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ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

“The Great Beauty” of Organolithium Chemistry: A Land Still Worth Exploring†

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

This Frontier highlights and analyses from the authors' perspective the impact to organic synthesis of some recent contributions from the organolithium field, also featuring the opportunities that are on the horizon.

Introduction

Since 1917, when organolithium compounds were born in the hands of Schlenk and Holtz by exchange reactions from diorganomercury derivatives, their intrinsic energy and vigour¹ let foresee that they would ultimately and greatly contribute to the burgeoning of organometallic chemistry, as indeed happened. As a matter of fact, organolithium chemistry bewitched and changed the life of all those people who pioneered it, such as Henry Gilman, George Wittig, and Karl Ziegler,² who developed new key reactions for this field, e.g., organolithium compounds by lithium-hydrogen and lithium-halogen exchange, and by transmetalation.

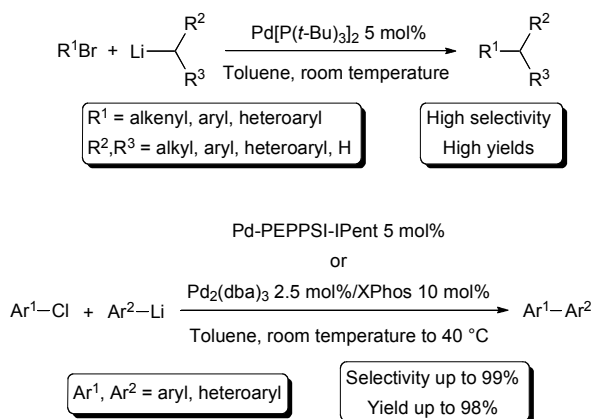
Nowadays, organolithium compounds are ubiquitous in organic synthesis,^{3a-c} and not a day goes by without the announcement of a new functionalized configurationally stable organolithium species,^{3d} a new challenging reaction, or a novel aspect of reactivity of an older one.⁴ Organolithium compounds are indeed reputed to exhibit an astonishing array of self-assembled structures and a careful exploitation of the *structure-reactivity relationship* can coax them to follow different and unusual pathways.^{3,5} The nature of the reaction medium, the mode of organolithium addition, the temperature, the concentration, and the presence of additives, influencing both *aggregation* and *solvation*,⁵ may in turn contribute to a fine-tuning of the reactivity, thereby allowing “optimization” of organolithium reactions.⁶ To give substance to that, in this Frontier some recent selected contributions to the organolithium field, showing how different experimental conditions and how known (if any) aggregation states can affect the reactivity, will be highlighted and critically reviewed.

Discussion

The development of transition metal-catalysed cross-coupling reactions has revolutionized the way for the selective formation of C–C bonds, thereby profoundly changing the protocols for

the construction of drugs, natural products, organic materials and polymers.⁷ Organolithium reagents, however, are often required for the preparation of softer nucleophiles such as Si, Sn, and B reagents, which are the active ingredients for performing Hiyama-Denmark, Stille, and Suzuki-Miyaura couplings with aryl/alkenyl halides, respectively. Therefore, a method to convert directly organolithium compounds into the corresponding cross-coupling products would be highly desirable. Which are the benefits and the drawbacks of the high reactivity of organolithiums in these transformations?

Cross-couplings of highly reactive organolithium species run under the existing protocols were often proven to suffer from lithium-halogen exchange leading to the formation of both dehalogenated and homocoupled products. On the other hand, a high reactivity could, in principle, alternatively promote couplings at lower temperatures. Seminal contributions to the field by Murahashi showed that alkenyl halides could indeed be reacted with organolithium reagents in the presence of Pd(0) compounds but only at high temperatures and after a long reaction time.⁸ Very recently, Feringa and co-workers have reported a practical and selective method for the direct catalytic cross-coupling of alkyl- and (hetero)aryllithium reagents with aryl- and alkenyl bromides in the presence of Pd[P(*t*-Bu)₃]₂ as the catalyst, LiBr being the only waste product (Scheme 1).^{9a} The process proceeds quickly under mild conditions (room temperature), with high efficiency, thus avoiding the notorious lithium-halogen exchange, and with a broad substrate scope, being indeed tolerated by halides, acetals, ethers, esters, amines and even alcohols with the exception of ketones and nitriles. The keys to success in this reaction are (a) the use of a non-polar solvent, which affects the reactivity of the organolithium reagent presumably by influencing the aggregation state (not investigated) (b) the slow addition of the organolithium to the reaction mixture, and (c) the right choice of a Pd-phosphine catalyst.



