

A wide mechanistic spectrum observed in three different reactions with organometallic reagents[†]

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The *halogen–lithium exchange* reaction is of one of the most powerful method for the preparation of organolithium compounds, but its mechanism is still controversial. To afford some new elements, we synthesized a new suitable fast radical clock, bearing a phenyl group at the alkene C-terminal. The examination of some mechanistic clues, as well as the identification of the unexpected by-products allowed the conclusion that the reaction proceeds by a polar mechanism and no evidence for radicals were found. The second reaction discussed is the *insertion of NO* in the N–Li bond of lithium amides. Evidence for the involving of paramagnetic and nitrosonium intermediates, as well as equilibria between different reactive species were essential for the proposal of a whole complex mechanism, which was confirmed by theoretical calculations. Finally, results on the *addition of heteroaromatic organocuprates* to α,β -unsaturated substrates are presented. Several reaction conditions were looked for to lead the reaction toward the more interesting 1,4-conjugated addition. Thus, addition of up to 6 equivalents of TMSCl to the reaction with arylcuprates leads to a clean addition yielding more than 95% of the 1,4-addition product. A further objective of the paper is to show how the search of unexpected routes of reaction allowed developing original pathways to lead them toward the formation of appealing functionalized compounds. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: halogen–lithium exchange; heteroaromatic organocuprates; NO insertion; TMSCl

INTRODUCTION

Organolithiums^[1–3] and lithium heterocuprates^[4,5] are widely applied by synthetic organic chemists as powerful tools for the construction of C–C bonds.^[6] Despite their important role, the mechanisms by which they are involved in organic reactions are far from being fully understood, though several sound studies have recently appeared.^[7–10] Among the recognized difficulties are the complicated structures of these reagents in solution,^[11] the formation of self and mixed aggregates, their fine sensitivity to solvent, temperature, salt- and mixing effects, order of the reagent addition, etc. Nevertheless, the tuning of some of these features is a powerful tool to lead their reactions to the desired goal.^[12] Detection of intermediates by NMR^[10,13–15] and EPR^[16] spectroscopy have allowed insight into the involvement of relatively unstable and complex structures in the reaction scheme. In the case of suspected participation of radical species, the use of radical clocks or radical probes is one of the most currently used tools.^[11] The study of product distribution under different reaction conditions, the kinetics of the reaction, the effect of UV radiation and of the addition of some additives and/or specific scavengers are among the most classical tools. Besides the experimental studies, and specially for the case of elusive or transient intermediates, theoretical calculations have prove to provide deep insight into the reaction pathways of the complex mechanisms in which these reagents intervene.^[17–19]

The conventional use of persistent and toxic solvents in traditional organic synthesis is highly questioned at present and this concern targeted the search for cleaner synthetic process ('green chemistry').^[20] In this sense, tandem reactions constitute

one of the most powerful synthetic strategies developed for building complex molecules from rather simple ones in a minimum number of operations.^[6] In the present paper, we describe three different reactions recently studied in our laboratory in which the detailed study of the reaction mechanisms, afforded new methodologies for the synthesis of useful functionalized structures, some of them in original *tandem* sequences. Those reactions are: (a) the halogen–lithium exchange with a suitable radical clock; (b) the insertion of NO into the N–Li bond of lithium amides and (c) the addition of heteroaryl organocuprates to α,β -unsaturated substrates. The search of unexpected routes of reaction allowed us to develop original pathways to lead the complex reaction scheme toward the formation of appealing functionalized compounds. A similar approach has been very recently reported by Shapiro and Toste in which they called a 'reactivity-based approach'.^[21] They described how a focus to

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[†] This article is published in *Journal of Physical Organic Chemistry* as a special issue on Tenth Latin American Conference on Physical Organic Chemistry, edited by Faruk Nome, Dept de Química, Universidade Federal de Santa Catarina, Campus Universitario – Trindade 88040-900, Florianópolis-SC, Brazil.

reaction mechanism and reactivity paradigms can lead to the rapid discovery of new synthetic tools.

