2, 21.4, 20.5. EI-MS *m/z* (%): 311 (M^+, 42), 293 (33), 210 (46), 182 (37), 153 (25), 86 (100).

2-(5-Chloro-2-hydroxyphenyl)-*N,N*-diisopropylacetamide (6f): General procedure starting from **4f**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6f** as a white solid (38 mg, 70%, R*f* = 0.25 PE/EtOAc 9/1 v/v), mp 155.0-157.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.44 (br s, 1H), 7.11 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.18 (br s, 1H), 3.67 (s, 2H) superimposed to 3.67 (br s, 1H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.28 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 172.1, 156.3, 129.8, 128.8, 124.3, 123.0, 119.6, 49.9, 46.9, 38.6, 21.4, 20.5. EI-MS *m/z* (%): 269 (M^+, 39), 226 (12), 141 (21), 86 (100), 77 (20), 43 (41).

2-(2-Hydroxy-5-(methylthio)phenyl)-*N,N*-diisopropylacetamide (6g): General procedure starting from **4g**. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **6g** as a white solid (47 mg, 83%, R*f* = 0.15 PE/EtOAc 9/1 v/v), mp 176.6-178.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.33 (br s, 1H), 7.18 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.04 (d, *J*

= 2.4 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.21 (br s, 1H), 3.68 (s, 2H) superimposed to 3.63 (br s, 1H), 2.42 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 6H), 1.26 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 172.4, 156.4, 131.8, 130.3, 127.5, 122.2, 119.1, 49.9, 46.8, 38.9, 21.4, 20.5, 18.9. EI-MS *m/z* (%): 281 (M^+, 53), 180 (87), 152 (64), 86 (100), 43 (30).

*5.6.9 Synthesis and analysis of deuterated compounds **o-D-1a** and **o-D-2r***

2-Deuteriophenyl-*N,N*-diisopropylcarbamate (*o*-D-1a): In an open screw cap vial under air, phenyl-*N,N*-diisopropylcarbamate **1a** (0.2 mmol, 1 eq., 44 mg) was dissolved in CPME (1 mL, 0.2 M) and the resulting mixture was vigorously stirred for 5 minutes at 0 °C. *s*-BuLi (1.4 M in cyclohexane, 0.4 mmol, 2 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring and quenched by addition of CD_3OD (1 mmol, 5 eq., 46 µL) after 2 seconds. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (PE/EtOAc 95/5 v/v) gave ***o*-D-1a** (95% D incorporation) as a colourless liquid (27 mg, 61 %, R*f* = 0.33 PE/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.33 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 4.11 (br s, 1H) superimposed to 3.94 (br s, 1H), 1.47-1.19 (br m, 12H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 154.0, 151.5, 129.3, 129.2, 125.1, 122.0, 121.7 (t, *J* = 24.5 Hz, 1C), 47.0, 46.1, 21.7, 20.6. ^{2}H NMR (92.07 MHz, CH_2Cl_2) δ 7.13 (s). EI-MS *m/z* (%): 222 (M^+, 2), 128 (98), 95 (62), 94 (53), 86 (100), 43 (59), 28 (44).

2-Deuterio-4-(methylthio)phenyl-*N,N*-diisopropylcarbamate (*o*-D-2r): In an open screw cap vial, 4-(methylthio)phenyl-*N,N*-diisopropylcarbamate **2r** (0.2 mmol, 1 eq., 53 mg) was dissolved in CPME (1 mL,) and the resulting mixture was vigorously stirred for 5 minutes. LiTMP (1 M in 2-MeTHF, 2 eq., 0.4 mmol) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of CD_3OD (1 mmol, 5 eq., 46 µL) after 2 seconds. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography on silica gel (PE/DEE 8/2 v/v) gave ***o*-D-2r** (81% D incorporation) as a colourless liquid (39 mg, 73%, R*f* = 0.42 PE/DEE 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2H), 7.07-7.03 (m, 1H), 4.09 (br s, 1H) superimposed to 3.94 (br s, 1H), 2.46 (s, 3H), 1.42-1.12 (br m, 12H). $^{13}C\{^{1}H\}$ NMR (150 MHz, CDCl3): δ 153.9, 149.4, 134.5, 128.5, 128.4, 122.5, 122.2 (t, *J* = 24.7 Hz, 1C), 47.0, 46.2, 21.7, 20.6, 17.1. ^{2}H NMR (92.07 MHz, CH_2Cl_2) δ 7.08 (s). EI-MS *m/z* (%): 268 (M^+,24), 141 (87), 128 (88), 68 (100), 43 (61), 28 (83).

References

1. M. Korb and H. Lang, *Chem. Soc. Rev.*, 2019, **48**, 2829-2882.
2. J. C. Riggs, K. J. Singh, M. Yun and D. B. Collum, *J. Am. Chem. Soc.*, 2008, **130**, 13709-13717.
3. J. Clayden, Y. J. Foricher and H. K. Lam, *Eur. J. Org. Chem.*, 2002, **2002**, 3558-3565.
4. J. S. Birks and J. G. Evans, *Cochrane Database Syst. Rev.*, 2015.
5. M. Emre, D. Aarsland, A. Albanese, E. J. Byrne, G. Deuschl, P. P. De Deyn, F. Durif, J. Kulisevsky, T. van Laar and A. Lees, *N. Engl. J. Med.*, 2004, **351**, 2509-2518.
6. M. Jóźwiak-Bebenista and J. Z. Nowak, *Acta Pol. Pharm.*, 2014, **71**, 11-23.
7. M. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni and V. Snieckus, *Eur. J. Org. Chem.*, 2018, **2018**, 440-446.
8. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879-1880.
9. W. Xiong, C. Qi, T. Guo, M. Zhang, K. Chen and H. Jiang, *Green Chem.*, 2017, **19**, 1642-1646.
10. D. Göbel, N. Clamor, E. Lork and B. J. Nachtsheim, *Org. Lett.*, 2019, **21**, 5373-5377.
11. K. Nakamura, K. Yasui, M. Tobisu and N. Chatani, *Tetrahedron*, 2015, **71**, 4484-4489.
12. M. Tobisu, K. Yasui, Y. Aihara and N. Chatani, *Angew. Chem. Int. Ed.*, 2017, **129**, 1903-1906.
13. D. J. Gale, J. Rosevear and J. F. Wilshire, *Aust. J. Chem.*, 1995, **48**, 997-1007.
14. J. Clayden, M. Helliwell, C. McCarthy and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3232-3249.
15. K. J. Singh, A. C. Hoepker and D. B. Collum, *J. Am. Chem. Soc.*, 2008, **130**, 18008-18017.
16. Y. Ma, R. A. Woltornist, R. F. Algera and D. B. Collum, *J. Org. Chem.*, 2019, **84**, 9051-9057.
17. K. Yamazaki, S. Kawamorita, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2010, **12**, 3978-3981.
18. V. Pace, L. Castoldi, A. R. Alcantara and W. Holzer, *Green Chem.*, 2012, **14**, 1859-1863.
19. P. Iqbal, K. Critchley, J. Bowen, D. Attwood, D. Tunnicliffe, S. D. Evans and J. A. Preece, *J. Mater. Chem.*, 2007, **17**, 5097-5110.
20. W. Conrad, B. Gesner, L. Levasseur, R. Murphy and H. Conrad, *J. Org. Chem.*, 1961, **26**, 3571-3574.
21. N. Taniguchi, *J. Org. Chem.*, 2007, **72**, 1241-1245.
22. B. D. Barve, Y.-C. Wu, M. El-Shazly, D.-W. Chuang, Y.-B. Cheng, J.-J. Wang and F.-R. Chang, *J. Org. Chem.*, 2014, **79**, 3206-3214.
23. V. S. Thirunavukkarasu, J. Hubrich and L. Ackermann, *Org. Lett.*, 2012, **14**, 4210-4213.
24. N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita and M. Uchiyama, *J. Am. Chem. Soc.*, 2016, **138**, 9166-9171.
25. C.-W. Chang and R.-J. Chein, *J. Org. Chem.*, 2011, **76**, 4154-4157.
26. H. J. Lo, C. Y. Lin, M. C. Tseng and R. J. Chein, *Angew. Chem. Int. Ed.*, 2014, **53**, 9026-9029.
27. S. Essig and D. Menche, *J. Org. Chem.*, 2016, **81**, 1943-1966.

CHAPTER 6: Fast and general route to ketones from amides and organolithiums compounds under aerobic conditions

Part of the results presented in this chapter are published in *Chem. Eur. J.* **2021**, 27, 2868-2874.

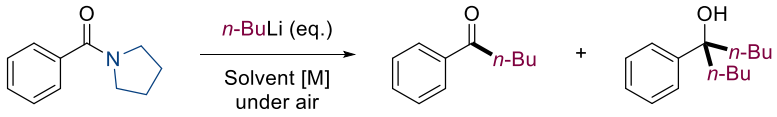
During our investigations on the *ortho*-metalation of hindered benzamides under bench conditions (protic solvent, in presence of air and moisture), we observed that the replacement of *t*-BuLi with easier-to-handle and less pyrophoric alkyllithiums led to the chemoselective formation of the corresponding aromatic ketones alongside with moderated quantities of the tertiary alcohol derived from the notorious over-addition process (ratios up to 88:12). Excited by the experimental evidence of the active role of DES in the stabilization of the tetrahedral intermediate (see paragraph 3.3), and motivated by our ongoing interest towards the still actual synthetic relevance of the preparation of ketones from amides (see paragraph 1.3), a systematic study has been undertaken in order to develop an easy and scalable methodology to performing the chemoselective synthesis of ketones from amides using polar organometallic reagents under our environmentally friendly bench conditions.

6.1 Optimization of the reaction conditions

We started our investigations focusing on the reactivity of the simple amide *N*-benzoylpirrolidine **1a** towards *n*-BuLi under various reaction conditions. In a preliminary experiment, amide **1a** (0.2 mmol) was dissolved in CPME (0.2 M, 1.0 mL) and reacted with *n*-BuLi (2 eq.) at 0 °C under air (Table 6.1, entry 1). Quenching the reaction after a very short time (20 s) by dilution with water, complete conversion, an impressive chemoselectivity (**2a**:**3a**, 94:6) and a good valerophenone **2a** yield (83%) were observed. An increase of **2a** yield was observed when the reaction was run at room temperature (Table 6.1, entry 2). The amount of CPME was lowered up to 0.5 M without any decrease in terms of conversion (Table 6.1, entry 3), while a further increase of concentration led to an uncompleted conversion (Table 6.1, entry 4 and 5). A possible reason for these results may be ascribed to the increase of hexane amount in the reaction mixture, arising from the stock solution of *n*-BuLi. Running the reaction in pure hexane led, in fact, to a considerable decrease of conversion and chemoselectivity (Table 6.1, entry 6), whereas using a CPME solution of *n*-BuLi no significant changes were observed (Table 6.1, entry 7). Lowering the organolithium from 2 to 1 eq. led to a moderate

decrease in terms of yield and conversion, while chemoselectivity remains unchanged (Table 6.1, entries 8-10). To evaluate the benefit of use CPME as solvent to promote this transformation, other common ethereal solvents were screened. Generally, all ethereal solvents gave very good results in term of conversion, **2a** yield and chemoselectivity, except for DEE because its low boiling point (Table 6.1, entries 11-15). CPME was thus selected as privileged ethereal reaction medium due to its eco-friendly features (see paragraph 2.2), thermal stability and ease of recycling (*vide infra*).

Table 6.1. Nucleophilic acyl substitution promoted by *n*-BuLi and *N*-benzoylpirrolidine **1a** under different reaction conditions.



1a **2a** **3a**

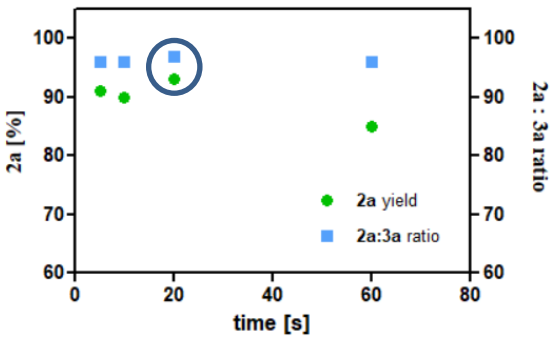
Entry	Solvent [M]	*n*-BuLi (eq.)	Conv. (%)[d]	**2a**:**3a** ratio[d]	**2a** yield (%)[e]
1[a],[b]	CPME [0.2]	2	100	94:6	83
2[a]	CPME [0.2]	2	100	95:5	94
3[a]	CPME [0.5]	2	100	97:3	93
4[a]	CPME [1.0]	2	97	95:5	91
5[a]	CPME [2.0]	2	96	92:8	72
6[a]	Hexane [0.5]	2	88	82:18	71
7[a]	CPME [0.5]	2[f]	100	96:4	83
8[a]	CPME [0.5]	1	69	96:4	63
9[a]	CPME [0.5]	1.2	89	96:4	78
10[a]	CPME [0.5]	1.5	97	97:3	83
11[a]	DEE [0.5]	2	100	92:8	88
12[a]	DME [0.5]	2	100	95:5	89
13[a]	TBME [0.5]	2	100	95:5	90
14[a]	2-MeTHF [0.5]	2	100	96:4	89
15[a]	1,4-Dioxane [0.5]	2	100	95:5	88
16[a]	Glycerol [0.5]	2	5	-	-
17[a]	H_2O [0.5]	2	13	50:50	4
18[c]	CPME, ChCl/Gly 1:2	2	67	95:5	62

[a] Reaction conditions: **1a** (0.2 mmol), solvents (DEE = diethyl ether, DME = 1,2-dimethoxyethane, TBME = *tert*-butyl methyl ether), *n*-BuLi (2.5 M in hexanes), at room temperature, under air. Quench with water after 20 seconds. [b] T = 0 °C. [c] Same reaction conditions but under heterogeneous conditions: CPME (0.2 mL, 1 M), ChCl/Gly 1:2 (1 g). [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [f] *n*-BuLi 1.9 M in CPME was used.

On the contrary, the use of protic reaction media such as glycerol (Gly) or water had a dramatic impact on the reaction outcomes, and no significative amounts of **2a** were detected in the reaction crude (Table 6.1, entries 16-17). According to our previous investigations on the possibility to use DESs as solvents to promote the S_NAc of hindered amides, **1a** was dissolved in a CPME (0.2 mL, 1 M)/ChCl/Gly 1:2 (1 g) mixture under vigorous stirring in order to create an emulsion, and then reacted with *n*-BuLi (2 eq.) (Table 6.1, entry 18). Quenching the reaction with water after 20 seconds led to a moderate recover of **2a** (62%) due to an incomplete conversion of **1a** (68%), while the chemoselectivity remains impressively high (95:5) despite the use of a protic reaction media. This result confirms our previously discussed hypothesis (paragraph 1.3): the DES is able to stabilize tetrahedral intermediates, however an incomplete conversion of the starting material due to the competitive protonolysis of the organolithiums makes homogenous conditions necessary to obtain the desired ketones in a quantitative fashion, with a resulting increase of the environmental benefit of the methodology (*vide infra*).

To summarise, the S_NAc of benzamide **1a** *en route* to ketone **2a** proceed very fast (20 s, Figure 6.1 a), in 0.2-1 M as optimal concentration range (Figure 6.1 b) in CPME as environmentally friendly solvent, using a moderate excess (2 eq.) of commercially available hexane-stock solution of *n*-BuLi (Figure 6.1 c).

a)



time (s)	**2a**, yield %	**2a:3a** ratio
5	91	96:4
10	90	96:4
20	93	96:4
60	85	96:4

b) **c)**

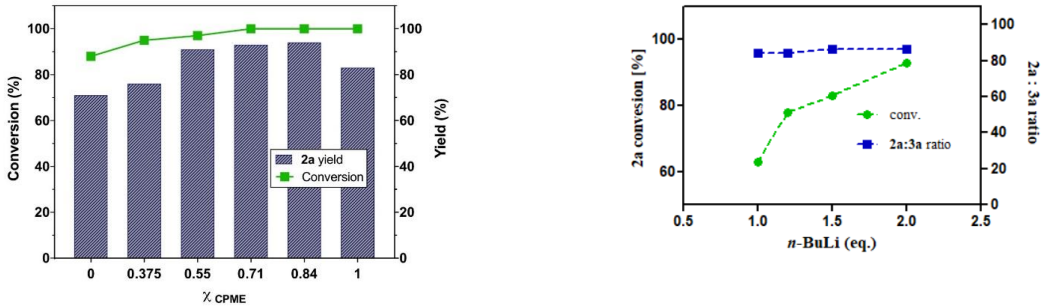
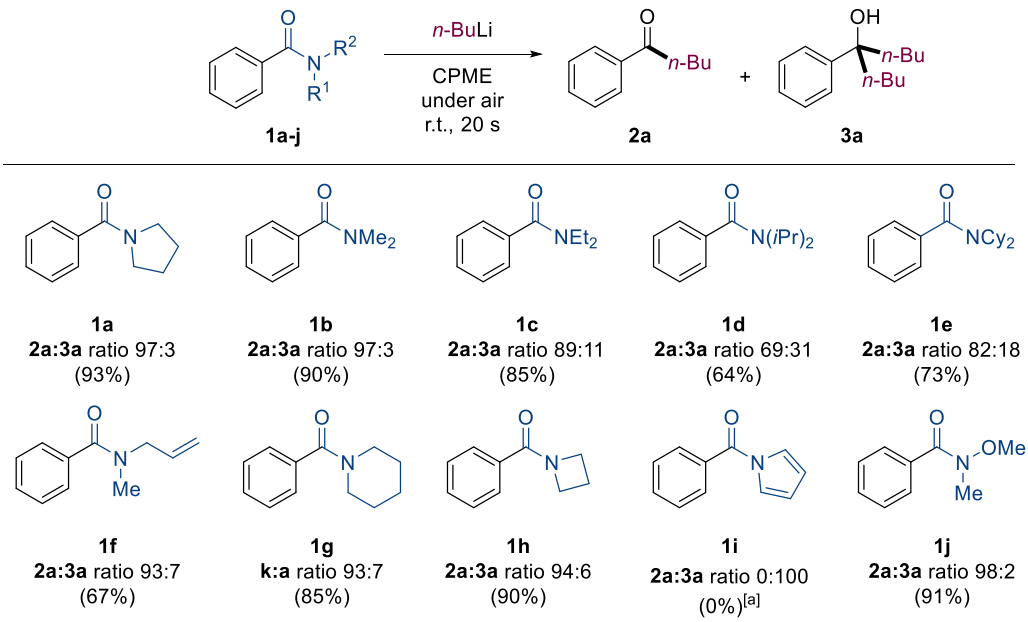


Figure 6.1. a) Effect of reaction time on the yield of **2a** (green circles) and **2a**:**3a** ratio (blue squares) in the reaction of **1a** with 2 eq. of *n*-BuLi, in CPME (0.5 M), at room temperature. The optimal reaction time is indicated inside the circle. **b)** Impact of the hexane/CPME ratio on conversion (green line) and yield (bars) of **2a** after 20 seconds reaction time, with 2 eq of *n*-BuLi, at room temperature. χ CPME: 0 (pure hexane), 0.375 (2.0 M in CPME), 0.55 (1.0 M in CPME), 0.71 (0.5 M in CPME), 0.84 (0.2 M in CPME), 1.0 (*n*-BuLi in pure CPME). **c)** Impact of *n*-BuLi equivalents on conversion and **2a:3a** ratio after 20 seconds reaction time, in CPME (0.5 M), at room temperature.

