

Metalation of Pyridines with *n*BuLi–Li–Aminoalkoxide Mixed Aggregates: The Origin of Chemoselectivity

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Abstract: The reactivity of alkyllithium–lithium–aminoalkoxide unimetallic superbases has been investigated. These systems are used for deprotonative lithiation of pyridine derivatives in apolar non-coordinating media with excellent regio- and chemoselectivity, in deep contrast with alkyllithium. With the aim of getting a better understanding of the chemistry behind these promising reagents, we have carried out a joint experimental and theoretical study of the metalation of 2-chloropyridine with combinations of *n*BuLi and (S)-(–)-*N*-methyl-2-pyrrolidinylmethoxide (LiPM). Nucleophilic addition or α -lithiation has been observed, depending on conditions (solvent, temperature, stoichiometry), while ortho-metalation was not detected. Theoretical calculations using Density Functional Theory (B3LYP/6-31G(d) method) have then been carried out in gas phase at 195 K to characterize the relevant chemical species (reactive aggregates, transition structures) and estimate free energies of activation and relative reaction rates. Solvent effects in hexane have been neglected according to previous calculations. The effect of coordinating solvents such as THF has been qualitatively discussed. A major achievement of the present work has been to demonstrate that chemoselectivity crucially depends on aggregate type: dimers systematically lead to nucleophilic addition, while tetramers lead to α -lithiation. Besides, the calculations predict dimers to be more reactive than tetramers, yet they are much less stable, so that the observed selectivity results from the combination of both properties. A simple procedure to evaluate the basicity of an organolithium compound has been proposed. It has allowed us to show that the *n*BuLi–LiPM tetramer has a significantly larger basicity than its corresponding dimer, which is not at all the case for *n*BuLi aggregates, thus explaining differences in selectivity. Solvent and temperature effects on *n*BuLi–LiPM reactivity have been analyzed. By increasing the temperature in hexane, or changing the solvent from hexane to THF, dimer concentration is expected to rise, and likewise the weight of nucleophilic addition rises, in agreement with the experimental findings.

1. Introduction

Organolithium compounds constitute a widely used class of reagents in organic synthesis.¹ A variety of *n*-butyllithium-based (*n*BuLi) reagents has been employed to achieve different functionalizations of aromatic compounds by metalation. However, the deprotonative lithiation of heteroaromatic systems remains problematic regarding chemo- and regioselectivity. In fact, though the presence of the heteroatom might potentially be useful to direct metalation by coordination to the reactive lithium aggregate, these systems often display π -deficiency, which makes them highly electrophilic and sensitive toward nucleophilic addition of the alkyllithium compound.

To overcome this side-reaction and favor lithiation, one alternative has consisted in turning alkyllithium species into sterically hindered non-nucleophilic lithium dialkylamides such as LDA (Lithium diisopropylamide)^{2,3} or LTMP (Lithium

2,2,6,6-tetramethylpiperide).⁴ These reagents have successfully effected the metalation of several pyridine derivatives but equilibrated reactions were observed in some cases and implied in situ trapping of lithio intermediates.⁵ Other alternatives have been reported. A well-known example is the combination of *n*BuLi with complexing agents such as TMEDA, known to disrupt the organolithium aggregates into much more reactive dimeric complexes.⁶ Another example is the mixture of *n*BuLi with potassium *tert*-butoxide to form the so-called LICKOR

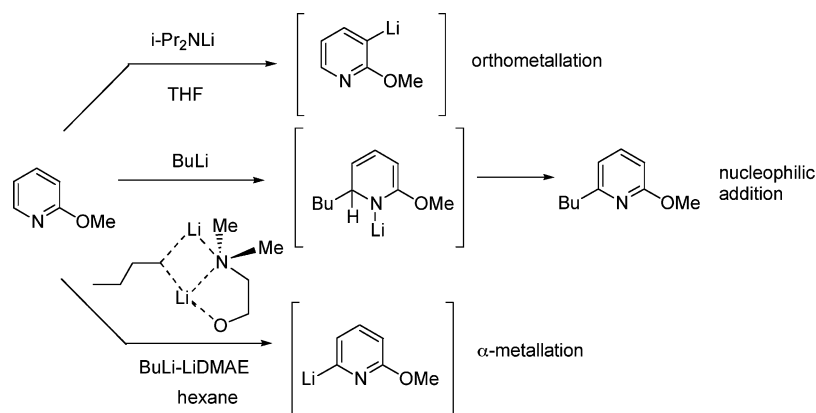
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Scheme 1



superbases, which exhibit enhanced basicity but rather poor regioselectivity in pyridine series.⁷