Scheme 1. Pd-catalysed cross-coupling using organolithium compounds.

The challenging direct cross-coupling of secondary alkyl lithium reagents with aryl and (stereodefined) alkenyl bromides could also be successfully performed with the same catalyst and under the above-described conditions, which, therefore, proved to be effective also for enhancing the rate of the reductive elimination step relative to that of the β -hydride elimination, the latter being often responsible for the intervention of isomerisation pathways. Hindered aryl bromides were efficiently cross-coupled with different secondary alkyl lithium reagents by using $\text{Pd}_2(\text{dba})_3$ -Qphos as the catalyst to furnish the expected alkylated products in good to excellent yields and high selectivity.^{9b} In a subsequent paper, the same authors reported that (hetero)aryl lithium reagents could also be successfully partnered, under mild conditions and short reaction times employing Pd-PEPPSI-IPent or $\text{Pd}_2(\text{dba})_3$ /XPhos as the catalyst, either with activated or deactivated aryl chlorides to give biaryl and heterobiaryl compounds. This is an important finding as aryl chlorides, which are desirable coupling partners because of their availability and low cost, are known to be rather reluctant to undergo coupling reactions (Scheme 1).^{9c}

The interplay of aggregation and solvation does have a strong effect especially in determining the carbenoid-like/carbanionic character of lithium carbenoids, which are species bearing a lithium and a particular nucleofugal heterosubstituent X (X = halogen, OR, NR_2) on the same carbon atom able to stabilize a negative charge.¹⁰ For a certain lithium carbenoid, the presence of such a heterosubstituent in its organic framework generally allows it to form “bridged structures” with the heteroatom bridging the carbon-lithium bond. This additional intramolecular coordination, lowering the symmetry and influencing the various bond lengths, might induce geometrical distortion of the structure, so that the corresponding architecture differs from the most common types and often exhibits both a complicated solution structure and a peculiar reactivity according to the experimental conditions (diluted or concentrated solution, higher or lower temperature, polar or non-polar solvents, etc.). From a structural point of view, the higher the elongation of the C–X bond and the greater the deshielding of the carbenoid C atom, the stronger the “carbenoid” character. The case of α -lithiated styrene oxide (which is an example of a Li/oxygen carbenoid) is particularly enlightening. The factors responsible of its dichotomous reactivity (nucleophilic or electrophilic behavior) have been recently carefully investigated employing a ^{13}C doubly enriched substrate and related to the different aggregation states favored

in solution under certain experimental conditions.¹¹ Over a range of concentrations, 0.075–0.03 M, α -lithiated styrene oxide was found to be mainly present in THF at 173 K as a THF-solvated monomer (**A**, Figure 1) (with a tetrahedral arrangement around the carbanionic carbon), in equilibrium with a complex mixture of stereoisomeric dimers of the type **B** (Figure 1). The reduced symmetry of some aggregates, due mainly to the partial breaking of some C α -Li bonds, further complicates their NMR spectra. The natural bond orbital analysis, in line with available spectroscopic data, suggests that an O-coordinated bridged dimer such as **B** does have a stronger “carbenoid” character than monomer **A**. This is also consistent with both the higher C α -O bond elongation predicted by calculations, and the larger downfield ^{13}C shift observed for the carbenoid ^{13}C atom in the case of all O-coordinated disolvated dimers ($\Delta\delta = 29.5$ – 31.5) with respect to the monomer ($\Delta\delta = 28.9$) (Figure 1). At a higher concentration, lithiated styrene oxide is more prone to self-associate to give higher aggregates (e.g., dimers of the type **B**) with partially C α -Li broken bonds, which proved to have a more pronounced “carbene-like” reactivity, and are most probably responsible of the formation of diastereomeric enediols as the result of an “eliminative dimerisation” reaction between two units of this lithiated species. This tendency may be cut down by adding N,N,N',N' -tetramethylethylenediamine (TMEDA) to the reaction mixture. Temperatures higher than 173 K contribute to enhance the electrophilicity as well and α -lithiated styrene oxide tends to be easily attacked by excess *s*-BuLi (if any) to give alkenes as a consequence of a “reductive alkylation” process; phenylacetaldehyde also forms further to a 1,2-H shift rearrangement.¹¹