6.2 Impact of the leaving group on the reaction outcomes

Cognizant of the above achievements, the effectiveness of the S_NAc reaction on different aromatic carboxylic acid amides **1** (0.5 M in CPME) by varying the nature of the amide leaving group (Scheme 6.1) was next investigated. After 20 seconds reaction time, similarly to **1a**, the simplest *N,N*-dimethylbenzamide **1b** delivered ketone **2a** in 90% yield and with an excellent **2a**:**3a** ratio (97:3) when reacted with *n*-BuLi (2 eq.), at room temperature, under air. An increase of the steric hindrance of the alkyl chains around the nitrogen atom of the amide (**1c-e**) reduced both the production of **2a** (up to 64%) and the **2a**:**3a** ratio (up to 69:31) in a proportional manner respect to the encumbrance on the nitrogen atom. Lower yields (67-85%) were detected when using *N*-allylated benzamide **1f** or *N*-benzoylpiperidine **1g** as the substrate, though still with an excellent ketone-to-alcohol ratio (97:3). Remarkably, the reaction of *n*-BuLi with a CPME solution of *N*-benzoylazetidine **1h**, which is characterised by a significant pyramidalization around the nitrogen atom,[1] at room temperature and under air, gave almost similar results (**2a** yield: 90% yield; **2a**:**3a** ratio: 94:6) compared to those obtained with simpler and cheaper amides like **1a**, **1b** and **1c**. Conversely, the described protocol does not apply well to derivatives like *N*-benzoylpyrrole **3i**. Indeed, the peculiar reactivity of these compounds relies on the exceptional stability of the corresponding tetrahedral

intermediates upon addition of an organometallic reagent, leading to pyrrolyl carbinols under kinetic conditions. Furthermore, the corresponding *O*-lithiated pyrrolyl carbinols are known to undergo a fast decomposition at temperatures higher than -30 °C (see section 1.3.2).[2] It is thus with no surprise that the reaction of **1i** with *n*-BuLi quickly provided the bis(alkylated) alcohol **3a** in 75% yield as the sole product. Finally, the treatment of a CPME solution of the Weinreb amide[3] **1j** with *n*-BuLi gave comparable results to those specified in the case of amides **1a** and **1b** as ketone **2a** was isolated in 91% yield and with a **2a**:**3a** ratio of 98:2. All in all, these results disclose that: a) amides **1a**, **1b, 1h** and **1j** stand on the same ground with reference to their reactivity toward organolithium reagents, and b) even in the absence of a strong internal chelation of the lithium cation (**1j**) or of an amide bond twisting (**1h**) the collapse of the tetrahedral intermediate[4] can equally be strongly disfavoured by simply using CPME as the solvent, at room temperature and under air, and commercial solution of alkyllithiums, with the S_NAc reactions taking place very fast (20 s) and in high yields (up to 93%).



Scheme 6.1. S_NAc on different benzamides **1a-j** using *n*-BuLi in CPME at room temperature, under air. Reaction conditions: **1** (0.2 mmol, 1.0 eq.), CPME (0.4 mL, 0.5 M), *n*-BuLi (2.5 M in hexanes, 0.4 mmol, 2 eq.), quench with water after 20 seconds. **2a**: **3a** ratios were determined by ^{1}H NMR integration on the crude reaction mixture. Yields in round brackets refer to valerophenone **2a** determined by ^{1}H NMR analysis using CH_3NO_2 as the internal standard. [a] Yield of **3a**: 75%.

6.3 Mechanistic investigations

A ^{1}H NMR analysis was then performed to investigate the formation and the stability of the tetrahedral intermediate under our bench conditions. After the addition of *n*-BuLi (2.0 M in cyclohexane, 0.38 mmol, 1.1 eq.) to a 0.5 M solution of **1a** (0.35 mmol, 1.0 eq.) in dry CPME (non-deuterated) under nitrogen, neither lithium pyrrolidin-1-ide nor starting material **1a** or valerophenone **2a** were detected in the ^{1}H NMR spectra (Figure 6.2). Evidence of the formation of the tetrahedral intermediate *tetr*-**1a** was assessed by a significant change of the aromatic pattern alongside with a remarkable upfield shift of the *N*-α methylenic protons of the pyrrolidine unit. Partial collapse of the tetrahedral intermediate into valerophenone **2a** was observed by ^{1}H NMR after several days of experiment (six days), while open-air conditions induced the instantaneous conversion of *tetr*-**1a** into the corresponding ketone (Figure 6.3).

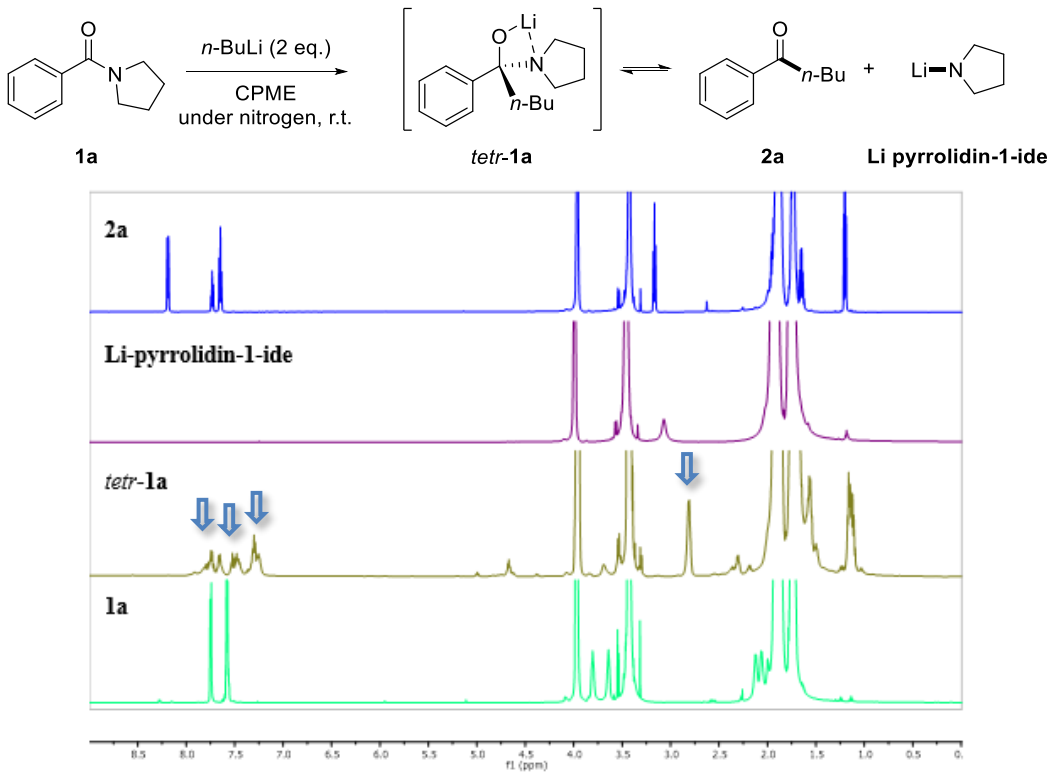


Figure 6.2. ^{1}H NMR evidence of *tetr*-**1a** formation. Experiments were recorded in dry non-deuterated CPME using $CDCl_3$ as an internal reference. Blue arrows indicate the signals of *tetr*-**1a**.

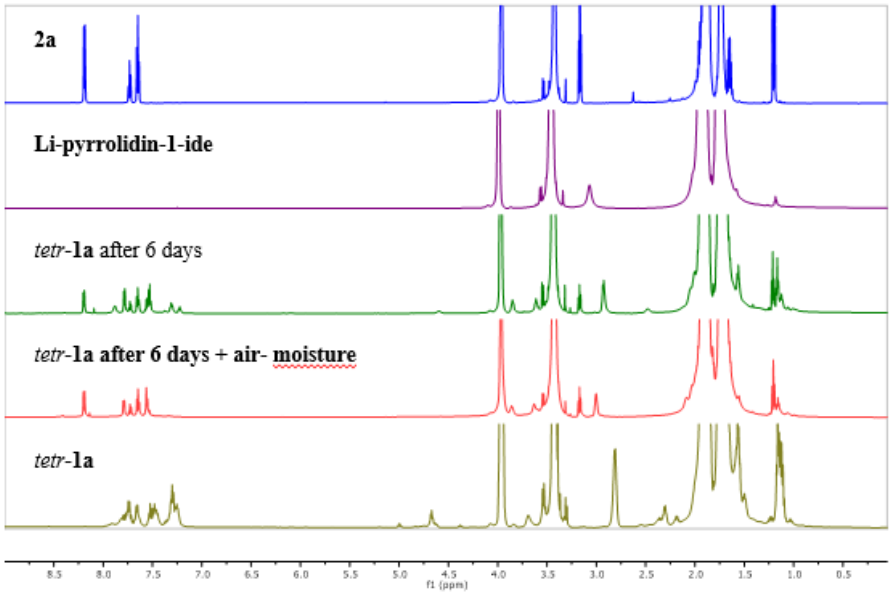


Figure 6.3. ^{1}H NMR evidence of *tetr*-**1a** degradation over time. Experiments were recorded in dry non-deuterated CPME using $CDCl_3$ as an internal reference.

To gain more insight into the unexpected remarkable stability of the tetrahedral intermediate under the aforementioned conditions and to support the observed ^{1}H NMR analysis (Figure 6.2), we investigated its geometry and calculated the free energy barriers of the S_NAc reaction by DFT computations (Figure 6.4). DFT calculations were run at the M06-2X/aug-cc-pVTZ//M06- 2X/6-311+G(d) level for amides **1a**, **1b**, and **1j**. The mechanism involves a multistep sequence: a) pre-complexation of the starting amide by O-Li coordination (TS1, Figure 6.4), b) evolution of TS1 to the corresponding monomeric tetrahedral intermediate (*tetr*-**1**, Figure 6.4), and c) the collapse of *tetr*-**1** into ketone **2a** through a second transition state (TS2, Figure 6.4). Computational results revealed that the addition of the organolithium reagent is a fast reaction (TS1, free energy barriers: 9-15 kcal mol^{-1}) producing relatively stable monomeric tetrahedral intermediates (*tetr*-**1a**, *tetr*-**1b**, *tetr*-**1j**, Figure 6.4) with respect to the starting reactants. The cleavage barrier of the C-N bond determines the kinetic stabilities of the intermediates. By considering the ZPE energy correction, our results are in fairly good agreement with the previous findings reported by Boche *et al.*,[4] where the reactivity of "classical" and Weinreb amides toward S_NAc was studied by DFT calculations using formamide and *N*-hydroxyformamide as model substrates, respectively. However, the free energy barriers of the second step are in contrast with the experimental stability of the tetrahedral intermediates. As an example, when the nucleophilic acyl substitution reaction of **1a** (0.2 mmol, 1 eq.) in dry CPME (1 mL, 0.2 M) with *n*-BuLi (0.4 mmol,

2 eq.) is performed under anhydrous conditions, aqueous quench after 24 hours affords the corresponding ketone **2a** with negligible formation of over-addition products (**2a** yield 70%; **2a**:**3a** ratio 98:2). By contrast, the free energy barriers of about 21 kcal mol^{-1} correspond to half-lives on the order of hundreds of seconds. Quantitative agreement with the experiments is obtained only considering the formation of putative dimeric aggregates in solution and including two explicit molecules of CPME in the computations. In this case, the free energy barriers of the second step raise to more than 40 $kcalmol^{-1}$ for both **1a** and **1b** (Figure 6.4). This calculated structure is in agreement with the previously isolated structure of tetrahedral intermediate by Adler *et al.*[5] When CPME was replaced by the non-coordinating solvent hexane, the free energy barriers of the dimeric form for the second step dropped down to 19 kcal mol^{-1}, which suggest low selectivity in hydrocarbons, in agreement with the experimental results. The decomposition rate of the tetrahedral intermediate in the presence of water was finally evaluated by DFT computations. Calculations were run on *tetr*-**1b** at the same theory level. Assuming that a fast acid-base equilibrium *en route* to an hydroxyamino derivative takes place, the free energy barrier for the amide decomposition into ketone **2a** and dimethylamine was quantitatively evaluated as 10.1 kcal mol^{-1} by adding one explicit molecule of water to PCM calculations. This result is in agreement with the notorious instability of these species in presence of water that rapidly collapse in the corresponding ketone.

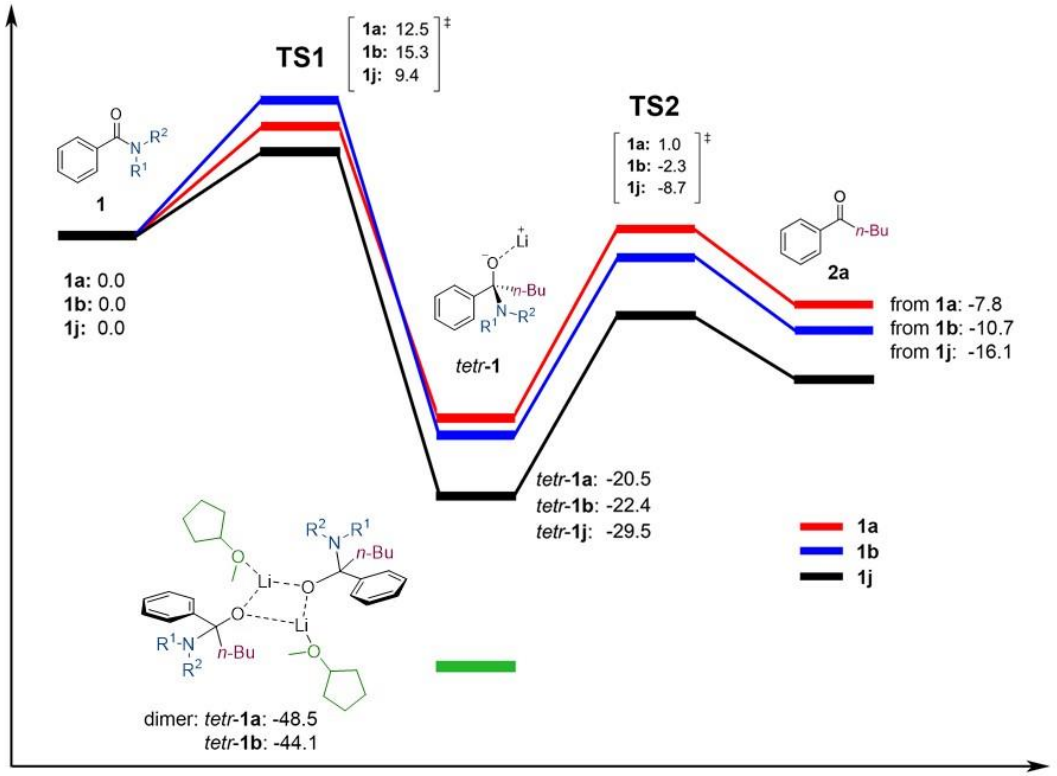


Figure 6.4. Reaction mechanism and calculated free energy barriers (kcal mol^{-1}) for products formation starting from monomeric or coordinated dimeric structures *tetr*-**1a**, *tetr*-**1b**, and *tetr*-**1j**. **1a**: R^1=R^2=-$(CH_2)_4$-; **1b**: R^1 = R^2 = Me; **1j**: R^1 = Me, R^2 = OMe.

6.4. Reaction substrate scope

With the optimized condition in hand, the applicability and the limits of this transformation were then explored. By reacting a variety of aliphatic and (hetero)aromatic *N*-acyl pyrrolidines **1a**, **1k-x** (Figure 6.5) with commercially available aliphatic and (hetero)aromatic organolithium reagents ranging from *n*-BuLi to *s*-BuLi, *t*-BuLi, *n*-HexLi, PhLi and 2-ThLi (Scheme 6.2), a wide range of ketones **2b**-**2ad** were synthesized in very satisfactory yields (53-93%).

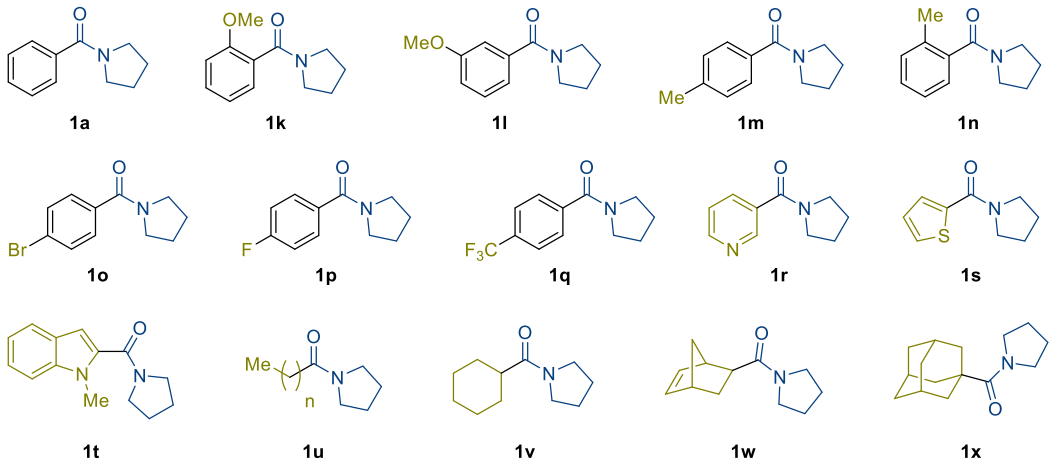
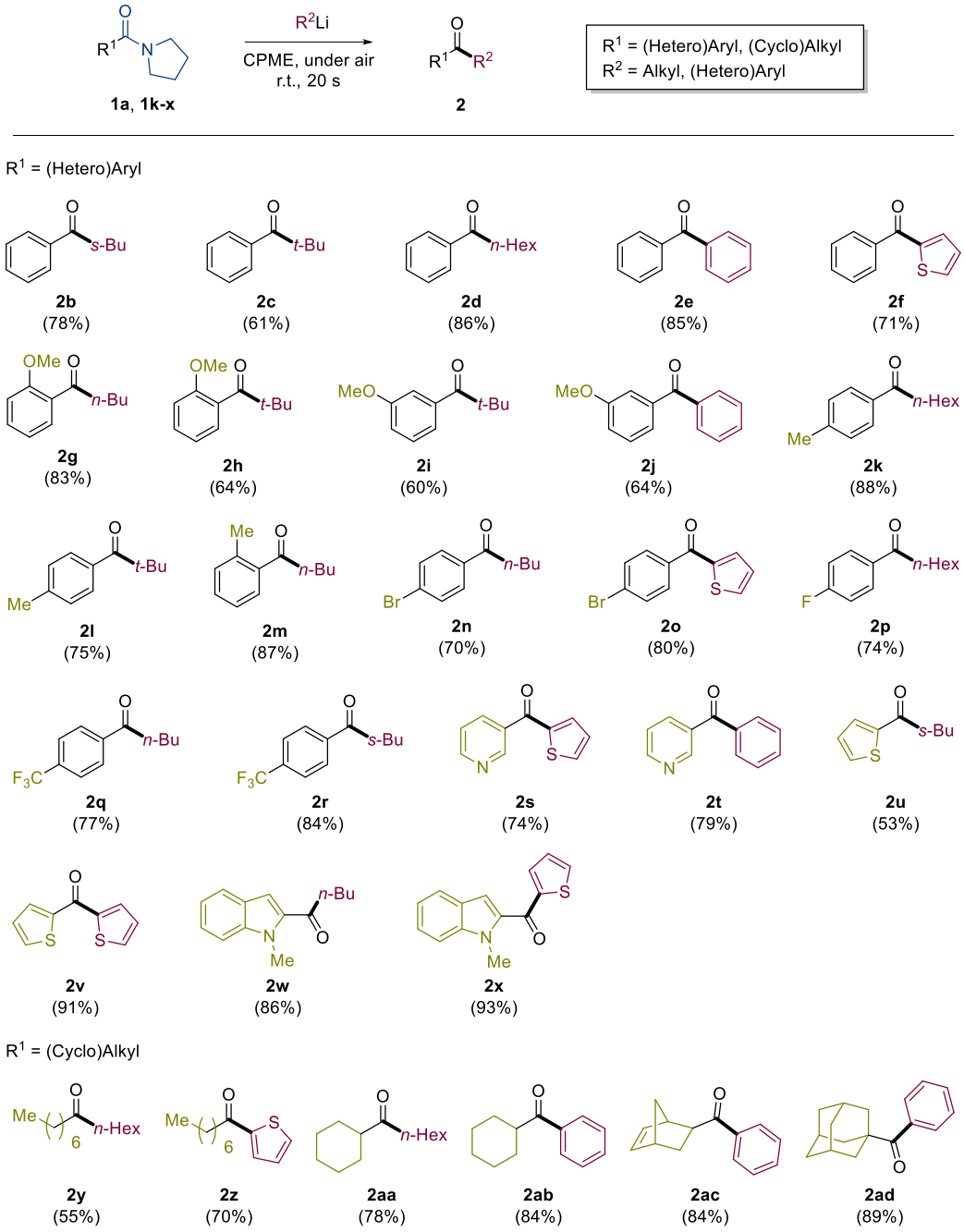


Figure 6.5. *N*-acylpyrrolidines **1a**, **1k-x** used for the substate scope analysis.