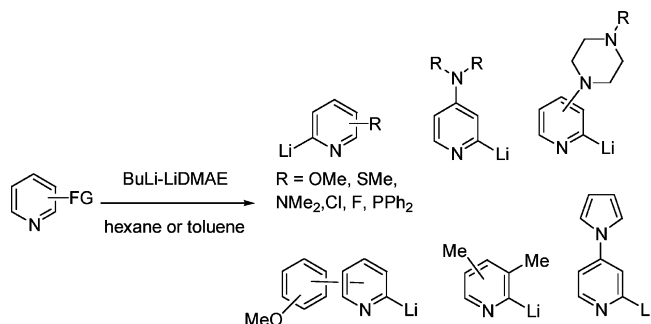
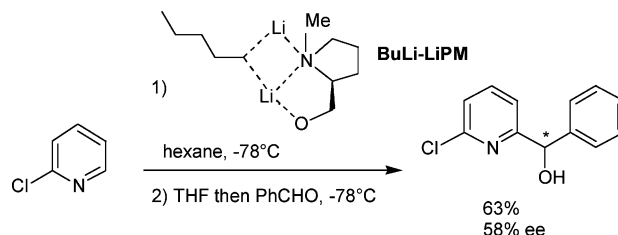
These results have encouraged the research of new reagents that would allow a fine-tuning of chemo and regioselectivity by an appropriate choice of ligands that associate a coordinating atom and an electron-rich atom. Application of this concept has led to the development of a new class of unimetallic superbases combining an alkyl lithium and a lithium aminoalkoxide.⁸ The parent reagent was BuLi-LiDMAE ($\text{LiDMAE} = \text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$). This superbase promoted the first α -metallation of 2-methoxy pyridine and lately of other substrates instead of the usual nucleophilic addition encountered with $n\text{BuLi}$ ⁹ or ortho-directed lithiation promoted by dialkylamides^{2,3} (Scheme 1).

The metallation occurred with tolerance of sensitive functionalities and numerous lithio-pyridine intermediates were generated (Scheme 2).^{10–12}

An important scope extension was the switching of the aminoalkoxide from LiDMAE to the chiral LiPM ($\text{LiPM} = (S)\text{-}(-)\text{-}N\text{-methyl-2-pyrrolidinylmethoxide}$). The obtained BuLi-LiPM reagent performed the first chemo-, regio- and enantioselective functionalization of halogenopyridines leading to chiral pyridylcarbinols in a one-pot fashion, an example of which is given in Scheme 3.¹³

While very promising, this latter process still suffers from moderate enantiomeric excesses and conversions. Unfortunately, there are significant difficulties to further progress in this direction

Scheme 2

Scheme 3. Regio- and Enantiocontrol using $n\text{BuLi-LiPM}$ with 2-Chloropyridine

due to the imprecise knowledge of the underlying reaction mechanisms and substrate–superbase interactions. This is explained by the marked trend of organolithium compounds to form aggregates and the intricate role of solvation effects on aggregation. Not surprisingly, a large number of theoretical investigations have been devoted to it,^{14–17} although only a few have focused on mixed alkyl lithium–lithium alkoxide aggregates.^{17–20}

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Using quantum chemistry calculations, we have recently analyzed²⁰ the thermodynamics of *n*BuLi–LiPM aggregation processes in different solvents (main results will be outlined below). This has allowed us to clarify the type of aggregates that are present in apolar media and in coordinating solvents such as THF, thereby opening the route to the investigation of reaction mechanisms.

In the present work, we have carried out a combined experimental and theoretical study with the aim of elucidating the mechanism of reactions between *n*BuLi–LiPM unimetallic superbases and pyridine derivatives, as well as the main factors that determine their particular chemo and regioselectivities. The superbases reactivity is compared to that of *n*BuLi. 2-Chloropyridine has been chosen as prototypical reagent since it is particularly sensitive to nucleophilic addition of BuLi²¹ (and is thus a good probe for aminoalkoxide effect on selectivity). As mentioned, experimental data on *n*BuLi–LiPM reactions has already been reported by some of us.^{10,12,13} In that work, we focused on the addition step of lithiopyridines to aldehydes without examining in detail the metalation step. To complete those results, it has been necessary to carry out a series of systematic experiments to examine the effect of stoichiometries, solvents and temperature on the selectivity. The corresponding data are presented and discussed in the first part of this work. Further details on the reactions can be found in the original references.^{10,12,13} Afterward, theoretical predictions for the reaction rates of α -metalation, ortho-metalation, and nucleophilic addition are reported and compared to experiment. From this comparison, we derive conclusions concerning the mechanism of the reactions, the role of solvent/temperature and the origin of chemoselectivity.