RESULTS AND DISCUSSION

The halogen–lithium exchange

Though the *halogen–lithium exchange* reaction is one of the most powerful methods for the preparation of organolithium compounds, the mechanism of the reaction is still controversial, as it appears in recent literature.^[7,8,13] At least four proposals are found: a concerted S_N2 displacement; a ‘four-centre’ mechanism; the intermediation of an ‘ate-complex’ or a single electron transfer mechanism, we have recently summarized the evidences afforded by the different adherents to one or the other mechanism in support of their belief.^[22] Bailey and Patricia reviewed the data and they noted, as do most recent workers in the field, that the pathway followed may be dependent on the reactants and reaction conditions.^[23]

In the reactions with organic halides an apparent dichotomy is observed between alkyl halides and aryl halides. For the case of alkyl halides some experimental evidences (ESR, NMR, rearrangements and secondary products) hint at the participation of radical intermediates whereas evidence based on stereochemistry results suggest the opposite. For aryl halides, data suggesting the intervention of an electron transfer (ET) in the halogen metal exchange reaction are provided by Bickelhaupt group.^[8,24] Nevertheless, in the aryl bromide used, the accessibility of the halogen for a nucleophilic attack is drastically hindered.

Therefore, to explore the possibility of an ET mechanism in the aryl halide–lithium exchange we designed a different approach. We synthesized a fast, specially designed, new radical clock: the 2-bromophenyl-3-phenylprop-2-enyl ether, **1**.^[22] The intramolecular cyclization of the radical derived from **1**, should be faster than $k_c > 8.1 \times 10^9 \text{ s}^{-1}$, at 30 °C. That value is the rate of cyclization of a substrate homologue to **1**, but where the double bond is not substituted by a phenyl; therefore, it is reasonable to expect that it should be a ‘slower’ radical probe.^[25,26] The kinetic accelerating effect of aryl group substitution in the opening and closing of carbonyl radicals has been recently used in intramolecular probe reactions.^[27]

The reaction of **1** with *n*-BuLi in THF at –85 °C is very fast and the only isolated product is an open-chain product, **2**, which is obtained with an almost quantitative yield. By quenching the reaction mixture at that temperature, with MeOD, **2** containing a high deuterium incorporation at the *ortho*-position (>95%) was isolated.

Nevertheless, in several organolithium reactions previously studied in our laboratory, critical information was gathered by careful searching and identification of side products.^[3,12,28] Therefore, to get insight into likely multi-mechanisms that could be involved, special efforts were devoted to the detection, isolation, characterization and quantitative determinations of likely side products. The search showed that tiny amounts of two unexpected compounds were also produced. Reactions

conditions were varied in several aspects to improve the production of those compounds in suitable amounts to allow their identification. The two unexpected by-products were **3** and **4**, whose structure are shown in the Scheme 1. The finding of a cyclic compound could, at first glance, indicate that a radical mechanism is involved, at least partially, forming **3**, as the result of a fast trapping of the carbaryl radical at the *ortho* position, by the known addition to the suitably located double bond.

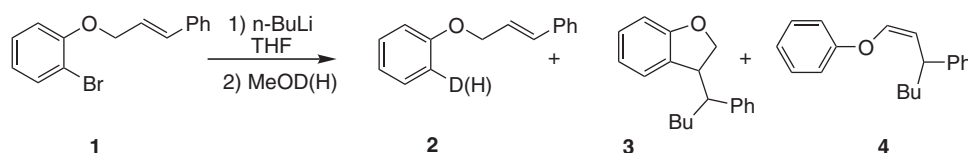
However, a fine tuning of several variables (temperature, time of reaction, solvent, etc.) showed that the finding of a cyclic structure was not the result of a radical mechanism. A critical analysis of the whole set of experiments indicates that an ET is not involved (on the contrary, results favoured a polar mechanism), and that formation of the three products can be rationalized as shown in Scheme 2. In the substrate **1**, the presence of both, O and Br, favours formation of the organolithium intermediate, through a previous ‘ate complex’ **5**, as a fleeting intermediate or transition state.^[11] Theoretical calculations show the lithium atom involved in a T-shaped hypervalent halogen species for bromine and iodine.^[29] Rapid quenching of the reaction at –85 °C, produces the open product **2** as observed.

Nevertheless, if the organolithium intermediate **6** is given time to react, the carbanionic intermediate could rearrange intramolecularly forming a more stable delocalized ambident anion **7** that could form the cyclic carbanion **8** that would then react with *n*-BuBr, present in the reaction mixture, forming product. An intramolecular rearrangement of the carbanionic intermediate with the allylic protons could also occur. Reaction of *n*-BuBr with the more abundant benzylic carbanion **9** produces the open substituted product. The *Z* stereochemistry is also in favour of the precursor proposed for **4**, which is stabilized by Li–O coordination.