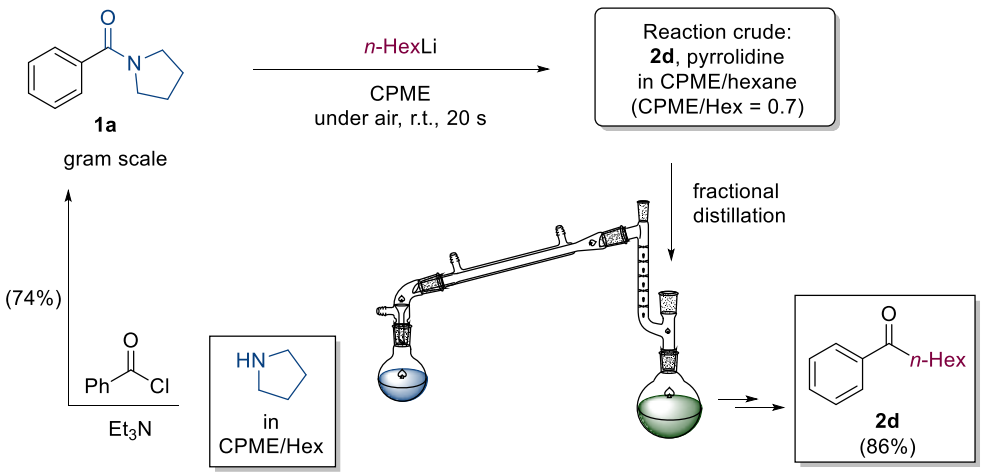
Unsubstituted **2b**-**f**, as well as ketones decorated with electron-donating (MeO, **2g-j**), neutral (Me, **2k-m**) or electron-withdrawing (Br, **2n**,**o**; CF_3, **2q**,**r**) substituents, were smoothly obtained with different ring substitution patterns [*ortho*- (**2g**-**h**,**m**), *meta*- (**2i**,**j**) and *para*- (**2k**-**l**, **2n**-**o**, **2q**-**r**)] in 60-88% yields. This transformation was proved to be highly chemoselective, and do not suffer competitive pathways such as D*o*M (**2g**-**j**), lateral lithiation (**2k**-**m**) or lithium-halogen exchange (**2n**,**o**) reactions. Therefore, nitro and cyano- electrophilic groups on the aromatic ring were too sensitive to competitive side-reactions under thermodynamic condition, and a complex mixture of products was detected when the corresponding *N*-acylpyrrolidines were treated with both alkyl- and aryllithiums. The same result was observed when the *N*-cynnamylpyrrolidine was used as substrate since the conjugated 1,4-addition was competitive under our bench conditions. On the other hand, assorted (hetero)aryl derivatives with a fluorine substituent (**2p**), electron-deficient (pyridine: **2s**,**t**), and electron-rich (thiophene: **2u**,**v**, *N*-methylindole: **2w**,**x**) heterocycles served as competent reaction partners as well, thereby delivering the desired ketones in 53-93% yield. It is worth noting that, under the above conditions, even (cyclo)alkyl (**2y**-**ab**), bicyclic (**2ac**) and sterically hindered adamantyl (**2ad**) ketones could be obtained from the corresponding acyl pyrrolidines in 55-89%. yield. Unfortunately, when the high sterically hindered *N*-mesitoylpyrrolidine (derived from 2,4,6-trimethylbenzoic acid) was used as acylating agent, only the starting material was recovered unreacted, demonstrating that this methodology was ineffective for the synthesis of 2,6-disubstuited aryl ketones.



Scheme 6.2. Synthesis of ketones **2** through the nucleophilic acyl substitution reaction between aliphatic and (hetero)aromatic *N*-acylpyrrolidines **1** and aliphatic and (hetero)aromatic organolithium reagents in CPME, at room temperature, under air. Reaction conditions: **1** (0.2 mmol, 1.0 eq.), RLi (0.4 mmol, 2 eq.), CPME (0.4 mL, 0.5 M), reaction time 20 seconds. Yields refer to products isolated after flash-column chromatography.

6.5 Scalability and recycling

To further explore the advantage of N-benzoylpirrolidines as acylating agents and CPME as reaction medium, the scalability of the process was investigated. To this end, a multigram-scale synthesis of 2d starting from 1a was achieved. By reacting a solution of 1a (11.4 mmol, 1.0 eq., 2 g, in 22 mL CPME) with n-HexLi (2.3 M in hexane, 22.8 mmol, 2 eq.), the reaction proceeded uneventfully in 20 seconds at room temperature, under air, and resulted in a quantitative formation of 2d in 90% yield (2 g) without any loss in terms of chemoselectivity (ketone-to-alcohol ratio 93:7). Notably, no VOCs are required during a multigram preparation of ketones since, after dilution of the reaction mixture with water, the high hydrophobicity of CPME allows a quantitative recovery of the product by simple separation of the two layers. Furthermore, in order to prepare additional starting material, the recyclability of both the solvent (CPME) and the pyrrolidine leaving group (b.p. = 87 °C) by distillation (Scheme 6.3) was finally investigated. To this end, a solution of 1a (5.7 mmol, 1.0 eq., 1 g, in 11 mL CPME) was reacted with n-HexLi (2.3 M in hexane, 15.4 mmol, 2 eq.). The resulting crude reaction mixture was carefully fractionally distilled. This favored an easy recovery of the CPME/hexane fraction containing the pyrrolidine. The latter was finally successfully acylated with benzoyl chloride, thereby affording the starting material 1a in 74% isolated yield and allowing, at the same time, the recovery of ketone 2d in 86% yield (1 g) after purification.



Scheme 6.3. Gram-scale synthesis of **2d** and recycling procedure of CPME and pyrrolidine from the acylation reaction. Reaction conditions: **1a** (5.7 mmol, 1.0 eq., 1 g), *n*-HexLi (11.4 mmol, 2 eq.), CPME (11 mL, 0.5 M), reaction time 20 seconds. Yields refer to products isolated after flash-column chromatography.

6.6 Conclusions

In conclusion, this systematic study discloses that there is no need to make use of chemically modified or activated amides as well as transition metal-catalysed C-N activation processes to promote and privilege nucleophilic acyl substitution reactions by organolithium reagents. Indeed, both aliphatic and (hetero)aromatic *N*-acylpyrrolidines have been found to successfully react with commercial solution of aliphatic and (hetero)aromatic organolithiums, with the desired ketones obtained in up to 93% yield and with an effective suppression of the notorious over-addition reaction, when using CPME as an environmentally responsible solvent. Furthermore, some practical aspects of this methodology make it particularly attractive from a sustainable point of view. All the described reactions run in open air and at room temperature with extremely fast reaction times (20 s), without the necessity to control the temperature and/or the atmosphere, and neither expensive electrophilic additives nor transition metal catalysts are required. These aspects poses no virtual limits to the tolerance of several electron-donating, electron-deficient and sterically hindered functional groups, and good chemoselectivities with no competition with potential D*o*M, LL and halogen-exchange pathways are also obtained. The utility and the sustainability of the process was further highlighted by its scalability and the recyclability/reusability of both the solvent and the pyrrolidine leaving group to prepare additional starting material. Finally, the experimental results are nicely supported by detailed DFT calculations that show how CPME stabilizes the dimeric tetrahedral intermediate, and by NMR spectroscopic investigations, which provide insights into the stability of the tetrahedral intermediate in CPME solution.

6.7 Experimental section

6.7.1 General informations

Materials and methods. Unless specified, all reagents were used as received without further purifications. Anhydrous tetrahydrofuran (THF) and cyclopentyl methyl ether (CPME) were distilled under nitrogen over Na/benzophenone ketyl prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Chromatographic separations were carried out under pressure on silica gel (40-63 µm, 230-400 mesh) using flash-column techniques. The following solutions of organolithium reagents were furnished by Merck-Aldrich and were used with the following concentration: *n*-BuLi 2.0 M in cyclohexane or 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane, *n*-HexLi 2.3 M in hexanes and PhLi 1.9 M in di-*n*-butyl ether. The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[6] Amides **1a-x** were synthesized according

to the procedures reported in the literature.[1-3, 7-17] Full characterisation data have been reported for both the newly synthesized compounds and the known compounds.

Instrumentation. ^{1}H NMR (600 MHz), ^{13}C{^{1}H} (150 MHz), ^{19}F (564 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad). Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS)

Nitromethane was used as the internal standard for quantitative NMR analysis of the crude reaction mixture. The amount of product was determined by applying the following equation (Eq. 1):

$$(1) \qquad yield\ (\%) = \frac{x\ (product) \cdot n\ (MeNO2)}{n(starting\ material)}\ \cdot\ f\ \cdot\ 100$$

where:

- *x* is the value of integral/number of protons;
- *n* is the amount of starting material or nitromethane in mmol;
- *f* the diluting factor used for the preparation of the sample

6.7.2 Preparation of 2-thienyllithium solution in CPME

In a Schlenk tube under a positive pressure of nitrogen, *t*-BuLi (1.7 M in pentane, 2.0 mmol, 2.0 eq.) was added dropwise to a precooled (-78 °C) stirred solution of 2-bromothiophene (1.0 mmol, 1.0 eq., 97 µL) in dry CPME (1 mL, 1 M). The reaction was stirred at -78 °C for 1 hours to yield a pale yellow solution of 2-thienyllithium (2-ThLi). The exact concentration was determined by titration with diphenylacetic acid prior to use.

6.7.3 Preparation of n-butyllithium solution in CPME

A solution of *n*-BuLi (2.5 M in hexanes, 5 mL) in dry CPME (5 mL) was added to a test tube fitted with a septum and flushed with dry argon. The tube was then placed under vacuum (45 mmHg) until 5 mL of concentrated solution was obtained. The resulting solution was diluted again with freshly distilled CPME (5 mL) and concentrated under vacuum up to a 5 mL residual volume. This procedure was repeated three times to completely remove residual traces of hexane. The final *n*-BuLi solution in CPME was titrated with diphenylacetic acid in anhydrous THF prior to use.

*6.7.4 Synthesis of amides **1a-x**: general procedure*

The appropriate carboxylic acid (10.0-50.0 mmol, 1.0 eq.) was dissolved in thionyl chloride (10 eq.) and the solution was heated at reflux (80 °C) overnight. The solution was

cooled to room temperature and the excess of thionyl chloride was removed under vacuum. The resulting acyl chloride was dissolved in dichloromethane (10-40 mL) then triethylamine (1.5 eq.) and diisopropylamine (1.2 eq.) were sequentially added dropwise at 0 °C. The mixture was warmed at room temperature and stirred until the reaction was completed (TLC, 4-5 hours). The mixture was firstly washed twice with 1 M aq. HCl (10-30 mL) then was washed twice with a saturated solution of Na_2CO_3 (10-30 mL) and finally was extracted with EtOAc (3x15-50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under vacuum to give the corresponding amide **1a-x** that was purified by flash column chromatography and/or by recrystallization.

*6.7.5 Synthesis and analysis of compounds **2a-ad***

Reactions were performed under air at room temperature. In an open screw cap vial, *N*-acylpyrrolidines **1a**, **1k-1x** (0.2 mmol, 1 eq.) were dissolved in CPME (0.4 mL, 0.5 M). The selected organolithium reagent (*n*-BuLi 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane, *n*-HexLi 2.3 M in hexane, PhLi 1.9 M in di-*n*-butyl ether, freshly prepared 2-ThLi, 0.4 mmol, 2.0 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 20 seconds (60 seconds for PhLi and 2-ThLi), and then diluted with water. The mixture was washed twice with 1 M HCl (5 mL) and extracted with DEE (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.

1-Phenylpentan-1-one (2a): general procedure starting from **1a** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **2a** as colourless liquid (21 mg, 65%, R_f = 0.54 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.73 (quint, *J* = 7.3 Hz, 2H), 1.42 (sext, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 200.8, 137.2, 133.0, 128.7, 128.2, 38.5, 26.6, 22.6, 14.1. EI-MS *m/z* (%): 162 (M^+, 80), 120 (49), 105 (100), 77 (46).[18]

2-Methyl-1-phenylbutan-1-one (2b): General procedure starting from **1a** and *s*-BuLi. Purification by flash column chromatography (PE/DEE 98/2 v/v) gave **2b** as a colourless oil (25 mg, 78%, R_f = 0.37 PE/DEE 98/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.40 (sext, *J* = 6.2 Hz, 1H), 1.87-1.80 (m, 1H), 1.53-1.46 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 204.6, 137.0, 132.9, 128.7, 128.4, 42.3, 26.8, 16.9, 11.9. EI-MS *m/z* (%):162 (M^+, 13), 134 (7), 105 (100), 77 (31).[19]

2,2-Dimethyl-1-phenylpropan-1-one (2c): General procedure starting from **1a** and *t*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **2c** as a colourless oil (20 mg, 61%, R_f = 0.62 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71-7.66 (m,

2H), 7.47-7.44 (m, 1H), 7.41-7.38 (m, 2H), 1.35 (s, 9H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 209.5, 138.8, 130.9, 128.2, 128.0, 44.4, 28.2. EI-MS *m/z* (%): 162 (M^+, 6),105 (100), 77 (25).[1]

1-Phenylheptan-1-one (2d): General procedure starting from **1a** and *n*-HexLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **2d** as colourless liquid (33 mg, 86%, R_f = 0.57 PE/DEE 95/5 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.41-1.30 (m, 6H), 0.91-0.88 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): 200.8, 137.2, 133.0, 128.7, 128.2, 38.8, 31.8, 29.2, 24.5, 22.7, 14.2. δ. EI-MS *m/z* (%): 190 (M^+, 10), 120 (77), 105 (100), 77 (40).[1]

Benzophenone (2e): General procedure starting from **1a** and PhLi. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2e** as a white solid (31 mg, 85%, R_f = 0.50 PE/EtOAc 9/1 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.83-7.78 (m, 4H), 7.61-7.58 (m, 2H), 7.50-7.47 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 196.9, 137.7, 132.6, 130.2, 128.4. EI-MS *m/z* (%): 182 (M^+, 74), 105 (100), 77 (56), 51 (18).[1]

Phenyl(thiophen-2-yl)methanone (2f): General procedure starting from **1a** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/EtOAc 95/5 v/v) gave **2f** as a white solid (27 mg, 71%, R_f = 0.25 *n*-hexane/EtOAc 95/5 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.89-7.85 (m, 2H), 7.73 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.65 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.62-7.57 (m, 1H), 7.53-7.48 (t, 2H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 188.4, 143.8, 138.3, 135.0, 134.4, 132.4, 129.3, 128.6, 128.1. EI-MS *m/z* (%): 188 (M^+, 100),187 (14), 111 (91), 105 (32), 77 (30).[1]

1-(2-Methoxyphenyl)pentan-1-one (2g): General procedure starting from **1k** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **2g** as a yellow oil (32 mg, 83%, R_f = 0.48 PE/DEE 95/5 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.43 (td, *J* = 7.2, 1.8 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.65 (quint, *J* = 7.5 Hz, 2H), 1.37 (sext, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 203.53, 158.41, 133.17, 130.23, 128.97, 120.73, 111.58, 55.59, 43.60, 26.66, 22.63, 14.10. EI-MS *m/z* (%): 192 (M^+, 1), 150 (18), 135 (100), 77 (18).[20]

1-(2-Methoxyphenyl)-2,2-dimethylpropan-1-one (2h): General procedure starting from **1k** and *t*-BuLi. Purification by flash column chromatography (*n*-hexane/EtOAc 95/5 v/v) gave **2h** as a colourless oil (24 mg, 64%, R_f = 0.32 *n*-hexane/EtOAc 95/5 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.34-7.30 (m, 1H), 7.03 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.94 (td, *J* = 7.4, 0.9 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 1.21 (s, 9H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 214.0, 155.4, 131.2, 130.0, 126.4, 120.3, 111.0, 55.5, 45.1, 26.9. EI-MS *m/z* (%): 192 (M^+, 4),135 (100), 77 (15).[21]

1-(3-Methoxyphenyl)-2,2-dimethylpropan-1-one (2i): General procedure starting from **1l** and *t*-BuLi. Purification by flash column chromatography (PE/EtOAc 95/5 v/v) gave **2i** as a colourless oil (23 mg, 60%, R_f = 0.35 PE/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.19-7.17 (m, 1H), 7.00 (ddd, *J* = 8.0, 2.6, 1.1 Hz, 1H), 3.83 (s, 3H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 209.3, 159.4, 140.1, 129.2, 120.2, 116.7, 113.4, 55.5, 44.4, 28.2. EI-MS *m/z* (%): 192 (M^+, 11),135 (100), 107 (18), 28 (39).[22]

(3-Methoxyphenyl)(phenyl)methanone (2j): General procedure starting from **1l** and PhLi. Purification by flash column chromatography (*n*-hexane/EtOAc 95/5 v/v) gave **2j** as a colourless oil (27 mg, 64%, R_f = 0.25 *n*-hexane /EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83-7.79 (m, 2H), 7.61-7.57 (m, 1H), 7.50-7.47 (m, 2H), 7.39-7.33 (m, 3H), 7.14 (ddd, *J* = 8.1, 2.7, 1.1 Hz, 1H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 196.7, 159.7, 139.0, 137.7, 132.6, 130.2, 129.4, 128.4, 123.0, 119.0, 114.4, 55.6. EI-MS *m/z* (%): 213 (17), 212 (M^+, 100),181 (15), 135 (72), 107 (17), 105 (60), 77 (47).[23]

1-(*p*-Tolyl)heptan-1-one (2k): General procedure starting from **1m** and *n*-HexLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2k** as a white solid (36 mg, 88%, R_f = 0.50 *n*-hexane/EtOAc 97/3 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 1.72 (quint, *J* = 5.5 Hz, 2H), 1.40-1.30 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 200.5, 143.7, 134.8, 129.3, 128.3, 38.7, 31.8, 29.2, 24.6, 22.7, 21.7, 14.2. EI-MS *m/z* (%): 204 (M^+, 8),134 (68), 119 (100), 91 (33).[24]

2,2-Dimethyl-1-(*p*-tolyl)propan-1-one (2l): General procedure starting from **1m** and *t*-BuLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2l** as a colourless oil (26 mg, 75%, R_f = 0.33 *n*-hexane /EtOAc 97/3 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 2.38 (s, 3H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 208.5, 141.6, 135.6, 128.8, 128.5, 44.2, 28.3, 21.6. EI-MS *m/z* (%): 176 (M^+, 3), 119 (100), 91 (24).[8]

1-(*o*-Tolyl)pentan-1-one (2m): General procedure starting from **1n** and *n*-BuLi. Purification by flash column chromatography (*n*-hexane/EtOAc 95/5 v/v) gave **2m** as a yellow oil (31 mg, 87%, R_f = 0.37 *n*-hexane/EtOAc 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.35 (td, *J* = 7.5, 1.1 Hz, 1H), 7.26-7.23 (m, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.48 (s, 3H), 1.68 (quint, *J* = 7.5 Hz, 2H), 1.39 (sext, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 205.2, 138.6, 137.9, 132.0, 131.1, 128.4, 125.7, 41.6, 26.7, 22.6, 21.3, 14.1. EI-MS *m/z* (%): 176 (M^+, 2),161 (13), 119 (100), 91 (36), 28 (12).[25]

1-(4-Bromophenyl)pentan-1-one (2n): General procedure starting from **1o** and *n*-BuLi. Purification by flash column chromatography (PE/DCM 9/1 v/v) gave **2n** as a colourless oil (34 mg, 70%, R_f = 0.44 PE/DCM 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 2.92 (t, *J* = 7.6 Hz, 2H), 1.71 (quint, *J* = 7.4 Hz, 2H), 1.40

(sext, J = 7.4 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.6, 135.9, 132.0, 129.7, 128.1, 38.4, 26.5, 22.6, 14.1. EI-MS *m/z* (%): 242 (M^+, 1), 240 (M^+, 1),200 (66), 198 (68), 185 (98), 183 (100), 157 (29), 155 (29), 28 (19).[8]

(4-Bromophenyl)(thiophen-2-yl)methanone (2o): General procedure starting from **1o** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2o** as a white solid (43 mg, 80%, R_f = 0.25 *n*-hexane/EtOAc 97/3 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.75-7.73 (m, 3H), 7.65-7.62 (m, 3H), 7.17 (dd, J = 4.8, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 187.2, 143.3, 137.0, 134.9, 134.7, 131.9, 130.9, 128.2, 127.4. EI-MS *m/z* (%): 268 (M^+, 55), 266 (M^+, 55),187 (28), 185 (22), 157 (14), 155 (14), 111 (100).[26]

1-(4-Fluorophenyl)heptan-1-one (2p): General procedure starting from **1p** and *n*-HexLi. Purification by flash column chromatography (PE/DEE 98/2 v/v) gave **2p** as a white solid (28,6 mg, 74%, R_f = 0.50 PE/DEE 98/2 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H), 7.14-7.10 (m, 2H), 2.93 (t, J = 7.4 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.40-1.30 (m, 6H), 0.89 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.1, 165.7 (d, J = 257.2 Hz, 1C), 133.7 (d, J = 2.3 Hz, 1C), 130.8 (d, J = 8.7 Hz, 1C), 115.8 (d, J = 21.7 Hz, 1C), 38.7, 31.8, 29.2, 24.5, 22.7, 14.2.^{19}F NMR (564 MHz, $CDCl_3$): δ -105.7 (m). EI-MS *m/z* (%): 208 (M^+, 3),138 (82), 123 (100), 95 (31).[27]