2. Results and Discussion

2.1. Experimental Data. Details on experimental methods are provided as Supporting Information. The various BuLi–LiPM combinations were prepared by adding *n*BuLi (*x* equiv.) to a solution of LiPM (*y* equiv.) in hexane at 0 °C. The reaction medium was then stabilized at the desired temperature and 2-chloropyridine was added as a solution in THF or hexane. The lithiation products were subsequently reacted with chlorotrimethylsilane and the reaction contents analyzed by GC. The GC was standardized using freshly prepared authentic samples of the known formed products **2** and **4**. The results of the reaction of 2-chloropyridine with BuLi or *n*BuLi–LiPM under various conditions are given in Scheme 4 and Table 1. Since we were mainly interested on chemo- and regio-selectivities, a detailed investigation on reaction kinetics was not carried out. However, some data are included in the Supporting Information for comparison with previous works on related reactions.

At first, whatever the conditions used, the ortho-metalation product **3** was never detected, while it is known to be obtained

Scheme 4

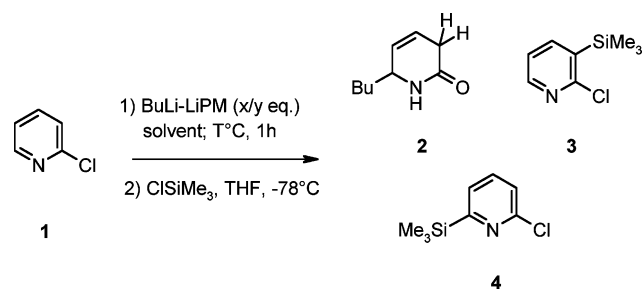


Table 1. Metalation of **1** with BuLi–LiPM under Various Conditions^a

entry	BuLi (equiv.)	LiPM (equiv.)	solvent	T °C	conv.% ^b	2 (%) ^b	3 (%)	4 (%) ^b
1	1	0	hexane	–78	37	30		
2	1	0	THF	–78	70	57		
3	1	1	hexane	–78	72	10		62
4	1	1	hexane	–40	55	28		27
5	1	1	hexane	0	35	-		
6	1	1	THF	–78	65	52		
7	2	2	hexane	–78	80	1		75
8	2.5	2.5	hexane	–78	95	tr.		93
9	3	3	hexane	–78	>99			98 (90) ^c

^a Reaction performed on 2 mmol of **1**. ^b GC yields. ^c Isolated yield after column chromatography.

exclusively with LTMP or LDA.^{3,22} A common feature to all metalations was the strong solvent dependence of the chemoselectivity. In noncoordinating hexane, BuLi alone gave **2**²³ resulting from nucleophilic addition of BuLi to the azomethine bond in moderate yield which was increased in THF (entries 1 and 2). In agreement with the investigations by Quéguiner and co-workers,²³ the butylpyridone **2** was the only addition product detected and isolated; other aromatized addition products such as 2-butylpyridine or 2-butyl-5-trimethylsilylpyridine were found absent of the reaction mixtures. The effect of LiPM on the reaction pathway was clearly observed. In agreement with BuLi–LiDMAE,¹⁰ BuLi–LiPM gave exclusively the clean α -metalation product **4** when used in hexane at –78 °C (entries 3,7–9) while only nucleophilic addition was observed in THF (entry 6) signifying a profound change in the reagent structure in the latter solvent. The product resulting from the ortho-metalation at C-3 was never obtained whatever the conditions used clearly indicating the high degree of regioselectivity at the α position. Interestingly, the increase of base amount not only improved the conversion, but also decreased the amount of nucleophilic addition product which became negligible providing that 2 eq. of BuLi–LiPM were used. The reaction was completed using 3 equiv. of BuLi–LiPM producing **4** in excellent yield (entry 9).

The metalation temperature effect was also examined using 1 equiv. of BuLi–LiPM. An increase of the temperature from –78 to 0 °C was found to be deleterious for conversion and chemoselectivity.