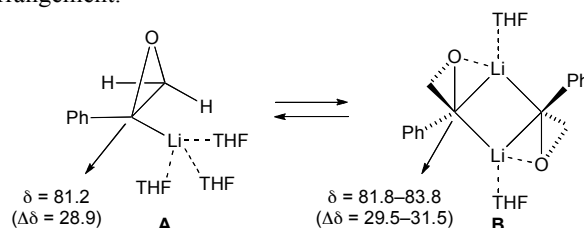


Figure 1. Selected aggregation states (**A** and **B**) of lithiated styrene oxide; chemical shifts (ppm) of the carbenoid atom determined in THF at 173 K (relative deshielding with respect to the nonlithiated precursor).

As for α -lithiated oxetanes, early studies by Klumpp and co-workers in the 1980s have showed that once these intermediates are generated in a non-polar solvent such as hexane they exhibit a strong electrophilic character, being indeed attacked, as soon as they are formed, by the same organolithium to give substitution products only.¹² On the other hand, in our own studies, we have reported for the first time that the carbanionic character of α -lithiated 2-phenyloxetane can be privileged and fruitfully exploited for synthesizing phenyl-substituted derivatives by reaction with different electrophiles only if generated in a polar solvent (THF), at -78°C , *s*-BuLi being the base of choice (Scheme 2).^{13a} Similarly, Bull and co-workers recently succeeded in the preparation of α -functionalized 2-arylsulfonyl oxetanes by running lithiation reactions of their precursors in THF at low temperature and using LiHMDS or *n*-BuLi as the base, according to the nature of the electrophiles (Scheme 2).¹⁴ Remarkably, an oxetane is also effective in directing *ortho*-lithiation in Et_2O but at higher temperatures (0°C or even room temperature) and without the need for the addition of co-solvents.^{13b}

Direct functionalization processes of tetrahydrofurans, the closest homologs to oxetanes, are extremely rare. It is long known that conventional organolithium bases promote decomposition triggering a [3+2] cycloreversion ending up with the formation of alkenes and lithium enolates of aldehydes. These fragmentation reactions invariably limited the utility of THF as a starting material. Mulvey and co-workers recently demonstrated that bases containing two different metals can indeed sedate the reactivity of THF-derived anions through either (a) a cooperative combination of zinc-carbon and sodium-oxygen bonding (structure **A**, Figure 2)^{15a} or (b) a stoichiometric stabilization of the heterocyclic oxygen and the α -deprotonated carbon atom synergistically provided by lithium and aluminum, respectively (structure **B**, Figure 2).^{15b} Of note, NMR experiments reveal that both the solid state structures **A** e **B** are also retained in non-polar solutions. Ensuring the nucleophilicity of these metalated species towards electrophiles, however, proved to be a challenging task.