1-(4-(Trifluoromethyl)phenyl)pentan-1-one (2q): General procedure starting from **1q** and *n*-BuLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2q** as a white solid (35 mg, 77%, R_f = 0.35 *n*-hexane/EtOAc 97/3 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 8.06 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 1.73 (quint, J = 7.6 Hz, 2H), 1.42 (sext, J = 7.6 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.6, 139.8, 134.3 (q, J = 32.8 Hz, 1C), 128.5, 125.8 (q, J = 2.9 Hz, 1C), 123.8 (q, J = 272.9 Hz, 1C), 38.8, 26.4, 22.5, 14.0. ^{19}F NMR (564 MHz, $CDCl_3$): δ -63.0 (s). EI-MS *m/z* (%): 230 (M^+, 1),188 (69), 173 (100), 145 (52).[28]

2-Methyl-1-(4-(trifluoromethyl)phenyl)butan-1-one (2r): General procedure starting from **1q** and *s*-BuLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2r** as a colourless liquid (39 mg, 84%, R_f = 0.40 *n*-hexane/EtOAc 97/3 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H), 3.39 (sext, J = 6.7 Hz, 1H), 1.87-1.80 (m, 1H), 1.55-1.46 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 203.5, 139.6, 134.2 (q, J = 32.9 Hz, 1C), 128.6, 125.8 (q, J = 4.3 Hz, 1C), 123.7 (q, J = 273.7 Hz, 1C) 42.6, 26.6, 16.6, 11.8. ^{19}F NMR (564 MHz, $CDCl_3$): δ -63.0 (s). EI-MS *m/z* (%): 230 (M^+, 1),173 (100), 145 (32), 28 (20).[29]

pyridin-3-yl(thiophen-2-yl)methanone (2s): General procedure starting from **1r** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/DEE 95/5 v/v) gave **2s** as a colourless oil (31 mg, 76%, R_f = 0.43 *n*-hexane/DEE 95/5 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.81 (d, J = 3.8 Hz, 1H), 8.16 (dt, J = 7.9, 2.0 Hz, 1H), 7.78 (dd, J = 5.0,

1.2 Hz, 1H), 7.65 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.19 (dd, *J* = 4.8, 3.8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 186.3, 152.9, 150.0, 143.2, 136.7, 135.4, 135.3, 133.9, 128.5, 123.6. EI-MS *m/z* (%): 189 (M^+, 100), 188 (25), 160 (11), 111 (90).[30]

Phenyl(pyridin-3-yl)methanone (2t): General procedure starting from **1r** and PhLi. Purification by flash column chromatography (*n*-hexane/EtOAc 7/3 v/v) gave **2t** as a white solid (29 mg, 79%, R_f = 0.25 *n*-hexane/EtOAc 7/3 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.82 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 6.9 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 7.5, 4.8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 194.9, 152.8, 150.9, 137.5, 136.8, 133.4, 133.4, 130.2, 128.8, 123.6. EI-MS *m/z* (%): 183 (M^+, 100),182 (36), 106 (16), 105 (64), 78 (19), 77 (42), 51 (20).[26]

2-Methyl-1-(thiophen-2-yl)butan-1-one (2u): General procedure starting from **1s** and *s*-BuLi. Purification by flash column chromatography (*n*-hexane/*i*-PrO_2 95/5 v/v) gave **2u** as a yellow oil (18 mg, 53%, R_f = 0.30 *n*-hexane/*i*-PrO_2 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (dd, *J* = 3.8, 0.7 Hz, 1H), 7.62 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 4.0 Hz, 1H), 3.21 (sext, *J* = 6.9 Hz, 1H), 1.87-1.80 (m, 1H), 1.55-1.48 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 197.55, 144.58, 133.64, 131.65, 128.20, 44.29, 27.19, 17.34, 12.02. EI-MS *m/z* (%): 168 (M^+, 16), 140 (12), 111 (100).

Di(thiophen-2-yl)methanone (2v): General procedure starting from **1s** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/*i*-Pr_2O 9/1 v/v) gave **2v** as a yellow solid (35 mg, 91%, R_f = 0.25 *n*-hexane/*i*-Pr_2O 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 3.8, 1.0 Hz, 2H), 7.70 (dd, *J* = 4.8, 1.0 Hz, 2H), 7.19 (dd, *J* = 5.2, 3.8 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 179.0, 143.1, 133.7, 133.3, 128.1. EI-MS *m/z* (%): 194 (M^+, 81),111 (100), 39 (16), 28 (36).[26]

1-(1-Methyl-1*H*-indol-2-yl)pentan-1-one (2w): General procedure starting from **1t** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 9/1 v/v) gave **2w** as white solid (37 mg, 86%, R_f = 0.43 PE/DEE 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.40-7.37 (m, 2H), 7.30 (s, 1H), 7.18-7.14 (m, 1H), 4.08 (s, 3H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.76 (quint, *J* = 7.7 Hz, 2H), 1.44 (sext, *J* = 7.7 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 194.6, 140.1, 135.1, 125.9, 125.9, 123.0, 120.8, 111.3, 110.5, 39.9, 32.3, 27.5, 22.7, 14.1. EI-MS *m/z* (%): 215 (M^+, 59), 173 (39), 159 (41), 158 (100), 144 (16), 131 (27), 89 (50).

(1-Methyl-1*H*-indol-2-yl)(thiophen-2-yl)methanone (2x): General procedure starting from **1t** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/EtOAc 95/5 v/v) gave **2x** as a yellow solid (45 mg, 93%, R_f = 0.30 *n*-hexane/EtOAc 95/5 v/v), mp 118.5-119.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.73-7.71 (m, 2H), 7.45-7.40 (m, 2H), 7.29 (s, 1H), 7.21-7.18 (m, 2H), 4.06 (s, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 179.8, 144.9, 140.3, 135.1, 134.0, 133.6, 128.0, 126.1, 125.9, 123.1, 121.0,

112.9, 110.5, 31.9. EI-MS *m/z* (%): 241 (M^+, 100), 240 (51), 208 (23), 144 (16), 111 (15), 89 (19). ESI-HRMS $[M+Na]^+$: *m/z* 264.0446, $C_{14}H_{11}NOSNa^+$ requires 264.0459.

Tetradecan-7-one (2y): General procedure starting from **1u** and *n*-HexLi. Purification by flash column chromatography (*n*-hexane/DEE 98/2 v/v) gave **2y** as a white solid (23 mg, 55%, R_f = 0.30 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.38 (t, *J* = 7.6 Hz, 4H), 1.58-1.53 (m, 4H), 1.30-1.24 (m, 14H), 0.89-0.86 (m, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 211.9, 43.0 (2C), 31.8, 31.8, 29.4, 29.2, 29.1, 24.0, 24.0, 22.8, 22.7, 14.2, 14.2. EI-MS *m/z* (%): 212 (M^+, 5),128 (26),127 (81), 113 (100), 85 (54), 71 (59), 59 (25), 58 (75), 57 (96), 55 (31), 43 (86), 41 (44).[31]

1-(Thiophen-2-yl)octan-1-one (2z): General procedure starting from **1u** and 2-ThLi. Purification by flash column chromatography (*n*-hexane/EtOAc 96/4 v/v) gave **2z** as a yellow liquid (29 mg, 70%, R_f = 0.28 *n*-hexane/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.62 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.12 (dd, *J* = 4.8, 3.8 Hz, 1H), 2.89 (t, *J* = 7.6 Hz, 2H), 1.77-1.72 (quint, *J* = 7.3 Hz, 2H), 1.38-1.28 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 193.8, 144.7, 133.5, 131.8, 128.2, 39.6, 31.8, 29.4, 29.2, 25.0, 22.8, 14.2. EI-MS *m/z* (%): 210 (M^+, 14),139 (16), 126 (100), 111 (81).[31]

1-Cyclohexyloctan-1-one (2aa): General procedure starting from **1v** and *n*-HexLi. Purification by flash column chromatography (*n*-hexane/DEE 98/2 v/v) gave **2aa** as a colourless oil (33 mg, 78%, R_f = 0.33 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (t, *J* = 7.2 Hz, 2H), 2.32 (tt, *J* = 11.4, 3.3 Hz, 1H), 1.82-1.75 (m, 4H), 1.67-1.64 (m, 1H), 1.56-1.51 (m, 2H), 1.35-1.15 (m, 11H), 0.87 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 214.7, 51.0, 40.8, 31.8, 29.2, 28.6, 26.0, 25.9, 23.8, 22.7, 14.2. EI-MS *m/z* (%): 196 (M^+, 15),126 (24), 113 (43), 111 (39), 83 (100), 55 (41), 43 (26), 41 (21).[32]

Cyclohexyl(phenyl)methanone (2ab): General procedure starting from **1v** and PhLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2ab** as a white solid (32 mg, 84%, R_f = 0.30 *n*-hexane/EtOAc 97/3 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.92 (m, 2H), 7.57-7.52 (m, 1H), 7.47-7.44 (m, 2H), 3.26 (tt, *J* = 11.4, 3.3 Hz, 1H), 1.90-1.83 (m, 4H), 1.76-1.72 (m, 1H), 1.54-1.45 (m, 2H), 1.44-1.34 (m, Hz, 2H), 1.32-1.22 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 204.1, 136.5, 132.9, 128.7, 128.4, 45.8, 29.6, 26.1, 26.0. EI-MS *m/z* (%): 188 (M^+, 32),105 (100), 77 (27), 28 (25).[20]

(Bicyclo[2.2.1]hept-5-en-2-yl)(phenyl)methanone (2ac): General procedure starting from **1w** and PhLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2ac** as a white solid (32 mg, as a 11:1 *endo*:*exo* mixture 84%, R_f = 0.30 *n*-hexane/EtOAc 97/3 v/v). Major diasteroisomer: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.56-7.53 (m, 1H), 7.48-7.44 (m, 2H), 6.18 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.82 (dd, *J* = 5.7, 2.9 Hz, 1H), 3.85 (ddd, *J* = 9.1, 4.4, 3.5 Hz, 1H), 3.26 (br s, 1H), 2.97 (br s, 1H), 1.97 (ddd, *J* = 11.6, 9.1, 3.7 Hz, 1H), 1.64 (ddd, *J* = 11.6, 4.4, 2.3 Hz, 1H), 1.50-1.46

(m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 201.0, 137.6, 137.3, 132.7, 132.0, 128.6, 128.4, 50.1, 47.6, 47.3, 43.1, 29.2. EI-MS *m/z* (%): 198 (M^+, 24), 133 (64), 120 (28), 105 (100), 77 (52), 66 (80).[33]

((Adamantan-1-yl)(phenyl)methanone (2ad): General procedure starting from **1x** and PhLi. Purification by flash column chromatography (*n*-hexane/EtOAc 97/3 v/v) gave **2ad** as a white solid (43 mg, 89%, R_f = 0.30 *n*-hexane/EtOAc 97/3 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.44-7.42 (m, 1H), 7.39-7.37 (m, 2H), 2.07 (br s, 3H), 2.01 (br s, 6H), 1.77-1.71 (m, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 210.34, 139.73, 130.26, 128.06, 127.23, 47.02, 39.20 (3C), 36.65(3C), 28.24(3C). EI-MS *m/z* (%): 240 (M^+, 24), 135 (100), 105 (10).[1]

*6.7.5 Multigram-scale synthesis of **2d***

In an open screw cap vial, phenyl(pyrrolidin-1-yl)methanone **1a** (11.5 mmol, 1.0 eq., 2.0 g) were dissolved in CPME (25 mL, 0.5 M). *n*-HexLi (2.3 M in hexanes, 0.4 mmol, 2.0 eq.) was rapidly spread over the mixture, which was kept under vigorous stirring for 20 seconds and then diluted with water. The mixture was washed with 1 M HCl (3 x 20 mL) and extracted with CPME (20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by flash column chromatography afforded **2d** as a colourless oil (2.0 g, 90%, R_f = 0.57 PE/DEE 95/5 v/v).

6.7.6 Experimental procedure for the recycle of CPME and pyrrolidine through the acylation reaction

In a 100 mL round-bottom flask, phenyl(pyrrolidin-1-yl)methanone **1a** (5.7 mmol, 1.0 eq., 1.0 g) was dissolved in CPME (11.4 mL, 0.5 M) under air. *n*-HexLi (2.3 M in hexane, 11.4 mmol, 2.0 eq.) was rapidly spread over the mixture at room temperature, which was kept under vigorous stirring and quenched after 20 seconds with a stoichiometric amount of water (11.4 mmol, 2.0 eq., 205 µL). The crude reaction mixture was transferred to a Claisen distillation apparatus fitted with a 20 cm Vigreux column. Fractional distillation at 760 mmHg afforded a mixed fraction containing all the volatiles components of the reaction crude (*n*-hexane, pyrrolidine and CPME).

The residual non-volatile fraction recovered from the distillation apparatus, containing mostly ketone **2d** and inorganic salts, was directly purified by flash column chromatography (PE/DEE 95/5 v/v%) to give pure 1-phenylheptan-1-one **2d** (931 mg, 86%).

The pyrrolidine solution in CPME/*n*-hexane was recycled as a substrate for the preparation of benzamide **1a**. Benzoyl chloride (6.8 mmol, 1.2 eq., 790 µL) and Et_3N (11.4 mmol, 2.0 eq., 1.58 mL) were quickly sequentially added to the pyrrolidine solution in CPME/*n*-hexane at 0 °C, and the mixture was stirred overnight at room temperature. The mixture was washed with 1 M HCl (2 x 20 mL) and saturated aq. $NaHCO_3$ (20 mL), followed by extraction with CPME (3 x 20 mL). The combined organic layers were dried over Na_2SO_4

and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded **1a** as a yellow oil (858 mg, 86%, R_f = 0.20 PE/EtOAc 1/1 v/v).

*6.7.7 ^{1}H NMR analysis of tetr-**1a***

Experiments were recorded in a NMR tube fitted with a rubber septum flushed with nitrogen. Dry non-deuterated CPME was used as the solvent and $CDCl_3$ as the internal reference. The S_NAc reaction was performed by addition of *n*-BuLi (2.0 M in cyclohexane, 0.38 mmol, 1.1 eq.) to a dry CPME solution (0.5 M, 0.7 mL) of **1a** (0.35 mmol, 1.0 eq, 61 mg) under a positive nitrogen atmosphere. Li-pyrrolidin-1-ide was generated by treatment of pyrrolidine with *n*-BuLi under the same reaction conditions above described.

*6.7.8 DFT calculations for amides **1a**, **1b** and **1j***

Minima and transition structures were determined within the Density Functional Theory (DFT-PCM),[34] and making use of the M06-2X functional.[35] The polarized split-valence shell 6-311+G(d) was used for the optimizations.[36-38] The nature of the critical points was checked by vibrational analysis.

All the molecules were considered as a solute in a polarized continuum, within the Solvation Model based on Density (SMD)[39] and Integral Equation Formalism-Polarizable Continuum Model (IEF-PCM) schemes.[40] For a better energy assessment, two molecules of explicit solvent (CPME) in interaction with the ionic centers, were added in the computations.

The optimizations were followed by aug-cc-pVTZ[41] single-point energy calculations (including PCM), and free energies were estimated by adding the thermochemical contributions obtained at M06-2X/6-311+G(d) level. These ΔG (at 298K) values at DFT(M06-2X)/aug-cc-pVTZ are reported throughout in the text.

A complete set of critical point geometries and energies is reported in the Supporting Information of the published paper.[17] All calculations were carried out by using the GAUSSIAN16 system of programs.

References

1. C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375-2378.
2. D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188-3191.
3. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815-3818.
4. M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **18**, 193-209.
5. M. Adler, M. Marsch, N. S. Nudelman and G. Boche, *Angew. Chem. Int. Ed.*, 1999, **38**, 1261-1263.
6. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879-1880.
7. R. Bisht, M. E. Hoque and B. Chattopadhyay, *Angew. Chem. Int. Ed.*, 2018, **57**, 15762-15766.
8. P.-Q. Huang, Y. Wang, K.-J. Xiao and Y.-H. Huang, *Tetrahedron*, 2015, **71**, 4248-4254.
9. M. Kim, S. Sharma, N. K. Mishra, S. Han, J. Park, M. Kim, Y. Shin, J. H. Kwak, S. H. Han and I. S. Kim, *Chem. Commun.*, 2014, **50**, 11303-11306.
10. D. Leow, *Org. Lett.*, 2014, **16**, 5812-5815.
11. V. Kumar and S. J. Connon, *Chem. Commun.*, 2017, **53**, 10212-10215.
12. X.-F. Wang, S.-S. Yu, C. Wang, D. Xue and J. Xiao, *Org. Biomol. Chem.*, 2016, **14**, 7028-7037.
13. H. C. Brown, D. Basavaiah, S. U. Kulkarni, H. D. Lee, E. Negishi and J. J. Katz, *J. Org. Chem.*, 1986, **51**, 5270-5276.
14. C. Qian, X. Zhang, Y. Zhang and Q. Shen, *J. Organomet. Chem.*, 2010, **695**, 747-752.
15. J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2016, **128**, 9206-9210.
16. M. Li, V. Carreras, A. Jalba and T. Ollevier, *Org. Lett.*, 2018, **20**, 995-998.
17. S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti and C. Prandi, *Chem. Eur. J.*, 2021, **27**, 2868-2874.
18. W.-B. Sheng, Q. Jiang, W.-P. Luo and C.-C. Guo, *J. Org. Chem.*, 2013, **78**, 5691-5693.
19. T. T. Dang and A. M. Seayad, *Adv. Synth. Catal.*, 2016, **358**, 3373-3380.
20. J.-C. Hsieh, Y.-C. Chen, A.-Y. Cheng and H.-C. Tseng, *Org. Lett.*, 2012, **14**, 1282-1285.
21. M. B. Díaz-Valenzuela, S. D. Phillips, M. B. France, M. E. Gunn and M. L. Clarke, *Chem. Eur. J.*, 2009, **15**, 1227-1232.
22. T. Ishii, Y. Kakeno, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, **141**, 3854-3858.
23. S. Bhadra, W. I. Dzik and L. J. Gooßen, *Angew. Chem. Int. Ed.*, 2013, **52**, 2959-2962.
24. L. Chu, J. M. Lipshultz and D. W. MacMillan, *Angew. Chem. Int. Ed.*, 2015, **54**, 7929-7933.
25. D. Aand, S. Karekar, B. Mahajan, A. B. Pawar and A. K. Singh, *Green Chem.*, 2018, **20**, 4584-4590.
26. T. S. Jiang and G. W. Wang, *Adv. Synth. Catal.*, 2014, **356**, 369-373.
27. N. U. H. Khan, B. C. Lee, S. Y. Lee, Y. S. Choe, C. H. Jun and D. Y. Chi, *J. Labelled Compd. Radiopharm.*, 2002, **45**, 1045-1053.
28. J. Wu, X. Yang, Z. He, X. Mao, T. A. Hatton and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2014, **126**, 8556-8560.