2.2. Computational Study. Reaction rate computations have been carried out in the framework of Density Functional Theory using the hybrid method B3LYP/6-31G(d),²⁴ which represents a good compromise between accuracy and computational cost,

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as shown in many related studies.^{15,18,25} Considering the large size of the systems, the use of higher-level methods was not possible (the role of diffuse functions and the magnitude of basis set superposition error has been discussed before²⁰). Full geometry optimization in the gas phase has been done for both reactants and transition structures followed by standard vibrational frequency to verify the nature of the stationary point (minimum or saddle point) and obtain thermal contributions to free energy at 1 atm and 195 K. Intrinsic reaction coordinate analyses have been done to check the species connected by a transition state. Thermodynamic contributions and final structures in the intrinsic reaction coordinate calculations are provided as Supporting Information. Reaction rates have been estimated in gas phase using Transition State Theory. Solvent effects in hexane can be safely neglected according to previous calculations²⁰ using the multipole-expansion continuum model.²⁶ For instance, free energy changes in going from gas phase to hexane were estimated to less than 1% for the processes of interest in the present work (dimer/tetramer equilibria). On the contrary, solvent effects in THF were found to be very large for aggregate equilibria²⁰ and their role on chemoselectivity will be qualitatively discussed below. All calculations have been done using the Gaussian 03 program.²⁷

In principle, several conformations and aggregate dimensions can be considered for each system. Conformations appearing to be the most appropriate ones from the chemical point of view have been selected, although computations for different initial geometries were done in some cases (only lowest energy structures are considered below). The size of the reactive aggregates is an intriguing question and deserves some comments. It is widely accepted that reactivity decreases with increasing aggregate size²⁸ so that reactive aggregates do not necessarily correspond to major aggregates in a given solvent (exceptions are possible²⁹ however). Most theoretical works in the literature have dealt with reactions in coordinating solvents and have focused on monomer or dimer reactions. However, for reactions in apolar media, the role of monomers is probably negligible (due to insignificant concentrations) while that of larger aggregates is potentially important. Therefore, we focus below on the reactivity of dimers and tetramers. Computations for the monomers have been done for comparison. The role of hexamers (the major species in apolar media) has been neglected since complexation with a Lewis base promotes their dissociation into smaller aggregates.²⁰ A further approximation in the present work concerns the type of *n*BuLi–LiPM superbase

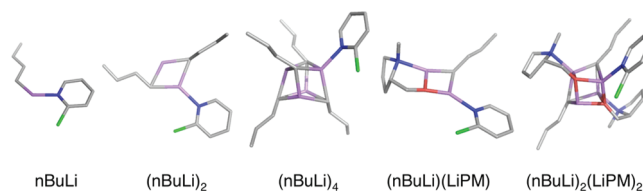
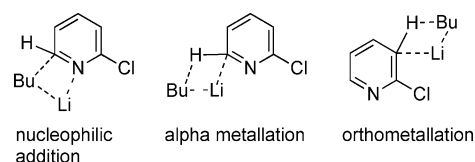


Figure 1. Optimized geometries for complexes of *n*BuLi and *n*BuLi–LiPM aggregates with 2-Cl-pyridine.

Table 2. Energies of Complexation with 2-Cl-Pyridine and Li...N Distances for Systems in Figure 1 (in kcal/mol and Å, Free Energy at 1 atm and 195 K)

aggregate	ΔE	ΔG	$d_{Li...N}$
<i>n</i> BuLi	−21.7	−14.4	2.049
(<i>n</i> BuLi) ₂	−13.2	−6.8	2.112
(<i>n</i> BuLi) ₄	−10.8	−4.3	2.159
(<i>n</i> BuLi)(LiPM)	−10.7	−2.8	2.125
(<i>n</i> BuLi) ₂ (LiPM) ₂	−8.9	−2.7	2.118

Scheme 5. Schematized Transition Structures for the Reactions Investigated^a



^a For simplicity, a single BuLi unit is drawn instead of the whole aggregate (dimers or tetramers shown in Figure 1).

tetramers considered: only the 2:2 aggregate has been studied since it is a little more stable than asymmetric 1:3 and 3:1 tetramers and is predominant in equimolar mixtures.²⁰