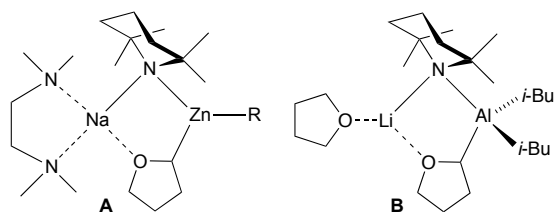
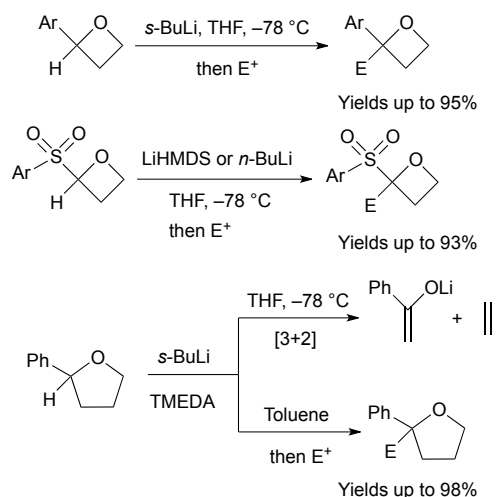


Figure 2. Synergic mixed-metal strategies for the stabilization of THF-derived anions by bimetallic [(Na and Zn) (structure **A**) and (Li and Al) (structure **B**)] chelation.

In a recent contribution from our group we found that cycloreversion of α -lithiated phenyltetrahydrofuran can be successfully tamed at $-78\text{ }^\circ\text{C}$ in a non-polar solvent (toluene) in the presence of TMEDA as ligand and that the nucleophilicity of the corresponding lithiated derivative proved to be excellent towards both heteroatom- and carbon-based halides (Scheme 2).¹⁶ Thus, once again, organolithium reactivity could be modulated by changing the nature of the solvent. The solution structure of this anion is currently being investigated by our group.



Scheme 2. Ring lithiation and functionalization of aryl(sulfonyl)oxetanes and phenyltetrahydrofuran.

Stereochemistry has always been a recurring theme when dealing with organolithium compounds that have a stereogenic lithium-bearing carbon atom, and asymmetric transformations based on deprotonation or dynamic resolution (kinetic or thermodynamic) of configurationally labile intermediates have become a powerful tool in organic synthesis.¹⁷ Which factors dictate the *configurational stability* of chiral organolithium compounds? The nature of the C–Li bond varies from compound to compound and although such a bond is known to be largely ionic (80-90%), it is widely accepted that a *small covalent contribution* cannot be neglected.¹⁸ Thus, unless factors that facilitate the dissociation of the lithium ion from the carbanion center come into play, it is unlikely that the lithium ion spontaneously edges away from the carbanion. The “degree of covalency” was found to vary with the temperature, solvent and structure of the organic skeleton and typical enantiomerisation mechanisms identified to date refer to dissociative and associative processes (e.g., the interconversion between contact and solvent-separated ion pairs (SSIPs), “conducted tour” mechanisms in which the lithium ion is coordinated to a Lewis basic site into the molecule, epimerization through a higher aggregate, etc.). Moreover, the effects of intra- and intermolecular chelating ligands on the inversion barriers of chiral organolithiums are not straightforward. In the case of aryl-substituted α -lithiated epoxides, however, a general trend became apparent in the presence of TMEDA, (–)-sparteine, and its (+)-surrogate: the rate of racemisation was slowed down in coordinating solvents (e.g., THF), and dramatically hindered in non-coordinating solvents (e.g., hexane), the calculated barriers to inversion and activation parameters suggesting a subtle interplay of different mechanisms in the enantiomerisation process.¹⁹

Recently, the first crystallographic evidence for the structure of a lithiated aryloxirane, namely α -lithiated *ortho*-trifluoromethylstyrene oxide, was reported.²⁰ This intermediate crystallizes out of a solution of Et_2O at $-78\text{ }^\circ\text{C}$ in the presence of TMEDA as a centrosymmetric (C_i) heterochiral dimer. This molecular structure represents a rare example of a lithium organic compound featuring a single σ -contact between lithium and a carbon atom and the first example of a dimeric Li/oxygen carbenoid displaying a central six-membered (O-Li-C)₂ planar core (Figure 3). The geometry around the benzylic carbon is strongly pyramidalized and the calculated C(7)–C(1) distance (1.47 Å) is also consistent with no π delocalization into the phenyl ring. Most significantly, the “carbenoid” character of such an aggregate is shown by the C(7)–O(2) bond, which proved to be remarkably elongated to 1.53 Å, the mean value for “C–O” bonds in nonlithiated styrene oxides being 1.44 Å.