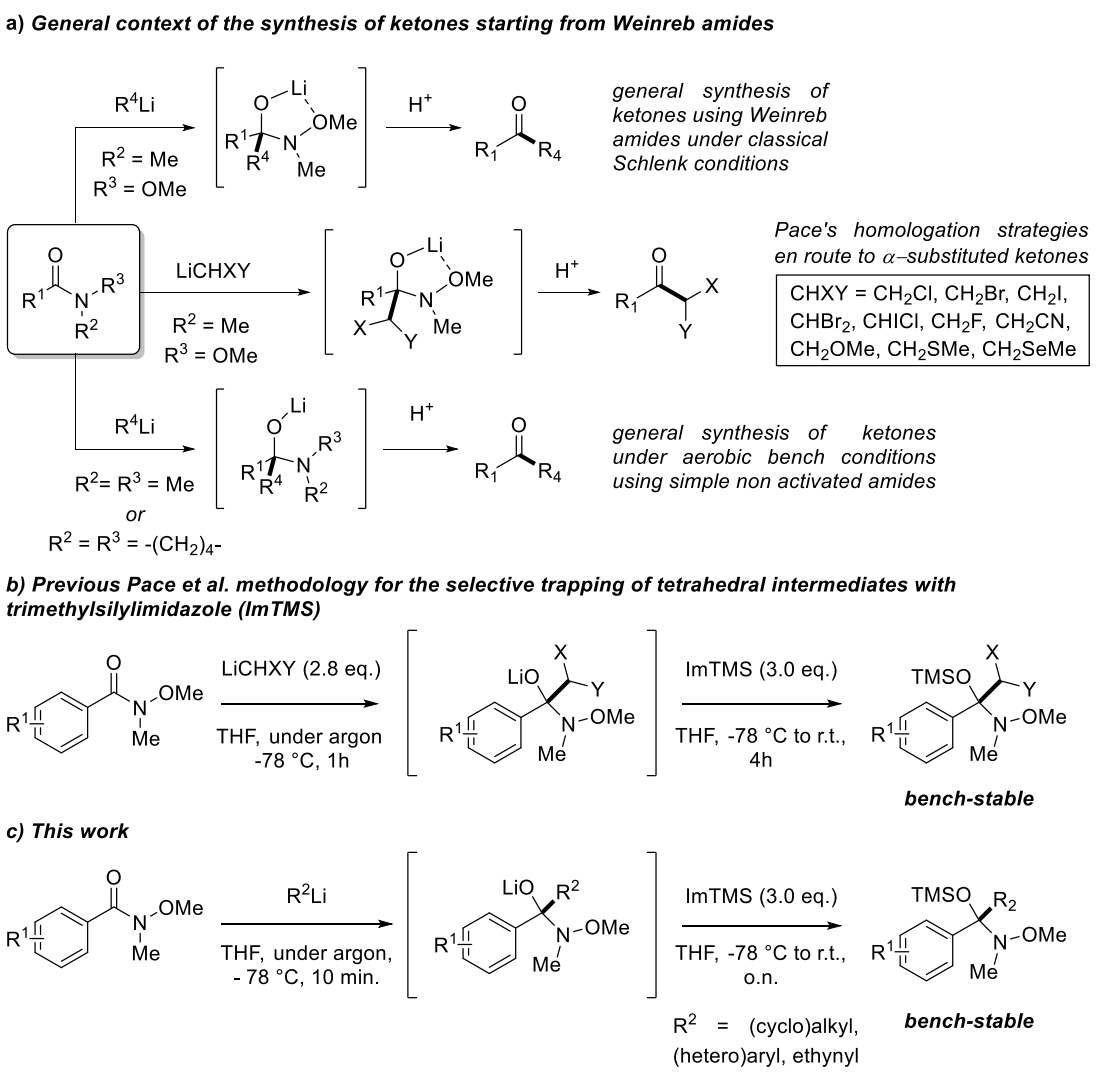
29. Y. Takada, S. Hayashi, K. Hirano, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2006, **8**, 2515-2517.
30. G. Li and M. Szostak, *Chem. Rec.*, 2020, **20**, 649-659.
31. T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Angew. Chem. Int. Ed.*, 2010, **49**, 1238-1240.
32. Y. Wei, B. Rao, X. Cong and X. Zeng, *J. Am. Chem. Soc.*, 2015, **137**, 9250-9253.
33. A. Gonzalez-de-Castro and J. Xiao, *J. Am. Chem. Soc.*, 2015, **137**, 8206-8218.
34. J. L. Calais, *Density-functional theory of atoms and molecules*, Wiley Online Library, 1993.
35. Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215-241.
36. A. McLean and G. Chandler, *J. Chem. Phys.*, 1980, **72**, 5639-5648.
37. R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, 1980, **72**, 650-654.
38. T. Clark, J. Chandrasekhar, G. W. Spitznagel and P. V. R. Schleyer, *J. Comput. Chem.*, 1983, **4**, 294-301.
39. A. V. Marenich, C. J. Cramer and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378-6396.
40. J. Tomasi, B. Mennucci and E. Cancès, *Journal of Molecular Structure: THEOCHEM*, 1999, **464**, 211-226.
41. R. A. Kendall, T. H. Dunning Jr and R. J. Harrison, *J. Chem. Phys.*, 1992, **96**, 6796-6806.

CHAPTER 7: Synthesis of bench stable *O*-TMS-protected hemiaminals formed upon addition of organolithiums to Weinreb amides

The research presented in this chapter was realized during the Erasmus period of my PhD at the Pharmaceutical Department of the University of Vienna in Prof. Pace research group. The results presented are not published yet.

The research line of Prof. Pace's group is mainly focused on the development of new synthetic transformations exploiting the high reactivity of functionalized lithium carbenoids as homologating agents.[1-10] In the course of their investigations aimed at finding new electrophilic platforms for lithium carbenoid-mediated transformations, Weinreb amides have received particular attention (Scheme 7.1 a).[11] The notorious beneficial complexation of the metal of the putative tetrahedral intermediate to form a five-membered cycle is the critical factor justifying the effectiveness in hampering common undesired drawbacks such as overaddition phenomena (see section 1.3.2). Thus, excellent performance of Weinreb amides as privileging acylating agents were observed for the preparation of α-substituted ketones *via* addition-elimination reaction. Major advantages are focused on the easy starting material preparation, mild reaction conditions required, good yield and high chemoselectivity (especially in presence of other sensitive electrophilic functional group) compared to the previously reported methods requiring harsh oxidating and/or carefully stoichiometric conditions or the same strategies using other acylating agents (*e.g.* esters or acyl chlorides).[11] Among the benefits of Weinreb amides, the notorious inherent nature of tetrahedral intermediate has implied severe difficulties for its isolation[12] (with the unique exception of stable carbinol derived from *N*-acylpyrroles)[13] and for its characterization to fully understand some mechanistic aspects and its synthetic potential. This problem was recently overcome by Pace *et al.* by the isolation of the *O*-TMS protected hemiaminal tetrahedral intermediates generated upon addition of a carbenoid reagent (mono- or dihalo-methyllithium) to Weinreb amides (Scheme 7.1 b).[14] Motivated by the Prof. Pace research group experience in the chemical manipulation of Weinreb amides in order to access stable tetrahedral intermediates, and on the basis of our recent studies on the kinetic stability of the tetrahedral intermediates derived from the addition of highly reactive organolithium species to simple *N,N*-dimethyl benzamides and *N*-acylpyrrolidines (see chapter 6),[15] we then focused our attention on the synthesis of *O*-TMS protected hemiaminals derived upon addition of alkyl and (hetero)aryllithiums to Weinreb amides in order to extend the applicability of the previous reported methodology (Scheme 7.1 c).

The results obtained during my six-month period as visiting PhD student in the laboratory of Prof. Pace research group are illustrated in this chapter.



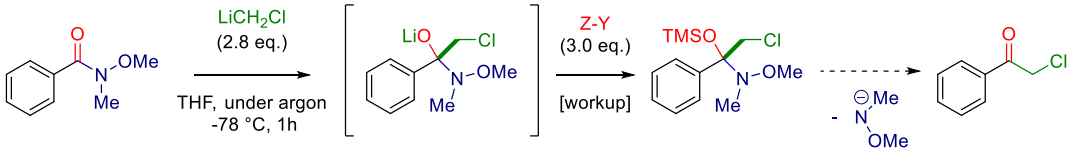
Scheme 7.1. a) General context of the synthesis of ketones from Weinreb amides; **b)** evidence and isolation of bench stable *O*-TMS protected hemiaminal tetrahedral intermediates derived from Weinreb amides and (di)-halomethyllithiums and **c)** extension of the methodology to generic organolithiums derivatives.

7.1 Preliminary investigation and optimization of the reaction condition

During the previous investigations carried out by the research group of Prof. Pace on the isolation of stable tetrahedral intermediates generated from the addition of lithium halocarbenoids to Weinreb amides, the use of ImTMS as silylating agent

among others was crucial, owing to its remarkable oxophilicity, to provide the adequate stability to the generated *O*-TMS hemiaminal **II** and to avoid the undesired elimination of the amide leaving group (leading to the formation of **III**) during the course of the reaction (Table 7.1, entries 1-5). On the other hand, to preserve the chemical integrity of **II** during the workup procedure, moderated basic 5% $NaHCO_3$ aqueous solution was used during the quenching, DEE as extraction solvent, while the purification was achieved on deactivated neutral alumina as stationary phase (AloxN-BG3) (Table 7.1, entries 6-9). Using SiO_2 also in presence of 10% of TEA caused the collapse of **II**, due to the natural SiO_2 acidity (Table 7.1, entries 6,7), while other neutral alumina of different Brockmann's grade (Alox-BG2 and Alox-BG4) permitted the recovery of the desired **II** but in low yield compared to AloxN-BG3 (Table 7.1, entries 8-9). The use of C_6D_6 as deuterated solvent instead of common moderate acidic $CDCl_3$ guaranteed stability also during NMR acquisition. Finally, all the reactions were run under classical Schlenk conditions (-78 °C during the addition of nucleophile in dry THF) since the presence of air and moisture could be deleterious for the hemiaminals formation.[14]

Table 7.1. Optimization of reaction conditions and isolation procedure using chloromethyllitium as nucleophile.[a]



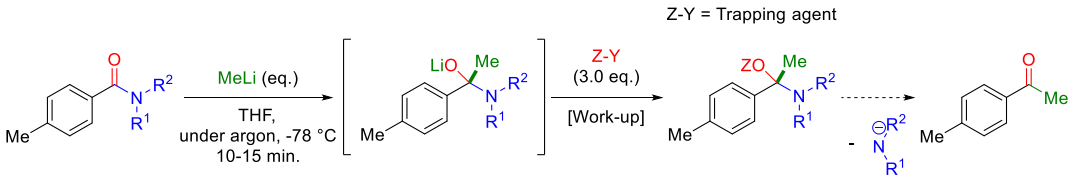
I *tetr*-I II III

Entry	Trapping agent Z-Y (3.0 eq.)	Conversion %/ ratio **II**:**III**[b]	Stationary phase	Yield of **II** (%)[c]
1	TMSCl-Py	87 / 5:1	AloxN-BG3	71
2	TMSCl-Im	90 / 20:1	AloxN-BG3	70
3	ImTMS	95 / 25:1	AloxN-BG3	90
4	ImTPS	86 / 0:1	-	-
5	ImTPS	89 / 0:1	-	-
6	ImTMS	95 / 25:1	SiO_2	-
7	ImTMS	95 / 25:1	SiO_2 (TEA 10%)	-
8	ImTMS	95 / 25:1	AloxN-BG4	78
9	ImTMS	95 / 25:1	AloxN-BG2	70

[a] $LiCH_2Cl$ was generated from ICH_2Cl (3.0 eq.) and MeLi-LiBr (2.8 eq.) in dry THF, at -78 °C, under argon. Barbier-type conditions were adopted. [b] Conversion and **II**:**III** ratio were calculated by ^1H NMR. [c] Yields refer to isolated and purified compounds using the indicated stationary phase. NMR spectra acquired using C_6D_6 for sample preparation.

Starting from these previously optimized conditions (Table 7.1, entry 3), we designed a short series of experiments in order to verify the compatibility of this methodology with generic alkyllithium reagents. We started our investigations using the simple Weinreb amide derived from 4-methylbenzoic acid **1a** (0.5 mmol, 1 eq.) as a model substrate, which was reacted with MeLi (0.6 mmol, 1.2 eq.) in dry THF (2 mL, 0.25 M) under argon atmosphere. After 10 minutes, ImTMS (1.5 mmol, 3 eq.) was added, and the reaction was slowly warmed to room temperature over a period of 4 hours. Quenching with 5% $NaHCO_3$ aqueous solution afforded the desired *O*-TMS protected hemiaminal **2a** in a comfortably 58% yield after column chromatography on AloxN-BG3 (Table 7.2, entry 1).

Table 7.2. Optimization of the reaction conditions and isolation procedure using Weinreb amide **1a** and MeLi as nucleophile. [a]



Entry	**1**: R^1, R^2	MeLi (eq.)	Z-Y (3.0 eq.)	Conv. %/ ratio **2**:**3**[b]	Stationary phase	Yield of **2a** (%)[c]
1	**1a**: R^1 = Me; R^2 = OMe	1.2	ImTMS	90 / 20:1	AloxN-BG3	58
2	**1a**: R^1 = Me; R^2 = OMe	1.5	ImTMS	95 / 20:1	AloxN-BG3	70
3	**1a**: R^1 = Me; R^2 = OMe	2.0	ImTMS	100 / 20:1	AloxN-BG3	72
4	**1a'**: R^1 = R^2 = Me	1.5	ImTMS	100 / 0:1	-	-
5	**1a''**: R^1 = R^2 = Et	1.5	ImTMS	95 / 0:1	-	-
6	**1a'''**: R^1 = R^2 = -$(CH_2)_4$-	1.5	ImTMS	98 / 0:1	-	-
7	**1a**: R^1 =Me; R^2 = OMe	1.5	ImTMS	95 /25:1	AloxN-BG2	70
8	**1a**: R^1 =Me; R^2 = OMe	1.5	ImTMS	95 / 25:1	AloxN-BG4	90

[a] Reaction conditions: to a solution **1** (0.5 mmol, 1.5 eq.) in dry THF (2 mL, 0.25 M), MeLi (eq.) was added at -78 °C, under argon. After 10-15 minutes, the selected trapping agents was added (1.5 mmol, 3.0 eq.) and the reaction was allowed to reach at room temperature for 4 hours. Quench with 5% $NaHCO_3$ aqueous solution. [b] Conversions and **2**:**3** ratio were calculated by ^1H NMR. [c] Isolated yields. NMR spectra were acquired using C_6D_6 for sample preparation.

Increasing the amount of MeLi to 1.5 eq. led to a slight increase of the yield to 70% (Table 7.2, entry 2), while using 2.0 eq. of nucleophile no significant changes were observed (Table 7.2, entry 3). We next evaluated the possibility to use simple non-chelating amides derived from *N,N*-dimethylamine (**1a'**), *N,N*-diethylamine (**1a''**) and pyrrolidine (**1a'''**) as acylating agents since, as shown in the previous chapter, they are able to form kinetically stable tetrahedral intermediates comparable to Weinreb amide-derived ones upon addition of organolithiums reagents under bench moisture-compatible conditions. However, in every case only ketone **3a** was obtained as the sole product (Table 7.2, entries 4-6).[16] Finally, the workup and purification procedures were further optimized in order to improve the yield of **2a**. After basic aqueous treatment ($NaHCO_3$ 5%) and extraction with DEE, the NMR spectra were recorded in C_6D_6, and the crude were purified by chromatography on neutral alumina with different Brockmann's grade (AloxN-BGX). Using Brockmann 2 grade neutral alumina (AloxN-BG2), derivative **2a** was obtained in 70% yield (Table 7.2, entry 7). However, the best result was achieved by employing Brockmann 4 grade neutral alumina (AloxN-BG4) affording derivative **2a** in 90% yield (Table 7.2, entry 8).

7.2 Reaction substrate scope

With the optimized condition in hands (Table 7.2, entry 8), we then applied the methodology to different Weinreb amides (Figure 7.1) using both commercially available and *in situ* prepared (hetero)aryl and (cyclo)alkyllithiums (Scheme 7.2).

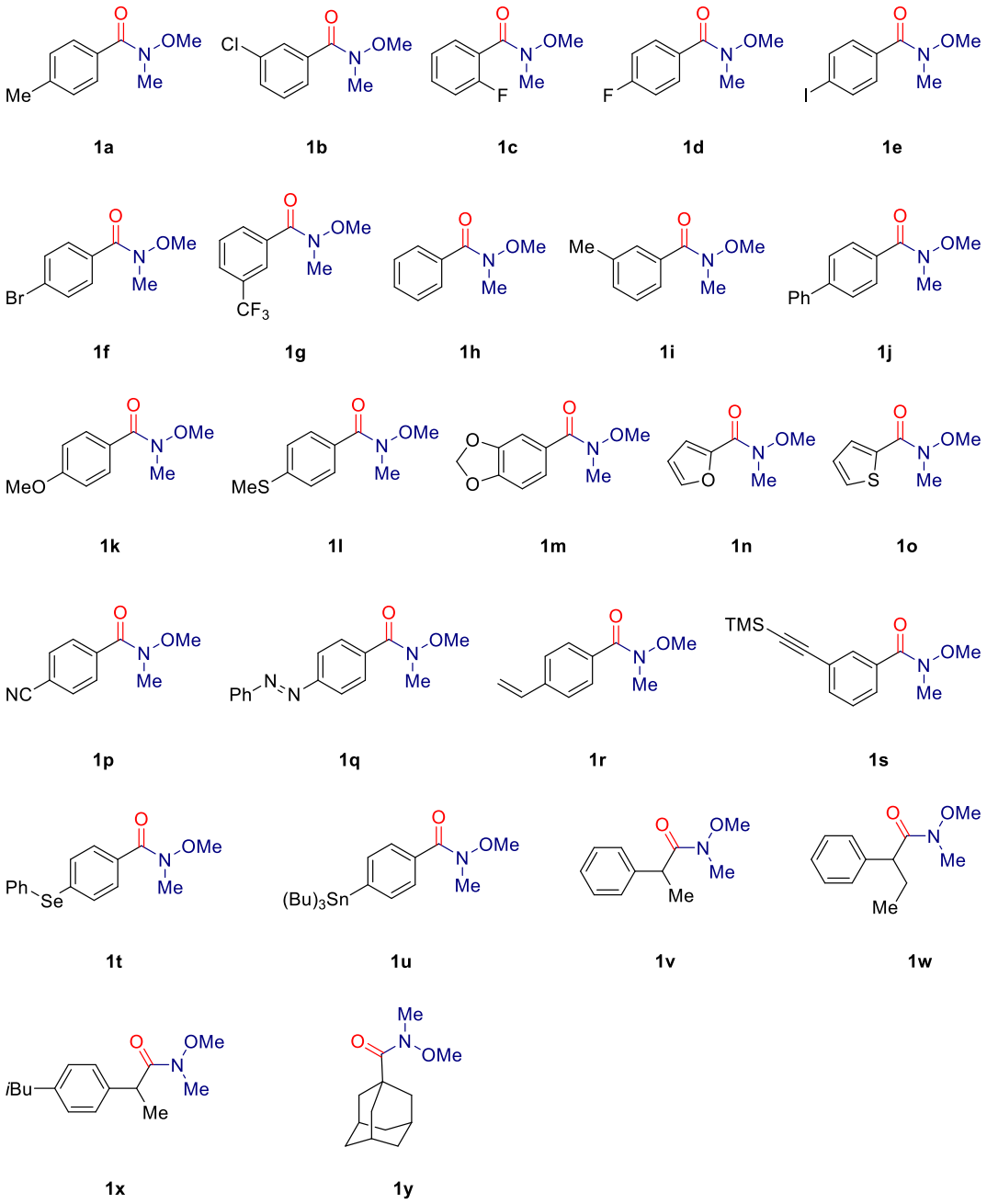


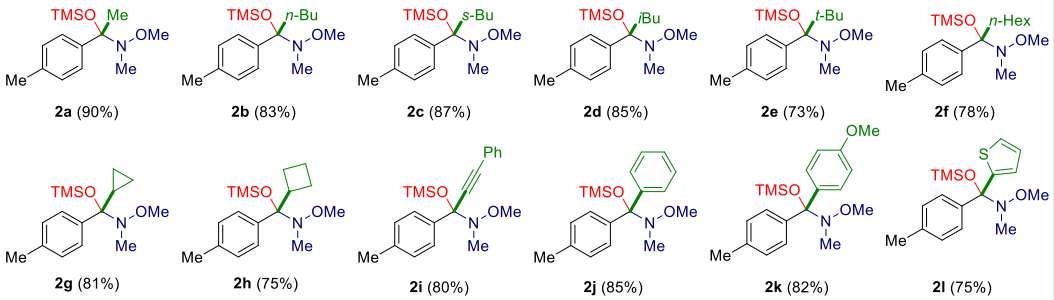
Figure 7.1. Weinreb amides **1a-y** used for the substate scope analysis.