2.3. Prereactive Complexes. Organolithium aggregates and 2-Cl-pyridine may form stable complexes whose structure is interesting to analyze before considering the associated transition structures. The optimized geometries of the complexes are presented in Figure 1 and some properties are collected in Table 2. All complexation energies are negative and large so that free energies remain negative in spite of the unfavorable entropic contribution characteristic of this type of processes. The complexation energy for the *n*BuLi monomer is close to that reported by Catak et al¹⁶ for *n*BuLi and pyridine at the B3LYP/6-31+G(d) level ($\Delta E = -19.8$ kcal/mol with zero-point energy corrections). Values for all of the other aggregates (dimers or tetramers) are significantly smaller. Interestingly, complexes with homoaggregates display lower formation energies than heteroaggregates of the same size and similarly dimers exhibit lower energies than tetramers of the same type.

2.4. Transition Structures. Optimized geometries for the transition structures (TS) of the studied reactions (see Scheme 5) are drawn in Figure 2. Notation is as follows: T or D holds for a TS involving a tetramer or a dimer, respectively; NA, α , or o subscripts hold for nucleophilic addition, α -metalation and ortho-metalation, respectively. Values of the forming C–C or C–H distances, energies ΔE^\ddagger and free energies ΔG^\ddagger of activation are summarized in Table 3 (values are given relative to separated aggregate and 2-Cl-pyridine reactant). The distances allow comparison of the reaction advancement between the processes. In general, the superbase *n*BuLi–LiPM leads to shorter distances (except for the T_{NA} TS) and the difference with respect to *n*BuLi is especially important for T _{α} . As far as activation energies are concerned, the most striking result is the large difference predicted between the two bases for the

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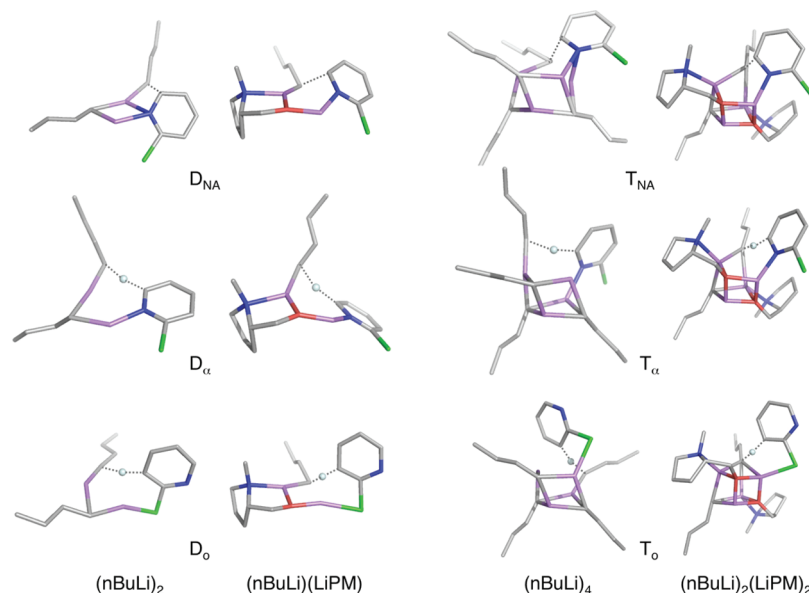


Figure 2. Transition structures for *n*BuLi and *n*BuLi–LiPM aggregates. Notation is as follows: T or D holds for a transition structure involving a tetramer or a dimer, respectively; NA, α or o indices hold for nucleophilic addition α -metalation and ortho-metalation, respectively. Hydrogen atoms are not shown for simplicity (except for the hydrogen atom being transferred in metalation processes).

Table 3. C–C and C–H Lengths (Å) for the Bonds Being Formed in the Transition Structures of Figure 2 and Energy and Free Energy of Activation (kcal/mol)^a

TS		C–Y length (Y = C or H)			Δ	ΔE^\ddagger			ΔG^\ddagger		
		<i>n</i> BuLi	<i>n</i> BuLi–LiPM	Δ		<i>n</i> BuLi	<i>n</i> BuLi–LiPM	Δ	<i>n</i> BuLi	<i>n</i> BuLi–LiPM	Δ
D _{NA}	CC	2.439	2.381	–0.058	0.6	1.3	0.7	9.0	10.2	1.2	
D _{α}	CH	1.481	1.461	–0.020	9.6	9.5	–0.1	13.2	14.4	1.2	
D _o	CH	1.586	1.533	–0.053	17.7	14.2	–3.5	21.6	19.4	–2.2	
T _{NA}	CC	2.234	2.340	0.106	18.8	12.1	–6.7	27.3	21.3	–6.0	
T _{α}	CH	1.682	1.455	–0.227	19.5	11.5	–8.0	24.7	16.2	–8.5	
T _o	CH	1.640	1.513	–0.127	24.9	21.3	–3.6	29.7	26.7	–3.0	