A multinuclear magnetic resonance investigation (¹H, ¹³C, ¹⁹F, ⁷Li), supported by DFT calculation, also revealed that such a solid structure is mainly retained in a THF solution in which a mixture of two interconverting diastereomeric dimeric aggregates, each one again featuring a single σ -contact between lithium and a carbon atom, was noticed. To explain the fast racemisation this intermediate undergoes in a relatively polar medium such as THF (the racemisation half life is 1.6 s at 157 K), a mechanism based on the direct equilibration of six-membered homo- and heterochiral dimers (most probably involving SSIPs, in agreement with the negative entropy of activation found) was proposed.²⁰ This would also support the experimental observation that the progress of racemisation of the above lithiated oxirane is indeed hampered at 195 K in non-coordinating solvents such as hexane (in which the formation of

SSIPs is energetically costly) in the presence of diamines such as TMEDA and (–)-sparteine.¹⁹

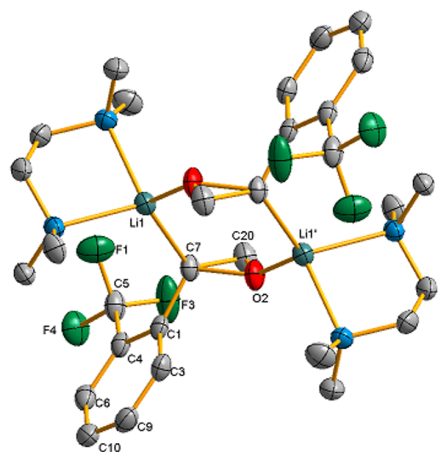
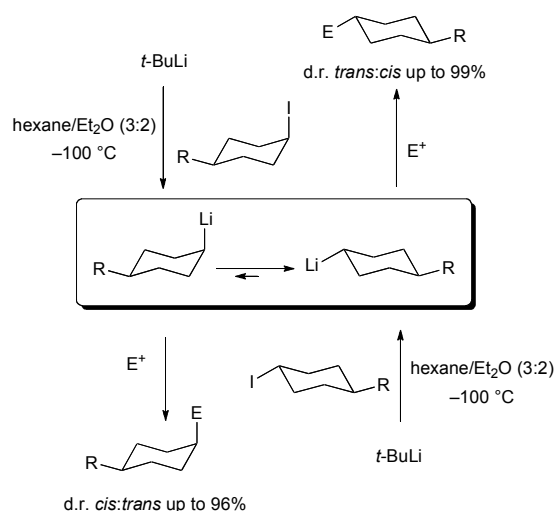


Figure 3. Molecular structure of α -lithiated *ortho*-trifluoromethylstyrene oxide complexed with TMEDA [(C₉H₇F₃LiO₁)₂·(TMEDA)₂] showing atomic numbering. Anisotropic displacement parameters are depicted at the 50% probability level. Hydrogen atoms are omitted for clarity.

Although the stereoselective generation and stereochemical behaviour of “stabilized” organolithiums (e.g., organolithium compounds bearing α -heteroatoms or conjugated with a π system, or stabilized by side-arm complexation, etc.) has been the object of extensive investigation,³ the stereoselective synthesis of “non-stabilized”, sp^3 -hybridized, organolithium compounds that exhibit synthetically useful configurational stability is still in its infancy. Pioneering studies by Letsinger^{21a} and Curtin^{21b} first showed that secondary acyclic organolithiums can be indeed prepared in optically active form (by halogen/Li exchange and transmetallation) only *at low temperature and in a non-coordinating solvent*, the rate of racemisation being greatly accelerated by a small amount of ether. Optically active *s*-BuLi, for example, retained 83% of its optical activity even after 4 hours once generated in pentane at -40°C .