As generally observed, neither the length of the alkyllithium chain nor the steric hindrance and the complexity of their structure influenced the formation of the *O*-TMS protected hemiaminals when the selected organolithium reacted with the model substrate **1a**. Indeed, using acyclic alkyllithiums such as MeLi (**2a**), *n*-

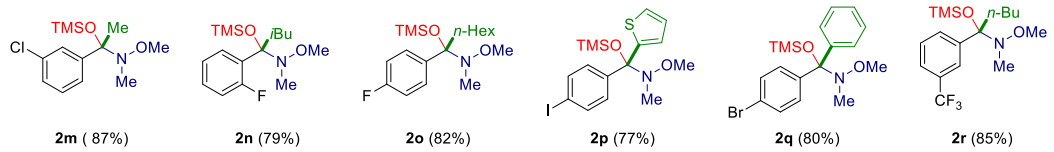
BuLi (**2b**), *s*-BuLi (**2c**), *i*BuLi (**2d**), *t*-BuLi (**2e**) and *n*-HexLi (**2f**) we obtained the desired products in good yields. Freshly prepared solutions of cyclopropyl- and cyclobutyllithium, starting from the commercially available cycloalkylbromide precursors and *t*-BuLi in THF, afforded the corresponding structurally congested cyclo-adducts (**2g**,**h**) in satisfactory yields. At the same, also the unsaturated lithium phenylacetylide preserved the chemical integrity the tetrahedral intermediate (**2i**). Finally, (hetero)aromatic organolithiums such as PhLi, freshly prepared 4-OMePhLi and 2-thienyllitium (2-ThLi) provided the nucleophilic counterparts efficiently leading to the formation of the corresponding hemiaminals **2j-l** in good yields. The scope of the reaction was further expanded using the (un)substituted Weinreb amides **1b-w** (Figure 7.1). Halogenated Weinreb amides reacted smoothly under our optimized condition, and neither the presence nor the position of the halogen functionalities (**2m-r**) influenced the outcome of the reaction. In particular, aryl iodide (**2p**) and bromide (**2q**) reacted with high chemoselectivity and no halogen-lithium exchange products were detected, making the compounds exploitable for further synthetic manipulations. Remarkably, fluorinated compounds (**2n**,**o**) were also obtained in good yield since the importance of the fluorine-containing aromatic molecules in biological field,[17, 18] while the high electrophilic trifluoromethyl group was beneficial for the reaction outcome (**2r**). As expected, the reaction worked well even for the neutral unsubstituted phenyl ring (**2s**,**t**), the 3-methyl benzoic acid derived Weinreb amide (**2u**) and the biphenyl analogue (**2v**). Electron rich arenes bearing a methoxy group reacted smoothly in the presence of *t*-BuLi and lithium dithiane *en route* to hemiaminals **2w** and **2x**; analogously, sulphur containing-amide (**2y**) and cyclic acetal (**2z**) were successfully tolerated. Electron rich heteroaromatic Weinreb amides derived from furan- and thiophene-2-carboxylic acid led to the corresponding *O*-TMS hemiaminals after reaction with alkyl, cycloalkyl and aryllithium (**2aa-ac**). To further extend the chemoselective profile of the reaction, amides bearing different competitive functionalities were evaluated. To our delight, competitive nitrile (**2ad**), diazo (**2ae),** vinyl (**2af**), alkyne (**2ag**), phenyl selenide (**2ah**) and tributyltin (**2ai**) functionalities remained unchanged with no evidence of collateral pathway such as nucleophilic addition (for **2ad-ag**) or lithium exchange (for **2ah**,**ai**). It is worth noting that even aliphatic and sterically hindered adamantyl carboxamides could be successfully used as acylating agents leading to the desired adducts in good yields (**2aj**, **2ak** and **2am**), while the applicability of the methodology was demonstrated using the Weinreb amide derivative of Ibuprofen (**2al**).

1a-z *tetr*-**1** **2a-am**

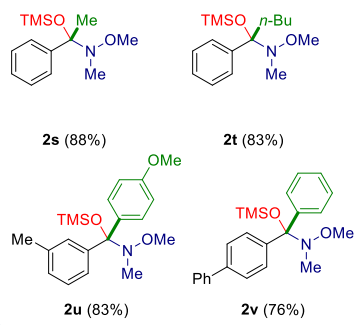
Using different nucleophilic sources



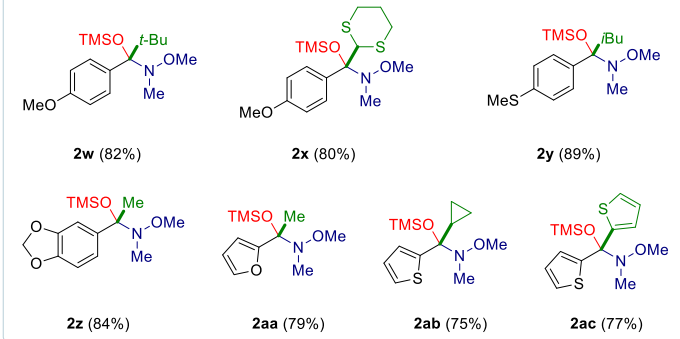
Halogenated and electron poor arenes



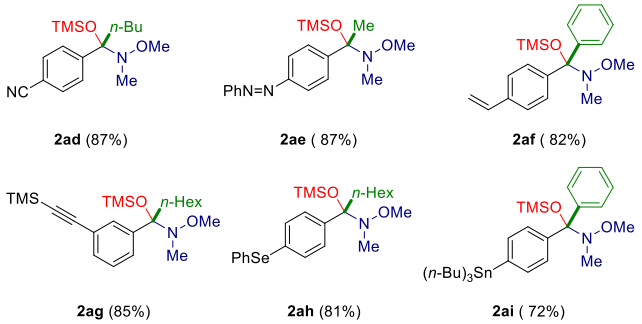
Unsubstituted and alkylsubstituted arenes



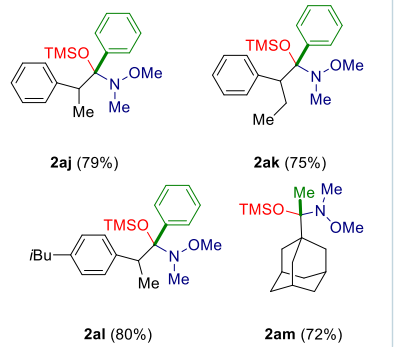
Electron rich-(hetero)aromatics



Functional group tollerability

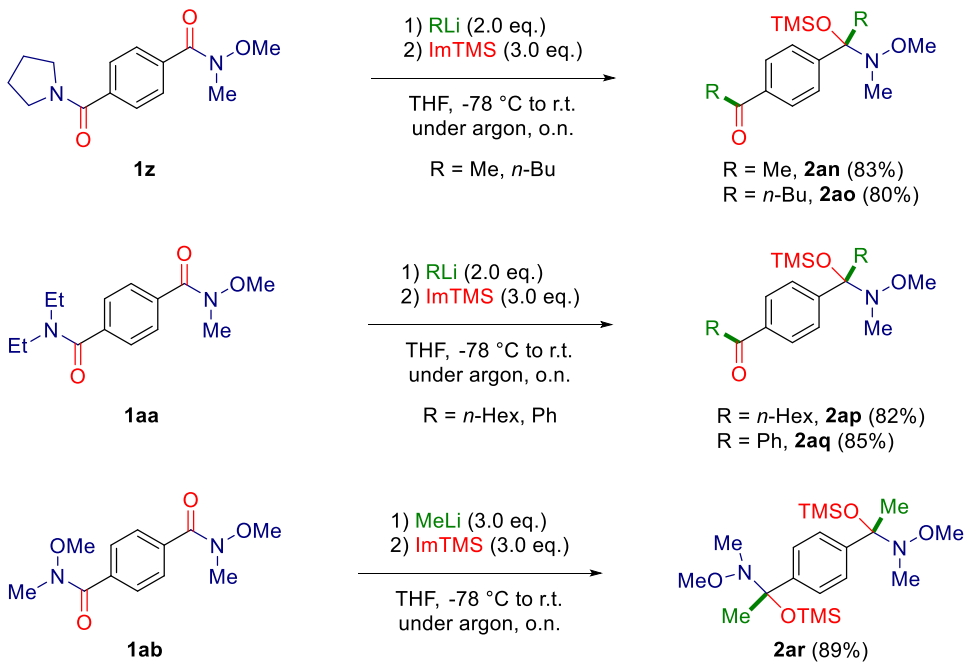


From aliphatics



Scheme 7.2. Synthesis of *O*-TMS-hemiaminals **2a-am** upon addition of organolithiums to Weinreb amides **1a-y**. Reaction conditions: to a solution **1** (0.5 mmol, 1.5 eq.) in dry THF (2 mL, 0.25 M), RLi (0.75 mmol, 1.5 eq.) was added at -78 °C, under argon. After 10-15 minutes, the ImTMS was added (1.5 mmol, 3.0 eq.) and the reaction was warmed to room temperature over 4 hours. Quench with 5% $NaHCO_3$ aqueous solution. NMR spectra were acquired using C_6D_6 for sample preparation.

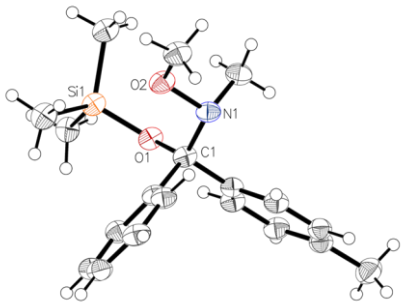
Finally, to corroborate the experimental evidence of the supremacy of Weinreb amides as electrophilic partner in the synthesis of *O*-TMS hemiaminals derived from tetrahedral intermediates, we tested the reactivity of different Weinreb amides presenting another non-chelating amide functionality in the *para* position of the aromatic ring (Scheme 7.3). Indeed, in these cases the nucleophilic addition of the organolithium occurred on both the electrophilic sites, but only the *O*-TMS protected hemiaminal intermediate arising from the Weinreb amide was isolated, while the competitive amide collapsed *in situ* into the corresponding ketone independently on the steric propriety of the amide both using alkyl or aryllithiums (**2an-aq**). Furthermore, when the reaction was carried out using a bis-Weinreb amide **1ab** the isolation of the high symmetric bis-tetrahedral intermediate **2ar** was feasible when 3.0 eq. of MeLi are used.



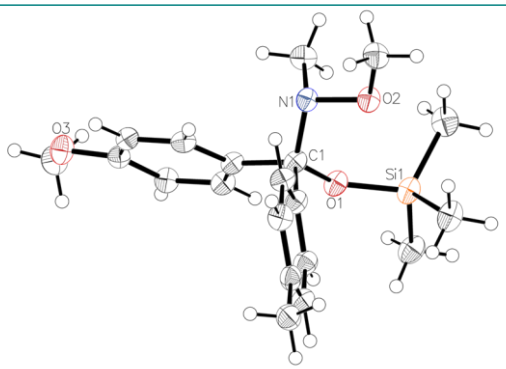
Scheme 7.3. Synthesis of *O*-TMS-hemiaminals **2an-ar** upon addition of organolithiums to 4-aminocarbamoyl Weinreb amides **1z-ab**.

7.3. Crystallographic characterization

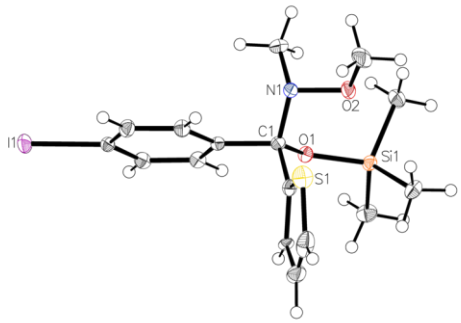
The exceptional stability of the *O*-TMS protected tetrahedral hemiaminals allowed their feasible crystallization by slow, room temperature evaporation of the C_6D_6 solution. Further evidence of their chemical structure was achieved *via* X-ray analysis (Figure 7.2). Representative compounds (**2j**, **2k**, **2p**, **2v**, **2ak**) were chosen and interesting structural features were revealed. Considering the four bond lengths around the tetrahedral quaternary carbon C1, the distance between the tetrahedral carbon (C1) and nitrogen atom (N1) is quite constant in a range between 1.464 Å and 1.477 Å, as well as the C1-O1 distance (1.410 - 1.424 Å) and the newly formed (Li)C-C1 bond (1.521 - 1.537 Å). As expected, the major difference was observed in the bond length between the tetrahedral carbon and the alpha-carbon of the Weinreb amide ((Am)C-C1). Indeed, using an aliphatic Weinreb amide we observed a longer (Am)C-C1 bond (1.573 Å) compared to the characteristic aromatic Weinreb amides (1.520 - 1.532 Å). Considering the aminic portion of the tetrahedral intermediate, the N1-OCH_3, and the N1-CH_3 distances are practically constant. Another interesting parameter is the mean of the all C1 angles revealing the tetrahedral nature of the synthetized species (109.1 - 111.2°). These data are in good accordance with the structure of the dimeric lithiated tetrahedral intermediate $[(Ph)_2(NMe_2)C(OLi)THF]_2$ **IV** formed upon addition of PhLi to simple *N,N*-dimethylamide, isolated and characterized by Boche *et. al.*[19] The replacement of lithium atoms with TMS group has not a dramatic effect on the overall bond lengths and the angles around the quaternary C1 atom. Major differences are observed in the C1-N1 bond length that is longer respect *O*-TMS hemiaminals (1.500 Å), whereas the C1-O1 bond is shorter (1.371 Å). In order to enrich the characterization of these species the chemical shift of the ^{13}C NMR of tetrahedral C1 is reported. As shown in Figure 7.2, this parameter is quite constant (93.6-99.3 ppm) and similar to **IV** (94.3 ppm), confirming the tetrahedral nature of these newly synthesized species. To summarise, the replacement of the lithium atom with TMS group in the tetrahedral intermediate guarantees particularly stability allowing the facile synthesis, isolation, purification, in some cases crystallization, and storage with minimum precaution adopted (store at -20 °C as solid or in C_6H_6 solution) but maintaining the structural issues of the corresponding highly instable lithiated species.



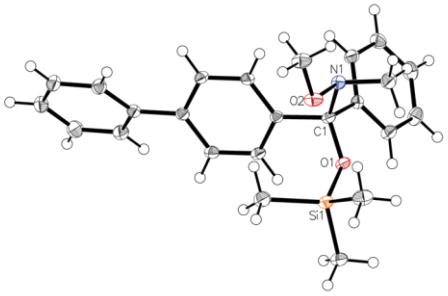
2j



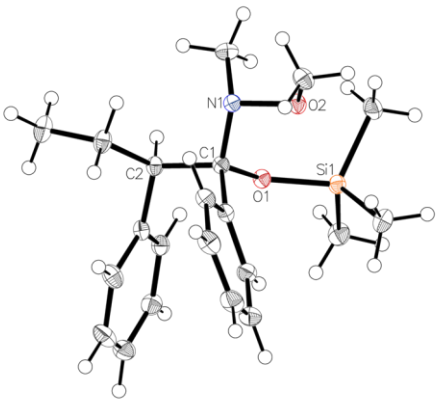
2k



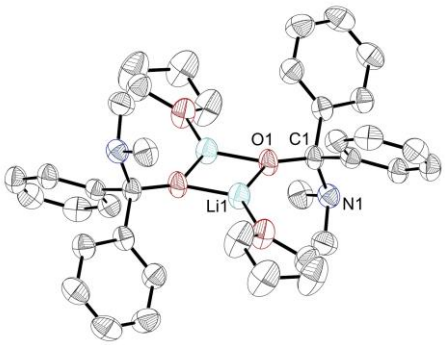
2p



2v

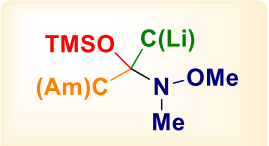


2ak



I

$[(Ph)_2(NMe_2)C(OLi)THF]_2$



Compound	2j	2k	2p	2v	2ak	IV[19]
Formula	$C_{19}H_{27}NO_2Si$	$C_{20}H_{29}NO_3Si$	$C_{16}H_{22}INO_2SSi$	$C_{24}H_{29}NO_2Si$	$C_{21}H_{31}NO_2Si$	$C_{19}H_{24}LiO_2$
Space Group	P -1	$P2_1/n$	P -1	P -1	P -1	P2(1)/c
Crystal system	triclinic	monoclinic	triclinic	triclinic	triclinic	monoclinic
a (Å)	7.544	16.201	8.676	7.697	9.511	10.594
b (Å)	9.524	7.554	9.936	12.027	9.828	9.285
c (Å)	13.629	16.895	11.753	12.226	12.336	17.755
α (°)	94.460	90.000	81.252	79.289	82.092	90.000
β (°)	103.672	103.876	75.310	80.249	86.101	93.927
γ (°)	102.48	90	80.367	87.507	64.391	90.000
Volume (Å^3)	920.4	2007.2	959.9	1096.0	1029.9	1742.3
R-Factor (%)	1.049	1.075	1.047	1.092	1.063	1.044
C1-N1 (Å)	1.464	1.471	1.474	1.477	1.474	1.500
C1-O1 (Å)	1.424	1.417	1.410	1.415	1.418	1.371
(Am)C-C1 (Å)	1.520	1.529	1.532	1.531	1.573	1.548
(Li)C-C1 (Å)	1.535	1.537	1.521	1.537	1.530	1.548
N1-OCH_3 (Å)	1.453	1.458	1.451	1.455	1.456	-
N1-CH_3 (Å)	1.468	1.469	1.473	1.473	1.467	1.482
C *sp*^{3} mean angle (°)	110.0	109.7	109.4	111.2	109.1	108.2
C *sp*^{3} ^{13}C δ (ppm)	97.5	97.3	93.6	97.4	99.3	94.3

Figure 7.2. Selected example of X-Ray analysis of solid compounds **2j**, **2k**, **2p**, **2v**, **2ak** in comparison with the crystal structure of dimeric lithiated tetrahedral intermediate **IV** reported by Adler *et al*. In the table, crystal parameters, bonds lengths, C sp^3 mean angles and C sp^3 ^{13}C NMR chemical shifts are summarized.

7.4 Conclusion

In summary, an efficient methodology for the isolation and characterization of *O*-TMS protected hemiaminals generated upon the addition of a generic alkyl and (hetero)aryllithium to Weinreb amides was described. The reaction has proven to be highly chemoselective allowing the formation of a plethora of derivatives presenting different functionalities. It is worth to mention some pivotal reaction conditions for the outcome of the methodology: a) the used of Schlenk condition; b) the employment of ImTMS as trapping agent; c) the use of Brockmann grade IV

neutral alumina as stationary phase for chromatography; d) benzene-d_6 for recording the NMR analysis. These precautions avoid the collapse of the tetrahedral intermediates during the course of reaction and during the workup and purification steps. In addition, the exceptionality of the Weinreb amide was highlighted by comparison with other amidic functionalities, obtaining the desired adduct only from the chelating amide. The possibility to obtain single crystals of some selected compounds, together with their X-Ray analysis, gave further evidence of their chemical stability and easy handling, which allowed an unprecedent crystallographic analysis of these stable tetrahedral intermediates. These results could in the future enrich the actual level of comprehension of the stability and manipulation of these interesting transient tetrahedral species.

7.5 Experimental section

7.5.1 General informations

Materials and methods. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe and used as received without further purifications. All the reactions were carried out under inert atmosphere of argon. THF was distilled over Na/benzophenone. Reactions were monitored by thin-layer chromatography (TLC) on aluminium sheets pre-coated with neutral aluminium oxide (60 Merck F254) with UV light (254 nm) as visualizing agent and/or phosphomolybdic acid in ethanol solution was used as revealing system. The following solutions of organolithium reagents were furnished by Aldrich and were used with the following concentration: *n*-BuLi 2.5 M in hexanes, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane, *n*-HexLi 2.3 M in hexane, MeLi 1.6 M in DEE, *i*BuLi 1.7 M in heptane, lithium phenylacetylide 1.0 M in THF, PhLi 1.8 M in dibutyl ether and 2-ThLi 1.0 M in THF. Cyclopropyllithium, cyclobutyllithium, (1,3-dithian-2-yl)lithium and 4-methoxyphenyllithium (4-OMePhLi) were prepared according to known procedures.[20] The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[21] Weinreb amides **1a-ab** were prepared according to known procedures.[22, 23, 24, 25]

Instrumentation. ^{1}H, ^{13}C, ^{19}F, ^{15}N, ^{77}Se, ^{119}Sn NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, 40 MHz ^{15}N, 76 MHz for ^{77}Se and 149 MHz for ^{119}Sn) at 298 K using a directly detecting broadband observe (BBFO) probe. The centre of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 7.16 ppm (^{1}H in C_6D_6), δ 77.00 ppm (^{13}C in $CDCl_3$) and δ 128.16 ppm (^{13}C in C_6D_6). ^{15}N NMR spectra (gs-HMBC, gs-HSQC) were referenced against neat, external nitromethane. For ^{19}F NMR spectra were referenced *via* the Ξ ratio (absolute referencing). ^{77}Se spectra were referenced against diphenyldiselane (δ Ph_2Se_2 463 ppm). ^{119}Sn NMR spectra were referenced against external Me_4Sn (0.0 ppm). Chemical shifts (δ) are given in parts per million (ppm) and

coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad).

7.5.2. Preparation of Neutral Aluminium Oxide Brockmann grade 4 (AloxN-BG4)

91 g of Aluminium Oxide Neutral (Brockmann grade 1, commercial) were put into a 500 mL flask and 9 g of distilled water were slowly added with a pipette on the glass surface. The flask was connected to a rotary evaporator and the mixture was stirred for 1 h at 20 °C *without* application of any reduced pressure. Once the mixture appeared homogeneous, the rotation was interrupted and the resulting AloxN-BG4 could be used as a normal stationary phase for liquid chromatography.

*7.5.3 Weinreb amides **1a-ab** synthesis: general procedure*

To a solution of the appropriate benzoic acid (1.0 eq., 5 mmol) in DCM (10 mL, 0.5 M) was added 1,1-carbonyldiimidazole (CDI) (1.1 eq., 5.5 mmol, 178 mg) at 0 °C. After stirring for 2 h at 0 °C, *N,O*-dimethylhydroxylamine hydrochloride (1.2 eq., 6 mmol, 555 mg) was added. The mixture was warmed at room temperature and stirred overnight. The mixture was firstly washed twice with 1 M aq. HCl (10 mL) then was washed twice with a saturated solution of Na_2CO_3 (10 mL) and finally was extracted with EtOAc (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under vacuum to give the corresponding amide **1a-ab** that was purified by flash column chromatography and/or by recrystallization.