^a The latter are given with respect to the separated aggregate and 2-Cl-pyridine reactant.

reactions through T_{NA} and T _{α} , the superbase *n*BuLi–LiPM leading to more stable transition structures. Another notable result is that free energies of activation involving dimers are considerably smaller than those involving tetramers, when comparing equivalent processes, thus confirming the higher reactivity of the smaller aggregates. It is worth noting that free energies of activation for processes involving dimers vary in the order nucleophilic addition < α -metalation < ortho-metalation, while in the case of tetramers, the order is α -metalation < nucleophilic addition < ortho-metalation. Since, experimentally, nucleophilic addition is observed with *n*BuLi and α -metalation is mainly obtained with mixed *n*BuLi–LiPM, our calculations suggest that dimers would be involved in the first case, while tetramers would be involved in the second. Further arguments supporting this statement will be presented in the next section. Ortho-metalation is clearly disfavored with respect to other processes because of the switch of strong Li–N interactions, not possible in ortho-metalation TSs owing to the long distances involved, to weak Li–Cl interactions.

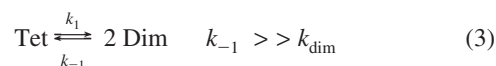
Computations of TSs involving *n*BuLi monomers lead to ΔG^\ddagger values of 6.0 kcal/mol, 5.5 and 10.0 kcal/mol for the nucleophilic addition, α -metalation, and ortho-metalation processes, respectively. The energetics for nucleophilic addition is comparable to the study reported by Catak et al¹⁶ using the B3LYP/6-31+G(d) method (estimated activation energy with respect to separated reactants at 0 K was 1.9 kcal/mol). One should note that, as expected, the reactivity of the monomer is predicted to

be larger than that of the dimer for the same process. In this case, α -metalation and nucleophilic addition are almost equally favorable suggesting that monomers should not be involved in the observed reactions.

2.5. Chemo- and Regioselectivity. The selectivity of the organolithium aggregates can be discussed by considering the relative reaction rates for nucleophilic addition, α -metalation and ortho-metalation involving either dimers (Dim) or tetramers (Tet):



(Pyr = 2-Cl-pyridine, Prod = reaction product). We shall assume first order reactions with respect to aggregate concentration. In addition, in order to compare the reaction rates between dimers and tetramers, we further assume the hypothesis of pre-equilibrium:



The computed free energy for this equilibrium, ΔG_{eq} , amounts 31.7 and 31.0 kcal/mol for *n*BuLi and *n*BuLi–LiPM, respectively.

Table 4. Predicted Relative Reaction Rates at 195 K^a

mechanism	<i>n</i> BuLi	<i>n</i> BuLi–LiPM
D _{NA}	1	6.2 × 10 ⁻⁹
D _α	2.0 × 10 ⁻⁵	1.5 × 10 ⁻¹³
D _o	7.9 × 10 ⁻¹⁵	3.3 × 10 ⁻¹⁹
T _{NA}	5.3 × 10 ⁻⁶	2.3 × 10 ⁻⁶
T _α	5.3 × 10 ⁻³	1
T _o	1.2 × 10 ⁻⁸	1.7 × 10 ⁻¹²

^a We assume [Tet] = 10⁻⁵ M.

The estimated relative reaction rates are summarized in Table 4 (some details on equations are given in the Supporting Information). The predicted chemo- and regioselectivities (corresponding to main reaction rates) are in perfect agreement with the experimental observations: *n*BuLi leads to nucleophilic addition, and the *n*BuLi–LiPM superbases leads to α-metalation. The computed rates do confirm the close relationship existing between selectivity and aggregate size that we have suggested above. The main reaction with *n*BuLi proceeds through a dimer (D_{NA} mechanism) while the main reaction with *n*BuLi–LiPM proceeds through a tetramer (T_α mechanism). This conclusion means that special attention should be paid to the aggregate size, considering quantum mechanical calculations on organolithium reactions. It is a fundamental parameter and theoretical studies based on too simple models (monomers or dimers) might lead to wrong conclusions.