Exploiting the fast Te/Li exchange, Reich then succeeded in the preparation of axial and equatorial cyclohexyllithium reagents with high isomeric purity in THF, which maintained their configurational integrity also after being trapped with electrophiles.²² An isomerisation involving an aggregation state higher than that present in THF (presumably a dimer or a higher aggregate) was postulated because the rate of equilibration proved to be strongly dependent on the total organolithium concentration. Remarkably, the configurational isomerisation was slowed down by the tridentate ligand *N,N,N',N'',N'''*-pentamethyldiethylenetriamine, which presumably inhibits aggregation by unexpectedly increasing the strength of lithium coordination. The final comment provided by Reich is quite enlightening and forewarning: “...there may be two “islands” of relatively high configurational stability for alkyl lithium reagents as solvent polarity is changed. One is hydrocarbon solvents in which the charge separation needed for C–Li bond reorganization is energetically costly, and a second one is in more polar solvents containing predominantly monomeric species where aggregate-assisted isomerization is inhibited”.

Recently, a practical preparation of stereodefined cyclic secondary alkyl lithium reagents has been reported by Knochel, Zipse and co-workers.²³ By adding *t*-BuLi to a hexane/ether (3:2) solution of *cis*- or *trans*-cycloalkyl iodide (inverse addition) at -100°C , I/Li exchange could be efficiently and cleanly performed, thereby suppressing unwelcome protolysis and the elimination side-reactions that predominate in the direct addition. Exploiting this protocol, both *cis*- and *trans*-cycloalkyllithium intermediates could be stereospecifically prepared. They maintained their configurational integrity long enough for laboratory timescale trapping experiments so as to furnish the corresponding stereodefined cyclohexane derivatives in high diastereomeric purity, up to 96% and 99% for *cis* and *trans* isomers, respectively (Scheme 3). Axially substituted cyclohexyllithium reagents proved to be, however, less thermodynamically stable with respect to the equatorially substituted counterparts and the presence of both coordinating oxygen functionalities inside the structure (e.g., MeO group) and polar solvents (e.g., THF) facilitates the isomerisation towards the latter, presumably by C–Li bond breaking. *Ab initio* calculations at the B3LYP or MP2 levels of theory suggest that the formation of hexameric cyclohexyllithium aggregates, displaying a large energy difference between the all-equatorial and all-axial species, is most probably responsible of the high stereochemical preference for the all-equatorial isomer once the equilibrium has been reached.²³ This represents another beautiful example of the influence of aggregation on the stereochemical behaviour.

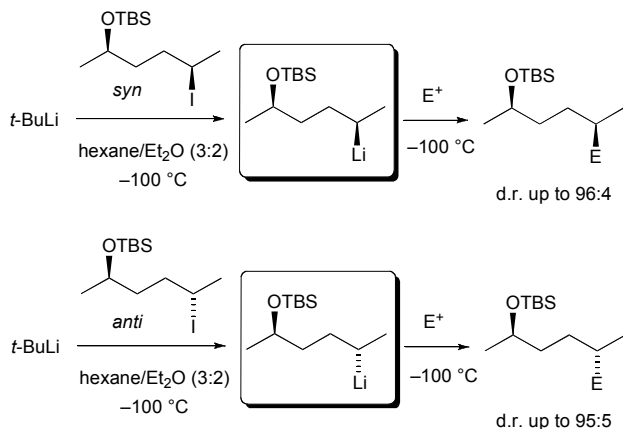


Scheme 3. Stereospecific preparation of *cis*- and *trans*-cycloalkyllithium compounds via stereoretentive iodine/lithium exchange and their reactions with electrophiles.

Similarly, by using the afore-mentioned optimized conditions, Knochel and co-workers were also able to access to functionalized stereodefined acyclic secondary alkyl lithium reagents from the corresponding alkyl iodides.²⁴ Of note, the reaction of both *syn* and *anti* lithium derivatives with several classes of electrophiles (including carbon electrophiles) occurred with excellent diastereoselectivities (up to 96:4) and overall retention of configuration. In this case, the two diastereomeric intermediates proved to have almost the same configurational stability and this explains the higher configurational stability exhibited by these acyclic secondary

alkyllithium compounds compared to that of the above cyclic analogues (Scheme 4).