*7.5.4. General Procedure for the Synthesis of O-TMS Hemiaminals **2a-ar***

The selected Weinreb amide (0.5 mmol, 1.0 eq.) was dissolved in dry THF (5 mL) and the solution was cooled to -78 °C under anhydrous conditions. The selected organolithium reagent (0.75 mmol, 1.5 eq.) was added dropwise, and the mixture was allowed to stir at -78 °C for 10 minutes. Then, 1-(trimethylsilyl)imidazole (1.5 mmol, 3 eq.) was added and the reaction was allowed to reach room temperature overnight. The reaction was quenched with 5% $NaHCO_3$ solution (5 mL) and extracted with DEE (3 x 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and, after removing the solvent under reduced pressure (bath 20 °C), the crude was purified by column chromatography on neutral alumina (grade IV).

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-1 [(trimethylsilyl)oxy] ethanamine (2a):** General procedure starting from **1a** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2a** as a colourless oil (120 mg, 90%, R_f = 0.82 *n*-hexane/ DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.63-7.58 (m, 2H), 7.09-7.05 (m, 2H), 3.43 (s, 3H), 2.38 (s, 3H), 2.14 (s, 3H), 1.74 (s, 3H), 0.34

(s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 143.6, 136.7, 128.9, 126.5, 94.1, 60.6, 36.4, 29.4, 21.0, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ -204.3 (s).

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]-1-pentanamine (2b):** General procedure starting from **1a** and *n*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2b** as a colourless oil (128 mg, 83%, R_f = 0.80 *n*-hexane/ DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.58-7.56 (m, 2H), 7.08-7-04 (m, 2H), 3.47 (s, 3H), 2.44-2.35 (m, 1H), 2.35 (s, 3H), 2.14 (s, 3H), 2.08-2.00 (m, 1H), 1.40-1.29 (m, 1H), 1.30-1.12 (m, 2H), 1.06-0.94 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H), 0.40 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 141.4, 136.7, 128.8, 127.1, 97.4, 60.5, 40.5, 36.7), 27.0, 23.4, 21.1, 14.3, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -203.9 (s).

***N*-Methoxy-*N*,2-dimethyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]-1-butanamine (2c):** General procedure starting from **1a** and *s*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2c** as a colourless oil (134 mg, 87%, R_f = 0.85 *n*-hexane/ DEE 98/2 v/v). The two diastereomers (dr 1:1) were note separable by chromatography. ^{1}H NMR (400 MHz, C_6D_6, mixture of diastereoisomers): δ 7.55-7.45 (br m, 4H), 7.05-7.03 (m, 4H), 3.40 (s, 3H), 3.39 (s, 3H), 2.43 (s, 3H), 2.42 (s, 3H), 2.35-2.25 (m, 2H), 2.20-2.14 (m, 1H) superimposed to 2.15 (s, 6H), 1.96-1.86 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.90-0.78 (m, 10H), 0.60-0.50 (m, 1H), 0.39 (s, 9H), 0.38 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6, mixture of diastereoisomers): δ 138.5, 138.5, 136.58, 136.57, 128.6, 128.0, 100.06, 100.03, 59.0, 58.9, 42.8, 42.2, 36.7, 36.4, 25.7, 25.2, 21.1, 15.2, 14.8, 12.7, 12.2, 2.90, 2.87. ^{15}N NMR (40 MHz, C_6D_6, mixture of diastereoisomers): δ -209.5 (s).

***N*-Methoxy-*N*,3-dimethyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]-1-butanamine (2d):** General procedure starting from **1a** and *i*BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2d** as a colourless oil (131 mg, 85%, R_f = 0.87 *n*-hexane/ DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.59-7.57 (m, 2H), 7.07-7.05 (m, 2H), 3.43 (s, 3H), 2.34 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H), 2.00 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.69-1.57 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.56 (d, *J* = 6.6 Hz, 3H), 0.41 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 141.3, 136.8, 128.8, 127.3, 97.2, 60.3, 48.8, 36.6, 24.7, 24.5, 24.1, 21.1, 3.1. ^{15}N NMR (40 MHz, C_6D_6): δ -203.0 (s).

***N*-Methoxy-*N*,2,2-trimethyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]-1-propanamine (2e):** General procedure starting from **1a** and *t*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2e** as a colourless oil (113 mg, 73%, R_f = 0.80 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.53-7.51 (m, 2H), 7.02-7.00 (m, 2H), 3.24 (s, 3H), 2.46 (s, 3H), 2.15 (s, 3H), 1.08 (s, 9H), 0.37 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 141.1, 136.4, 128.9, 127.6, 101.4, 57.6, 40.6, 38.5, 28.3, 21.0, 3.3. ^{15}N NMR (40 MHz, C_6D_6): δ -208.8 (s).

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]-1-heptanamine (2f):** General procedure starting from **1a** and *n*-HexLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2f** as a colourless oil (131 mg, 78%, R_f = 0.65 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.60-7.58 (m, 2H), 7.09-7.05 (m, 2H), 3.48 (s, 3H), 2.47-2.38 (m, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 2.10-2.01 (m, 1H), 1.46-1.33 (m, 1H), 1.30-1.12 (m, 3H), 1.18-1.09 (m, 3H), 1.06-0.96 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.42 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 141.4, 136.7, 128.8, 127.1, 97.4, 60.5, 40.7, 36.7, 32.3, 30.1, 24.8, 23.0, 21.1, 14.2, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -203.8 (s).

1-Cyclopropyl-*N*-methoxy-*N*-methyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]methanamine (2g): General procedure starting from **1a** and freshly prepared cyclopropyllithium. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2g** as a colourless oil (119 mg, 81%, R_f = 0.90 *n*-hexane/ DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.56-7.54 (m, 2H), 7.02-6.98 (m, 2H), 3.48 (s, 3H), 2.55 (s, 3H), 2.12 (s, 3H), 1.53 (br s, 1H), 0.44-0.37 (m, 2H), 0.37 (s, 9H), 0.28-0.23 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 139.7, 136.8, 128.3, 128.2, 96.7, 60.1, 37.1, 21.0, 20.5, 3.2, 2.8. ^{15}N NMR (40 MHz, C_6D_6): δ -206.0 (s).

1-Cyclobutyl-*N*-methoxy-*N*-methyl-1-(4-methylphenyl)-1-[(trimethylsilyl)oxy]methanamine (2h): General procedure starting from **1a** and freshly prepared cyclobutyllithium. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2h** as a colourless oil (115 mg, 75%, R_f = 0.88 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.60-7.58 (m, 2H), 7.08-7.06 (m, 2H), 3.19-3.14 (s, 3H), 3,17 (m, 1H), 2.43 (s, 3H), 2.15 (s, 3H), 2.05-1.95 (m, 1H), 1.93-1.84 (m, 2H), 1.76-1.69 (m, 1H), 1.63-1.51 (m, 1H), 1.39-1.29 (m, 1H), 0.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 139.6, 136.7, 128.5, 128.3, 98.0, 59.8, 43.4, 37.1, 24.8, 24.5, 21.1, 17.6, 2.9. ^{15}N NMR (40 MHz, C_6D_6): δ -209.0 (s).

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-3-phenyl-1-[(trimethylsilyl)oxy]-2-propyn-1-amine (2i):** General procedure starting from **1a** and lithium phenylacetylide. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2i** as a colourless oil (141 mg, 80%, R_f = 0.40 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.98-7.94 (m, 2H), 7.43-7.41 (m, 2H), 7.08-7.06 (m, 2H), 6.96-6.94 (m, 3H), 3.56 (s, 3H), 2.63 (s, 3H), 2.11 (s, 3H), 0.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 140.7, 138.0, 131.9, 128.8, 128.69, 128.67, 127.7, 123.2, 90.4, 90.2, 86.8, 61.1, 37.2, 21.1, 1.9. ^{15}N NMR (40 MHz, C_6D_6): δ -206.2 (s).

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-1-phenyl-1-[(trimethylsilyl)oxy]methanamine** (**2j):** General procedure starting from **1a** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2j** as a white solid (140 mg, 85%, R_f = 0.72 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.77-7.73 (m, 2H), 7.65-7.63 (m, 2H), 7.16-7.12 (m, 2H),

7.02-6.98 (m, 1H), 6.98-6.94 (m, 2H), 3.40 (s, 3H), 2.40 (s, 3H), 2.05 (s, 3H), 0.27 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 146.6, 143.6, 136.5, 128.9, 128.1, 127.1, 127.0, 97.5, 58.1, 35.8, 21.0, 2.7.

***N*-Methoxy-1-(4-methoxyphenyl)-*N*-methyl-1-(4-methylpheny)-1-[(trimethylsilyl)oxy]methanamine (2k):** General procedure starting from **1a** and freshly prepared 4-OMePhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2k** as a white solid (147 mg, 82%, R_f = 0.45 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.68-7.64 (m, 4H), 7.01-6.98 (m, 2H), 6.76-6.74 (m, 2H), 3.43 (s, 3H), 3.26 (s, 3H), 2.44 (s, 3H), 2.08 (s, 3H), 0.29 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 159.1, 143.9, 138.7, 136.4, 128.8, 128.3, 127.0, 113.5, 97.3, 58.1, 54.7, 35.8, 21.0, 2.8.

***N*-Methoxy-*N*-methyl-1-(4-methylphenyl)-1-(2-thienyl)-1-[(trimethylsilyl)oxy]methanamine (2l):** General procedure starting from **1a** and 2-ThLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2l** as a brown oil (126 mg, 75%, R_f = 0.80 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.74-7.70 (m, 2H), 6.99-6.97 (m, 2H), 6.97 (dd, *J* = 3.6, 1.3 Hz, 1H), 6.83 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.66 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.45 (s, 3H), 2.44 (s, 3H), 2.07 (s, 3H), 0.25 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 150.6, 142.6, 137.1, 128.8, 127.3, 126.4, 125.9, 124.8, 95.6, 58.5, 36.0, 21.0, 2.4. ^{15}N NMR (40 MHz, C_6D_6): δ -208.8 (s).

1-(3-Chlorophenyl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]ethanamine (2m): General procedure starting from **1b** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2m** as a colourless oil (125 mg, 87%, R_f = 0.78 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.80-7.78 (m, 1H), 7.43-7.39 (m, 1H), 7.10-7.08 (m, 1H), 6.93-6.89 (m, 1H), 3.33 (s, 3H), 2.22 (s, 3H), 1.56 (s, 3H), 0.26 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 148.7, 134.4, 129.5, 127.6, 127.0, 124.7, 93.7, 60.6, 36.3, 29.2, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -205.7 (s).

1-(2-Fluorophenyl)-*N*-methoxy-*N*,3-dimethyl-1-[(trimethylsilyl)oxy]-1-butanamine (2n): General procedure starting from **1c** and *i*BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2n** as a colourless oil (124 mg, 79%, R_f = 0.85 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.85-7.81 (m, 1H), 6.92-6.88 (m, 2H), 6.82-6.78 (m, 1H), 3.44 (s, 3H), 2.56-2.50 (m, 1H), 2.39-2.34 (m, 1H), 2.27 (s, 3H), 1.68-1.58 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H), 0.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 160.1 (d, *J* = 249.5 Hz, 1C), 131.0 (d, *J* = 11.8 Hz, 1C), 130.0 (d, *J* = 3.5 Hz, 1C), 129.8 (d, *J* = 8.3 Hz, 1C), 123.8 (d, *J* = 3.6 Hz, 1C), 116.2 (d, *J* = 24.0 Hz, 1C), 96.0 (d, *J* = 7.1 Hz, 1C), 60.5, 45.9 (d, *J* = 3.0 Hz, 1C), 36.9, 25.2, 24.2, 23.8, 3.0. ^{19}F NMR (376 MHz, C_6D_6): δ -108.9 (m). ^{15}N NMR (40 MHz, C_6D_6): δ -206.0 (s).

1-(4-Fluorophenyl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]-1-heptanamine (2o): General procedure starting from **1d** and *n*-HexLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2o** as a colourless oil (140 mg, 82%, R_f = 0.90 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.46-7.43 (m, 2H), 6.88-6.84 (m, 2H), 3.43 (s, 3H), 2.38-2.30 (m, 1H), 2.24 (s, 3H), 1.96-1.89 (m, 1H), 1.34-1.09 (m, 7H), 0.89-0.84 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H), 0.37 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 162.5 (d, J = 245.0 Hz, 1C), 140.0 (d, J = 3.1 Hz, 1C), 128.8 (d, J = 7.8 Hz, 2C), 114.8 (d, J = 21.0 Hz, 2C), 97.0, 60.5, 40.6, 36.5, 32.2, 30.0, 24.7, 23.0, 14.2, 2.6. ^{19}F NMR (376 MHz, C_6D_6): δ -115.9 (m). ^{15}N NMR (40 MHz, C_6D_6): δ -204.7 (s).

1-(4-Iodophenyl)-*N*-methoxy-*N*-methyl-1-(2-thienyl)-1-[(trimethylsilyl)oxy]methanamine (2p): General procedure starting from **1e** and 2-ThLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2p** as a white solid (172 mg, 77%, R_f = 0.53 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.45-7.43 (m, 2H), 7.35-7.33 (m, 2H), 6.82 (dd, J = 3.6, 1.2 Hz, 1H), 6.81 (dd, J = 5.1, 1.2 Hz, 1H), 6.63 (dd, J = 5.1, 3.6 Hz, 1H), 3.34 (s, 3H), 2.31 (s, 3H), 0.18 (s, 9H). ^{13}C NMR (100 MHz, C_6D_6): δ 149.8, 145.1, 137.2, 129.3, 126.6, 125.9, 125.1, 95.2, 93.6, 58.5, 35.9, 2.3.

1-(4-Bromophenyl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]methanamine (2q): General procedure starting from **1f** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2q** as a white solid (158 mg, 80%, R_f = 0.48 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.61-7.59 (m, 2H), 7.41-7.37 (m, 2H), 7.23-7.19 (m, 2H), 7.14-7.10 (m, 2H), 7.02-6.98 (m, 1H), 3.30 (s, 3H), 2.27 (s, 3H), 0.19 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 145.7, 145.4, 131.3, 128.8, 128.2, 127.4, 126.8, 121.3, 97.0, 58.0, 35.6, 2.6.

***N*-Methoxy-*N*-methyl-1-[3-(trifluoromethyl)phenyl]-1-[(trimethylsilyl)oxy]-1-pentanamine (2r):** General procedure starting from **1g** and *n*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2r** as a colourless oil (154 mg, 85%, R_f = 0.65 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 8.09-8.07 (m, 1H), 7.65-7.63 (m, 1H), 7.34-7.31 (m, 1H), 7.04-7.00 (m, 1H), 3.36 (s, 3H), 2.33-2.22 (m, 1H), 2.18 (s, 3H), 1.97-1.90 (m, 1H), 1.30-1.10 (m, 3H), 0.85-0.75 (m, 1H), 0.71 (t, J = 7.3 Hz, 3H), 0.33 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 145.6, 130.6 (q, J = 31.9 Hz, 1C), 130.5 (q, J = 1.3 Hz, 1C), 128.6, 125.2 (q, J = 272.1 Hz, 1C), 124.3 (q, J = 3.8 Hz, 1C), 123.9 (q, J = 4.0 Hz, 1C), 96.9, 60.5, 40.2, 36.5, 26.6, 23.1, 14.1, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -205.9 (s). ^{19}F NMR (376 MHz, C_6D_6): δ -62.2 (s).

***N*-Methoxy-*N*-methyl-1-phenyl-1-[(trimethylsilyl)oxy]ethanamine (2s):** General procedure starting from **1h** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2s** as a colourless oil (111 mg, 88%, R_f = 0.77 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.68-7.64 (m, 2H),

7.24-7.20 (m, 2H), 7.13-7.09 (m, 1H), 3.41 (s, 3H), 2.32 (s, 3H), 1.69 (s, 3H), 0.32 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 146.4, 128.2, 127.4, 126.5, 94.1, 60.6, 36.4, 29.4, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ -204.6 (s).

***N*-Methoxy-*N*-methyl-1-phenyl-1-[(trimethylsilyl)oxy]-1-pentanamine (2t):** General procedure starting from **1h** and *n*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2t** as a colourless oil (123 mg, 83%, R_f = 0.88 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.66-7.62 (m, 2H), 7.24-7.20 (m, 2H), 7.12-7.08 (m, 1H), 3.45 (s, 3H), 2.43-2.35 (m, 1H), 2.30 (s, 3H), 2.06-1.99 (m, 1H), 1.39-1.07 (m, 3H), 1.01-0.89 (m, 1H), 0.75 (t, J = 7.3 Hz, 3H), 0.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 144.3, 128.1, 127.4, 127.1, 97.4, 60.5, 40.4, 36.7, 26.9, 23.3, 14.3, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -204.1 (s).

***N*-Methoxy-1-(4-methoxyphenyl)-*N*-methyl-1-(3-methylphenyl)-1-[(trimethylsilyl)oxy]methanamine (2u):** General procedure starting from **1i** and freshly prepared 4-OMePhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2u** as a white solid (149 mg, 83%, R_f = 0.45 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.67-7.61 (m, 4H), 7.15-7.11 (m, 1H), 6.88-6.84 (m, 1H), 6.76-6.72 (m, 2H), 3.43 (s, 3H), 3.25 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H), 0.29 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 159.1, 146.7, 138.6, 137.4, 128.3, 128.1, 127.8, 124.1, 113.5, 97.4, 58.1, 54.7, 35.9, 21.6, 2.8. ^{15}N NMR (40 MHz, C_6D_6): δ -210.1 (s).

1-(4-Biphenylyl)-*N*-methoxy-*N*-methyl-1-phenyl-1-[(trimethylsilyl)oxy]methanamine (2v): General procedure starting from **1j** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2v** as a white solid (226 mg, 76%, R_f = 0.70 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.80-7.76 (m, 4H), 7.46-7.41 (m, 4H), 7.21-7.17 (m, 3H), 7.15-7.07 (m, 2H), 7.05-6.97 (m, 1H), 3.42 (s, 3H), 2.42 (s, 3H), 0.29 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 146.3, 145.4, 141.3, 140.2, 129.0, 128.2, 127.5, 127.4, 127.4, 127.26, 127.0, 97.4, 58.1, 35.8, 2.8.

***N*-Methoxy-1-(4-methoxyphenyl)-*N*,2,2-trimethyl-1-[(trimethylsilyl)oxy]-1-propanamine (2w):** General procedure starting from **1k** and *t*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2w** as a colourless oil (133 mg, 82%, R_f = 0.60 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.53-7.48 (m, 2H), 6.79-6.75 (m, 2H), 3.35 (s, 3H), 3.25 (s, 3H), 2.46 (s, 3H), 1.08 (s, 9H), 0.37 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6) δ: 159.2, 136.0, 130.0, 112.3, 101.2, 57.6, 54.7, 40.7, 38.5, 28.3, 3.3. ^{15}N NMR (40 MHz, C_6D_6): δ -208.8 (s).

1-(1,3-Dithian-2-yl)-*N*-methoxy-1-(4-methoxyphenyl)-*N*-methyl-1-[(trimethylsilyl)oxy]methanamine (2x): General procedure starting from **1k** and freshly prepared (1,3-dithian-2yl)lithium. Purification by column chromatography on neutral

alumina (Brockmann grade IV, *n*-hexane/DEE 9/1 v/v) gave **2x** as a colourless oil (155 mg, 80%, R_f = 0.38 *n*-hexane/DEE 9/1 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.86-7.84 (m, 2H), 6.83-6.81 (m, 2H), 5.05-5.03 (m, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 2.43 (s, 3H), 2.43-2.31 (m, 3H), 2.2-2.21 (m, 1H), 1.37-1.28 (m, 2H), 0.51 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 160.1, 132.4, 129.9, 112.9, 97.6, 59.4, 57.9, 54.6, 36.5, 30.7, 30.4, 25.8, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -211.8 (s).

***N*-Methoxy-*N*,3-dimethyl-1-[4-(methylsulfanyl)phenyl]-1-[(trimethylsilyl)oxy]-1-butanamine (2y):** General procedure starting from **1l** and *i*BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 9/1 v/v) gave **2y** as a colourless oil (140 mg, 89%, R_f = 0.25 *n*-hexane/DEE 9/1 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.52.7.50 (m, 2H), 7.16-7.14 (m, 2H), 3.40 (s, 3H), 2.33-2.27 (m, 1H) superimposed to 2.27 (s, 3H), 2.01 (s, 3H), 1.95 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.64-1.54 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.56 (d, *J* = 6.6 Hz, 3H), 0.40 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 141.0, 138.0, 127.9, 126.1, 97.0, 60.3, 48.7, 36.6, 24.7, 24.4, 24.2, 15.3, 3.0. ^{15}N NMR (40 MHz, C_6D_6): δ -203.4 (s).