Values in Table 4 assume [Tet] = 10⁻⁵ M. Owing to the equilibrium represented by eq 3, changing the concentration of [Tet] will modify the relative rates between D and T mechanisms so that decreasing [Tet] should favor D mechanisms. Since the predicted relative rates for secondary processes are very (or even negligibly) small, chemoselectivity is not expected to change for reasonable changes of concentration. However, it must be noticed that the nature of aggregates evolves along the experiments, concomitantly with *n*BuLi concentration diminution. The relative amount of LiPM/*n*BuLi changes, so that for a sufficiently advanced reaction 2:2 tetramers are not necessarily the main reactive species. In addition, the formed products (lithiated pyridine) may participate to the formation of aggregates. The observation of significant amounts of secondary products under certain conditions is probably connected to that.

2.6. Origin of Chemoselectivity: Superbasicity, Solvent and Temperature Effects. Differences in reactivity between *n*BuLi and *n*BuLi–LiPM are now interpreted in terms of their different chemical properties. To this aim, two main questions must be answered: why the *n*BuLi–LiPM superbase reaction involves the tetramer rather than the dimer (in contrast to *n*BuLi), and why the *n*BuLi–LiPM tetramer leads to α-metalation rather than to nucleophilic addition (in contrast to the *n*BuLi–LiPM dimer).

Actually, these two questions are interrelated. On one hand, one has to keep in mind that the relative dimer/tetramer stability is similar for the base and the superbase so that differences in base/superbase selectivity must come from differences in relative dimer/tetramer reactivity. As already said and confirmed by the calculations above, one generally expects aggregate reactivity to decrease with increasing aggregate size. However, inspection of activation free energies in Table 3 shows that α-metalation with *n*BuLi–LiPM displays a singular behavior. For this reaction, Δ*G*[‡] values for D_α and T_α differ by only 1.8 kcal/mol (in all other reactions, the equivalent difference varies between 7 and 18 kcal/mol). In other words, the metalation ability of the (*n*BuLi)₂(LiPM)₂ tetramer seems to be abnormally high.

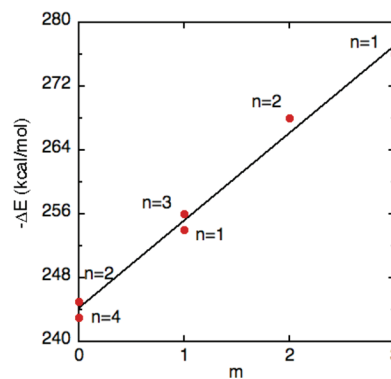
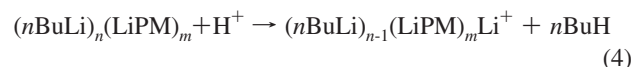


Figure 3. Protonation energies for (*n*BuLi)_{*n*}(LiPM)_{*m*} aggregates in gas phase according to eq 4.

The metalation ability of a given organolithium system may be associated to its intrinsic basicity and therefore it is interesting to discuss this property for the species considered in our work. Superbases are defined³⁰ as stronger bases than a proton sponge (1,8-bis(dimethylamino)naphthalene: DMAN) with absolute proton affinity larger than 245.3 kcal. In the context of organolithium chemistry, however, there is not a clear-cut definition. Superbases are considered in general as the combination of an organolithium compound and a heavy alkali metal alkoxide exhibiting an enhanced reactivity with respect to that of the parent compounds.³¹ Combination of organolithium compounds and lithium alkoxides does not lead in general to superbases³¹ and therefore, the unusual properties observed for the mixed *n*BuLi–LiPM aggregates deserves some explanation.

The basicity of B is defined from the free energy released in the process: B + H⁺ → BH⁺. Similarly, for an organolithium compound RLi, the basicity may be gauged by the energy released in the process: RLi + H⁺ → Li⁺ + RH. For *n*BuLi and *n*BuLi–LiPM aggregates, this equation may be written:



The corresponding energies in gas phase are represented in Figure 3 (we do not take into account geometry relaxation in the charged aggregates). Some interesting remarks can be made:

- For *m* = 0, i.e., for *n*BuLi aggregates, proton affinity is slightly below that of the proton sponge, 245.3 kcal/mol that, as said above, can be considered as the limit for superbasicity.
- For *m* > 0, i.e., for *n*BuLi–LiPM aggregates, proton affinity is beyond this threshold and remarkably, it increases linearly with the number of LiPM monomers.
- As a consequence, the basicity of (*n*BuLi)₂(LiPM)₂ is much larger than that of (*n*BuLi)(LiPM), while those of (*n*BuLi)₄ and (*n*BuLi)₂ are quite close.