Thus, in the absence of destabilizing 1,3-diaxial interactions that strive to shift the equilibrium towards the more thermodynamically stable form, stereodefined open-chain secondary alkyllithiums are surprisingly configurationally stable on the timescale of their reactions (even after 1 h at $-100\text{ }^{\circ}\text{C}$ in hexane/ether) and can be stereospecifically trapped with electrophiles. This work really opens new avenues for preparing novel and more functionalized enantiomerically enriched lithiated intermediates to be used to forge new C–C bonds with high stereoselectivities.



Scheme 4. Diastereoselective preparation of *syn* and *anti* acyclic secondary alkyllithium reagents and their quenching reactions with electrophiles.

Conclusions

In summary, it is clear that the way to prepare and to use organolithium compounds, the degree of aggregation, the reaction medium as well as the temperature can all have a dramatic and significant impact on the reactivity, stereochemical behaviour, and also on the selectivity of such intermediates. More in general, understanding the reactivity of organolithium compounds is strongly connected to understanding their structure.

To what can we look forward in the future? Building on the above described recent findings, (a) the preparation of challenging unstabilized stereodefined tertiary organolithium reagents and (b) the direct catalytic cross-coupling of functionalized enantio- and/or diastereomerically enriched secondary and tertiary alkyllithiums with both aryl and alkenyl halides, under mild conditions, appear to be goals worth pursuing.

The development of new methodologies enabling organolithium reactions to be performed under more environmentally benign conditions, in line with the principles of green chemistry (e.g., prevention of waste, atom economy, safer solvents, milder temperatures, minimal by-product formation, etc.), would be of considerable utility as well. In particular, experimental evidence of chemical reactions accelerated by water despite the non-solubility of the reactants, that is run under so-called “on water conditions”,²⁵ have been wide-spreading in recent years.²⁶ At a first sight, it might sound absurd to try to run organolithium reactions in water as organolithiums are well-known to be moisture-sensitive species. A perusal of the literature, however, showed that water can also act as a polar ligand towards lithium.²⁷ The astonishing

X-ray structure reported in particular for the water-complexed lithium salt of the organic compound $[\text{LiCH}(\text{CN})_2 \cdot \text{H}_2\text{O} \cdot \text{TMEDA}]$,^{27b} unveils (a) the willingness of water to be engaged in hydrogen bonding both as donor and acceptor, and (b) the lack of TMEDA–Li interactions, which is unprecedented. Finally, the authors commented that “... pK_a considerations alone are insufficient to determine whether water will be incorporated into lithiated organic-state structures.”

Hydrogen bonding at the water/organic compound interface is among one of the key factors computationally predicted to contribute to the rate enhancements in water.²⁶ A recent paper by Madsen and Holm²⁸ indeed showed that, in the presence of protic reagents such as water, the rate of Grignard addition to carbonyl compounds is almost comparable to that of protonation by the reagent. Thus, some hot aspects worth investigating in the case of organolithium reagents would be the following: Under which conditions water could act as an effective polar ligand? How much reactive is “coordinated water” compared to “free water”? Could the proton transfer to the carbanion be mediated by a preliminary co-ordination of H_2O to the Li^+ centre? Yes, organolithium chemistry is a land still worth exploring and, in the authors’ opinion, organolithium compounds are like wild Thoroughbred Horses, potentially able to win the most impressive races in organic synthesis once enabled to run at their best!

Acknowledgements

This work was financially supported by the Interuniversities Consortium C.I.N.M.P.I.S., and by the German-Italian bilateral program Vigoni for the year 2011 (Code: E65E06000080001) funded by DAAD and the Italian Ateneo Italo-Tedesco. We also thank both Professor Saverio Florio and Professor Dietmar Stalke for valuable discussions.

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† Dedicated to the memory of Professor Per Ahlberg.

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This Frontier highlights and analyses from the authors' perspective some recent selected contributions from the organolithium field with an eye towards new challenging research directions.
50x42mm (300 x 300 DPI)