1-(1,3-Benzodioxol-5-yl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]ethanamine (2z): General procedure starting from **1m** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 8/2 v/v) gave **2z** as a colourless oil (119 mg, 84%, R_f = 0.27 *n*-hexane/DEE 8/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.28 (d, *J* = 1.8 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 3.38 (s, 3H), 2.35 (s, 3H), 1.67 (s, 3H), 0.29 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 148.0, 147.2, 140.7, 119.8, 107.8, 107.6, 101.0, 94.0, 60.6, 36.3, 29.4, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ -204.6 (s).

1-(2-Furyl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]ethanamine (2aa): General procedure starting from **1n** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2aa** as a colourless oil (100 mg, 79%, R_f = 0.62 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.06 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.29 (dd, *J* = 3.2, 0.9 Hz, 1H), 6.07 (dd, *J* = 3.2, 1.8 Hz, 1H), 3.39 (s, 3H), 2.50 (s, 3H), 1.79 (s, 3H), 0.22 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 157.6, 141.5, 110.4, 107.2, 90.5, 60.6, 36.6, 25.4, 2.1. ^{15}N NMR (40 MHz, C_6D_6): δ -208.3 (s).

1-Cyclopropyl-*N*-methoxy-*N*-methyl-1-(2-thienyl)-1-[(trimethylsilyl)oxy]methanamine (2ab): General procedure starting from **1o** and freshly prepared cyclopropyllithium. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ab** as a colourless oil (107 mg, 75%, R_f = 0.90 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ: 6.98 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.86 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.72 (dd, *J* = 5.1, 3.5 Hz, 1H), 3.48 (s, 3H), 2.56 (s, 3H), 1.59-1.51 (br m, 1H), 0.45-0.38 (br m, 2H), 0.33-0.27 (br m, 2H) superimposed

to 0.31 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 147.9, 126.4, 125.4, 124.8, 95.3, 60.1, 37.1, 20.4, 3.5, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -205.3 (s).

***N*-Methoxy-*N*-methyl-1,1-di(2-thienyl)-1-[(trimethylsilyl)oxy]methanamine (2ac):** General procedure starting from **1o** and 2-ThLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ac** as a colourless oil (126 mg, 77%, R_f = 0.55 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.10 (dd, J = 3.6, 1.3 Hz, 2H), 6.86 (dd, J = 5.1, 1.3 Hz, 2H), 6.68 (dd, J = 5.1, 3.6 Hz, 2H), 3.45 (s, 3H), 2.49 (s, 3H), 0.19 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 149.0, 126.8, 126.5, 125.4, 93.4, 58.9, 36.3, 1.9. ^{15}N NMR (40 MHz, C_6D_6): δ -208.0 (s).

4-(4-Butyl-3,6,6-trimethyl-2,5-dioxa-3-aza-6-silaheptan-4-yl)benzonitrile (2ad): General procedure starting from **1p** and *n*-BuLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ad** as a colourless oil (139 mg, 87%, R_f = 0.20 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.33-7.31 (m, 2H), 7.11-7.09 (m, 2H), 3.34 (s, 3H), 2.28-2.20 (m, 1H), 2.10 (s, 3H), 1.84-1.76 (m, 1H), 1.21-1.08 (m, 3H), 0.75 (t, J = 7.2 Hz, 3H), 0.69-0.64 (m, 1H), 0.31 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 148.8, 131.7, 127.6, 118.9, 111.8, 96.8, 60.5, 40.0, 36.5, 26.6, 23.1, 14.2, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -206.2 (s).

***N*-Methoxy-*N*-methyl-1-{4-[(*E*)-phenyldiazenyl]phenyl}-1-[(trimethylsilyl)oxy]ethanamine (2ae):** General procedure starting from **1q** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ae** as a red oil (155 mg, 87%, R_f = 0.40 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 8.12-8.08 (m, 2H), 8.05-8.03 (m, 2H), 7.77-7.75 (m, 2H), 7.21-7.16 (m, 2H), 7.06-7.08 (m, 1H), 3.40 (s, 3H), 2.33 (s, 3H), 1.67 (s, 3H), 0.32 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 153.4, 152.5, 149.4, 131.1, 129.3, 127.4, 123.4, 123.0, 94.0, 60.6, 36.4, 29.1, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ 127.7, 127.3, -205.3 (s).

***N*-Methoxy-*N*-methyl-1-phenyl-1-[(trimethylsilyl)oxy]-1-(4-vinylphenyl)methanamine (2af):** General procedure starting from **1r** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2af** as a colourless oil (140 mg, 82%, R_f = 0.55 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.73-7.71 (m, 2H), 7.66-7.63 (m, 2H), 7.20-7.18 (m, 2H), 7.14-7.12 (m, 2H), 7.02-6.98 (m, 1H), 6.53 (dd, J = 17.6, 10.9 Hz, 1H), 5.56 (dd, J = 17.6, 1.0 Hz, 1H), 5.04 (dd, J = 10.9, 1.0 Hz, 1H), 3.39 (s, 3H), 2.37 (s, 3H), 0.25 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, C_6D_6): δ 146.2, 146.0, 137.0, 136.6, 128.2, 127.2, 127.2, 126.9, 126.2, 113.5, 97.4, 58.1, 35.8, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -210.6. (s)

***N*-Methoxy-*N*-methyl-1-{3-[(trimethylsilyl)ethynyl]phenyl}-1-[(trimethylsilyl)oxy]-1-heptanamine (2ag):** General procedure starting from **1s** and *n*-HexLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ag** as a colourless oil (178 mg, 85%, R_f = 0.75 *n*-

hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 8.02 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.45-7.42 (m, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 3.38 (s, 3H), 2.36-2.29 (m, 1H), 2.21 (s, 3H), 1.97-1.89 (m, 1H), 1.32-1.23 (m, 1H), 1.17-1.02 (m, 6H), 0.91-0.85 (m, 1H), 0.79 (t, *J* = 7.0 Hz, 3H), 0.34 (s, 9H), 0.21 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 144.7, 131.2, 130.7, 128.2, 127.5, 123.5, 106.5, 97.1, 94.1, 60.5, 40.4, 36.6, 32.2, 29.9, 24.6, 23.0, 14.2, 2.6, 0.1. ^{15}N NMR (40 MHz, C_6D_6): δ -204.7 (s).

***N*-Methoxy-*N*-methyl-1-[4-(phenylselanyl)phenyl]-1-[(trimethylsilyl)oxy]-1-heptanamine (2ah):** General procedure starting from **1t** and *n*-HexLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ah** as a colourless oil (194 mg, 81%, R_f = 0.62 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.47-7.44 (m, 6H), 6.95-6.93 (m, 3H), 3.42 (s, 3H), 2.38-2.31 (m, 1H), 2.26 (s, 3H), 2.00-1.92 (m, 1H), 1.35-1.28 (m, 1H), 1.22-1.06 (m, 6H), 0.98-0.87 (m, 1H), 0.81 (t, *J* = 7.0 Hz, 3H), 0.37 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 143.5, 133.6, 132.4, 131.5, 130.6, 129.6, 128.3, 127.5, 97.2, 60.5, 40.5, 36.7, 32.2, 30.0, 24.7, 23.0, 14.2, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -204.7 (s). ^{77}Se NMR (76 MHz, C_6D_6): δ 409.3 (s).

***N*-Methoxy-*N*-methyl-1-phenyl-1-[4-(tributylstannyl)phenyl]-1-[(trimethylsilyl)oxy]methanamine (2ai):** General procedure starting from **1u** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ai** as a colourless oil (217 mg, 72%, R_f = 0.75 *n*-hexane/DEE 98/2 v/v).^{1}H NMR (400 MHz, C_6D_6): δ 7.81-7.80 (m, 2H), 7.77-7.75 (m, 2H), 7.53-7.51 (m, 2H), 7.13-7.09 (m, 2H), 6.99-6.95 (m, 1H), 3.41 (s, 3H), 2.39 (s, 3H), 1.60-1.52 (m, 6H), 1.37-1.28 (m, 6H), 1.07-1.03 (m, 6H), 0.87 (t, *J* = 7.4 Hz, 9H), 0.27 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 146.3, 140.3, 136.4, 128.1, 127.2, 127.0, 126.8, 97.5, 58.1, 35.8, 29.5, 27.8, 13.9, 9.8, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -210.5 (s). ^{119}Sn NMR (149 MHz, C_6D_6): δ -45.0 (s).

***N*-Methoxy-*N*-methyl-1,2-diphenyl-1-[(trimethylsilyl)oxy]-1-propanamine (2aj):** General procedure starting from **1v** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2aj** as a colourless oil (135 mg, 79%, R_f = 0.70 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.09-7.04 (m, 8H), 6.82-6.78 (m, 2H), 3.36 (br s, 1H), 3.29 (s, 3H), 2.52 (s, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 0.22 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 142.1, 140.5, 130.9, 129.4, 127.5, 126.9, 126.7, 126.5, 99.5, 58.4, 48.4, 35.5, 16.2, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -210.6 (s).

***N*-Methoxy-*N*-methyl-1,2-diphenyl-1-[(trimethylsilyl)oxy]-1-butanamine (2ak):** General procedure starting from **1w** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2ak** as a white solid (134 mg, 75%, R_f = 0.75 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.14-7.00 (m, 8H), 6.75-6.71 (m, 2H), 3.31 (s, 3H), 3.15-3.11 (m, 1H), 2.51 (s, 3H), 2.10-2.06 (m, 1H), 1.56-1.43 (m, 1H), 0.69 (t, *J* = 7.4 Hz, 3H), 0.23 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6):

δ 141.2, 139.7, 131.6, 129.2, 129.1, 127.0, 126.7, 126.6, 99.3, 58.6, 57.4, 35.8, 22.9, 12.5, 3.2. ^{15}N NMR (40 MHz, C_6D_6): δ -210.0 (s).

2-(4-Isobutylphenyl)-*N*-methoxy-*N*-methyl-1-phenyl-1-[(trimethylsilyl)oxy]-1-propanamine (2al): General procedure starting from **1x** and PhLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2al** as a colourless oil (160 mg, 80%, R_f = 0.85 *n*-hexane/DEE 98/2 v/v). The two diastereomers (dr 1:1) were note separable by chromatography. ^{1}H NMR (400 MHz, C_6D_6, mixture of diastereoisomers): δ 7.48-7.44 (m, 2H), 7.24-7.18 (m, 2H), 7.15-7.06 (m, 7H), 6.90 (d, *J* = 8.1 Hz, 4H), 6.79 (d, *J* = 8.1 Hz, 4H), 3.39 (br s, 2H), 3.30 (s, 6H), 2.54 (s, 6H), 2.36 (d, *J* = 7.1 Hz, 4H), 1.81-1.71 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 6H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.25 (s, 18H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6, mixture of diastereoisomers): δ 141.8, 140.7, 139.7, 139.4, 130.7, 129.0, 127.7, 127.51, 127.47, 127.41, 126.4, 99.6, 58.4, 48.1, 45.3, 35.5, 30.5, 22.4, 16.1, 3.1. ^{15}N NMR (40 MHz, C_6D_6, mixture of diastereoisomers): δ -210.6 (s).

1-(Adamantan-1-yl)-*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]ethanamine (2am): General procedure starting from **1y** and MeLi. Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 98/2 v/v) gave **2am** as a colourless oil (112 mg, 72%, R_f = 0.78 *n*-hexane/DEE 98/2 v/v). ^{1}H NMR (200 MHz, C_6D_6): δ 3.33 (s, 3H), 2.61 (s, 3H), 2.08-1.93 (m, 3H), 1.84-1.62 (m, 12H), 1.35 (s, 3H), 0.24 (s, 9H). ^{13}C{^{1}H} NMR (50 MHz, C_6D_6): δ 97.4, 59.6, 41.7, 40.1, 37.8, 37.6, 29.4, 18.4, 2.5. ^{15}N NMR (40 MHz, C_6D_6): δ -205.9 (s).

1-[4-(3,4,6,6-Tetramethyl-2,5-dioxa-3-aza-6-silaheptan-4-yl)phenyl]ethanone (2an): General procedure starting from **1z** and MeLi (2 eq.). Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 9/1 v/v) gave **2an** as a colourless oil (122 mg, 83%, R_f = 0.28 *n*-hexane/DEE 9/1 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.84-7.82 (m, 2H), 7.62-7.60 (m, 2H), 3.38 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.63 (s, 3H), 0.32 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 196.2, 151.0, 136.8, 128.3, 126.6, 94.0, 60.6, 36.4, 29.1, 26.2, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ -205.8 (s).

1-[4-(4-Butyl-3-ethyl-6,6-dimethyl-2,5-dioxa-3-aza-6-silaheptan-4-yl)phenyl]-1-pentanone (2ao): General procedure starting from **1z** and *n*-BuLi (2 eq.). Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 96/4 v/v) gave **2ao** as a colourless oil (152 mg, 80%, R_f = 0.58 *n*-hexane/DEE 94/6 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.93-7.91 (m, 2H), 7.66-7.63 (m, 2H), 3.43 (s, 3H), 2.62-2.58 (m, 2H), 2.40-2.32 (m, 1H), 2.27 (s, 3H), 2.03-1.95 (m, 1H), 1.71-1.64 (m, 2H), 1.37-1.10 (m, 5H), 0.98-0.86 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.3 Hz, 3H), 0.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 198.6, 148.9, 136.8, 128.0, 127.3, 97.3, 60.5, 40.2, 38.3, 36.7, 26.8, 26.7, 23.3, 22.8, 14.3, 14.2, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -205.3 (s).

1-[4-(4-Hexyl-3,6,6-trimethyl-2,5-dioxa-3-aza-6-silaheptan-4-yl)phenyl]-1-heptanone (2ap): General procedure starting from **1aa** and *n*-HexLi (2 eq.). Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 94/6 v/v) gave **2ap** as a colourless oil (178 mg, 82%, R_f = 0.50 *n*-hexane/DEE 94/6 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.96-7.94 (m, 2H), 7.68-7.65 (m, 2H), 3.44 (s, 3H), 2.68-2.58 (m, 2H), 2.42-2.33 (m, 1H), 2.29 (s, 3H), 2.06-1.95 (m, 1H), 1.76-1.68 (m, 2H), 1.40-1.32 (m, 1H), 1.28-1.10 (m, 12H), 0.94-0.84 (m, 1H) superimposed to 0.87 (t, *J* = 7.2 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.41 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 198.7, 148.9, 136.8, 128.1, 127.3, 97.3, 60.6, 40.5, 38.6, 36.4, 32.2, 32.1, 30.0, 29.4, 24.7, 24.6, 23.0, 22.9, 14.3, 14.2, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -205.2 (s).

Phenyl[4-(3,6,6-trimethyl-4-phenyl-2,5-dioxa-3-aza-6-silaheptan-4-yl)phenyl]methanone (2aq): General procedure starting from **1aa** and PhLi (2eq.). Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 8/2 v/v) gave **2aq** as a colourless oil (178 mg, 85%, R_f = 0.18 *n*-hexane/DEE 8/2 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.75-6.67 (m, 6H), 7.63-7.61 (m, 2H), 7.16-7.09 (m, 3H), 7.02-6.98 (m, 3H), 3.35 (s, 3H), 2.34 (s, 3H), 0.24 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 195.3, 150.6, 145.6, 138.5, 136.7, 131.9, 130.2, 130.1, 128.4, 128.3, 127.5, 126.84, 126.78, 97.3, 58.1, 35.7, 2.7. ^{15}N NMR (40 MHz, C_6D_6): δ -211.3 (s).

1,1'-(1,4-Phenylene)bis{*N*-methoxy-*N*-methyl-1-[(trimethylsilyl)oxy]}ethanamine (2ar): General procedure starting from **1ab** and MeLi (3 eq.). Purification by column chromatography on neutral alumina (Brockmann grade IV, *n*-hexane/DEE 9/1 v/v) gave **2ar** as a white solid (190 mg, 89%, R_f = 0.70 *n*-hexane/DEE 9/1 v/v). ^{1}H NMR (400 MHz, C_6D_6): δ 7.72-7.68 (m, 4H), 3.42 (s, 6H), 2.36 (s, 6H), 1.74 (s, 6H), 0.34 (s, 18H). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 145.3, 126.1, 94.1, 60.6, 36.5, 29.3, 2.6. ^{15}N NMR (40 MHz, C_6D_6): δ -204.5 (s).

7.5.6 X-ray Analysis

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromator, Mo K/α INCOATEC micro focus sealed tube and Oxford cooling system. The structures were solved by Intrinsic Phasing, Charge Flipping and Direct Methods. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: Bruker SAINT software package[26] using a narrow-frame algorithm for frame integration, SADABS[27] for absorption correction, OLEX2[28] for structure solution, refinement, molecular diagrams and graphical user-interface, Shelxle[29] for refinement and graphical user-interface SHELXS-2015[30] for structure solution, SHELXL-2015[31] for refinement, Platon[32] for symmetry check.

References

1. L. Ielo, V. Pillari, M. Miele, D. Castiglione and V. Pace, *Synlett*, 2021, **32**, 551-560.
2. R. Senatore, M. Malik, T. Langer, W. Holzer and V. Pace, *Angew. Chem. Int. Ed.*, 2021, **60**, 24854-24858.
3. V. Pace, L. Castoldi, E. Mazzeo, M. Rui, T. Langer and W. Holzer, *Angew. Chem. Int. Ed.*, 2017, **129**, 12851-12856.
4. L. Ielo, L. Castoldi, S. Touqeer, J. Lombino, A. Roller, C. Prandi, W. Holzer and V. Pace, *Angew. Chem. Int. Ed.*, 2020, **132**, 21038-21043.
5. M. Miele, R. D'Orsi, V. Sridharan, W. Holzer and V. Pace, *Chem. Commun.*, 2019, **55**, 12960-12963.
6. V. Pace, L. Castoldi, P. Hoyos, J. V. Sinisterra, M. Pregnolato and J. M. Sánchez-Montero, *Tetrahedron*, 2011, **67**, 2670-2675.
7. L. Castoldi, S. Monticelli, R. Senatore, L. Ielo and V. Pace, *Chem. Commun.*, 2018, **54**, 6692-6704.
8. V. Pace, L. Castoldi, A. D. Mamuye and W. Holzer, *Synthesis*, 2014, **46**, 2897-2909.
9. V. Pace, L. Castoldi, S. Monticelli, M. Rui and S. Collina, *Synlett*, 2017, **28**, 879-888.
10. L. Ielo, S. Touqeer, A. Roller, T. Langer, W. Holzer and V. Pace, *Angew. Chem. Int. Ed.*, 2019, **131**, 2501-2506.
11. R. Senatore, L. Ielo, S. Monticelli, L. Castoldi and V. Pace, *Synthesis*, 2019, **51**, 2792-2808.
12. M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **18**, 193-209.
13. D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188-3191.
14. L. Castoldi, W. Holzer, T. Langer and V. Pace, *Chem. Commun.*, 2017, **53**, 9498-9501.
15. S. Ghinato, D. Territo, A. Maranzana, V. Capriati, M. Blangetti and C. Prandi, *Chem. Eur. J.*, 2021, **27**, 2868-2874.
16. J. Chen, J. W. Lim, D. Y. Ong and S. Chiba, *Chem. Sci.*, 2022, **13**, 99-104.
17. J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506.
18. Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422-518.
19. M. Adler, M. Marsch, N. S. Nudelman and G. Boche, *Angew. Chem. Int. Ed.*, 1999, **38**, 1261-1263.
20. V. Pace, L. Castoldi, S. Monticelli, S. Safranek, A. Roller, T. Langer and W. Holzer, *Chem. Eur. J.*, 2015, **21**, 18966-18970.
21. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879-1880.
22. V. Pace, L. Castoldi, A. R. Alcántara and W. Holzer, *RSC Adv.*, 2013, **3**, 10158-10162.
23. V. Pace, I. Murgia, S. Westermayer, T. Langer and W. Holzer, *Chem. Commun.*, 2016, **52**, 7584-7587.
24. S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson and V. Pace, *ChemSusChem*, 2019, **12**, 1147.
25. R. Senatore, L. Ielo, E. Urban, W. Holzer and V. Pace, *Eur. J. Org. Chem.*, 2018, **2018**, 2466-2470.
26. Bruker SAINT V8.38B Copyright © 2005-2019 Bruker AXS.
27. G. M. Sheldrick, 1996, SADABS. University of Göttingen, Germany.
28. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339-341.

29. C. B. Hübschle, G. M. Sheldrick and B. Dittrich, *J. Appl. Crystallogr.*, 2011, **44**, 1281-1284.
30. G. M. Sheldrick, 2015, SHELXS. University of Göttingen, Germany.
31. G. M. Sheldrick, 2015, SHELXL. University of Göttingen, Germany.
32. A. L. Spek, *Acta Cryst. D*, 2009, **65**, 148-155.