The higher basicity of mixed aggregates come from the stabilizing effect of the LiPM amino groups in the charged aggregate through interaction with the Li atoms. One argument supporting this interpretation is the fact that mixed aggregates *n*BuLi–ROLi (*R* = alkyl) do not exhibit enhanced basicity with respect to *n*BuLi.³¹

When the experimental conditions are such that the concentration of (*n*BuLi)₂(LiPM)₂ aggregates is disfavored with respect

(30) Ishikawa, T., *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; John Wiley & Sons: Chichester, West Sussex, U.K., 2009.

(31) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115.

to that of the dimer ($n\text{BuLi}$)(LiPM), the metalation ability of the superbases should be reduced. The observed solvent and temperature effects can be explained in this way. Although, as said above, the dimer/tetramer equilibrium for $n\text{BuLi}$ –LiPM is not quite sensitive to solvent effects in apolar media such as hexane, it undergoes a remarkable modification in THF. Thus, ΔG_{eq} changes²⁰ from 31.0 kcal/mol in gas phase to 30.8 kcal/mol in hexane and 17.2 kcal/mol in THF (after correction by solvent concentration, see Table 6 and eq 7 in ref 20). In such a case, the concentration of the more reactive dimers is large enough for this aggregate to become the reactive species and, consequently, chemoselectivity changes from metalation in hexane to nucleophilic addition in THF. Likewise, when the temperature rises in hexane, the dimer/tetramer equilibrium is shifted toward the dimer because of its largest entropy contribution (note that in coordinating solvents such as THF, the opposite would be true).²⁰ If the dimer concentration increase is large enough, then it can contribute to the whole reactivity of the superbases so that some addition product is also obtained, as actually observed (compare reactions at $-78\text{ }^\circ\text{C}$ and $-40\text{ }^\circ\text{C}$ in Table 1).

3. Conclusions

The present study has shown that, like the parent BuLi –LiDMAE reagent, mixed $n\text{BuLi}$ –LiPM compounds are very useful metalating agents to synthesize α -functionalized pyridine derivatives. The chemoselectivity is strongly dependent on the metalation solvent used. While in apolar hexane, metalation was favored, in THF, nucleophilic addition occurred. The reagent/substrate ratio was found to dramatically modify the reaction pathway. The metalation occurred exclusively providing that at least 2 equiv. of $n\text{BuLi}$ –LiPM were used.

Quantum chemical computations on transition structures through dimers and tetramers for different reactions have allowed us to describe the mechanisms involved and interpret

the experimental findings. Both, the $n\text{BuLi}$ base and $n\text{BuLi}$ –LiPM superbases display the following common trends: dimers are more reactive than tetramers, dimers favor nucleophilic addition, and tetramers favor α -metalation. Overall, the observed α -metalation ability of equimolar mixtures of $n\text{BuLi}$ –LiPM compounds in hexane can be explained by the simultaneous fulfillment of two requirements: a very low stability of the ($n\text{BuLi}$)(LiPM) dimer and a sufficiently high reactivity of the ($n\text{BuLi}$)₂(LiPM)₂ tetramer. Factors favoring the [Tet]/[Dim] ratio should therefore favor α -metalation over nucleophilic addition, thus explaining the dependence of experimental data on solvent, temperature and reagent/substrate ratio. The superbases behavior of $n\text{BuLi}$ –LiPM aggregates in hexane has been explained by the stabilizing effect of intramolecular $\text{Li}\cdots\text{N}$ interactions.

Although further research efforts will be necessary to better understand chemoselectivity in organolithium processes, the experimental and theoretical results discussed in the present work have allowed us to identify some key features. Their knowledge will be especially helpful to (1) develop new computational procedures with predictive power and (2) design new agents to prepare metalated heterocycles with improved enantioselectivities in the addition to prochiral electrophiles.

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Supporting Information Available: Details on experimental procedures, kinetics study, complete ref 27, Cartesian coordinates of optimized structures and total energies (reagents, complexes, transition structures, IRC calculations), thermochemistry, equations used to compute relative rates. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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