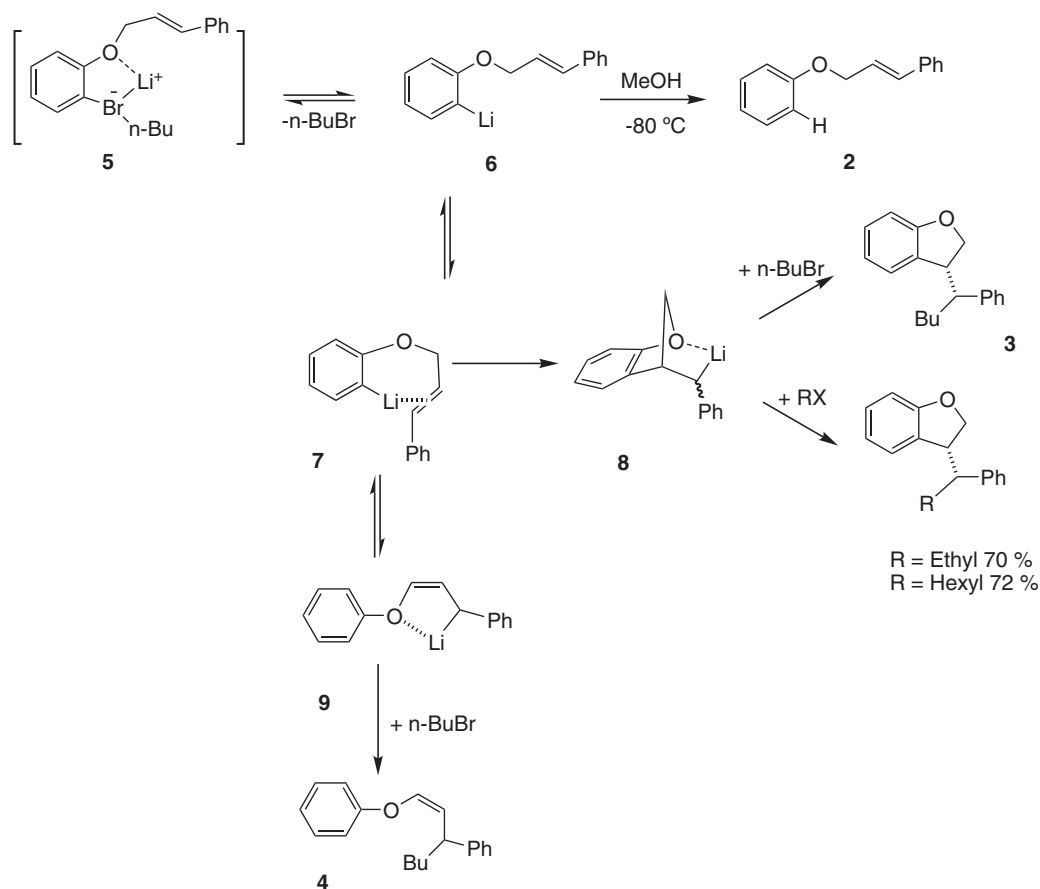
Recent attempts, trying to afford additional mechanistic evidences show the extraordinary sensitivity of this reaction to the temperature. When the reaction is carried out at –78 °C, only the cyclization product with the butyl group incorporated is formed **3**, even in the presence of a suitable electrophile. Nevertheless, the same reaction carried out at –80 °C yields a 60.3% of the corresponding cyclic derivative using 1,3-dibromopropane as electrophile, 32.7% of the open product **2** and only 6.9% of **4**. This result is a further evidence for the existence of intermediates **6–8**. Interestingly, when the reaction was carried out in hexane as solvent, instead of THF, the only product was **2** and no cyclization product was found, likely the well known higher self-aggregation of the organolithium reagent in hexane prevents and/or retards the rearrangement to form the precursor **8**. All these new results are additional evidence that **6** is the carbanionic intermediate formed, and that the halogen–lithium exchange for the case of this type of substrate, occurs through a polar mechanism and no radicals are involved.^[30]

The insertion of NO in the N–Li bond of lithium amides

Our first study on the title reaction reported that, under specific reaction conditions, the reaction afforded a new methodology for



Scheme 1.



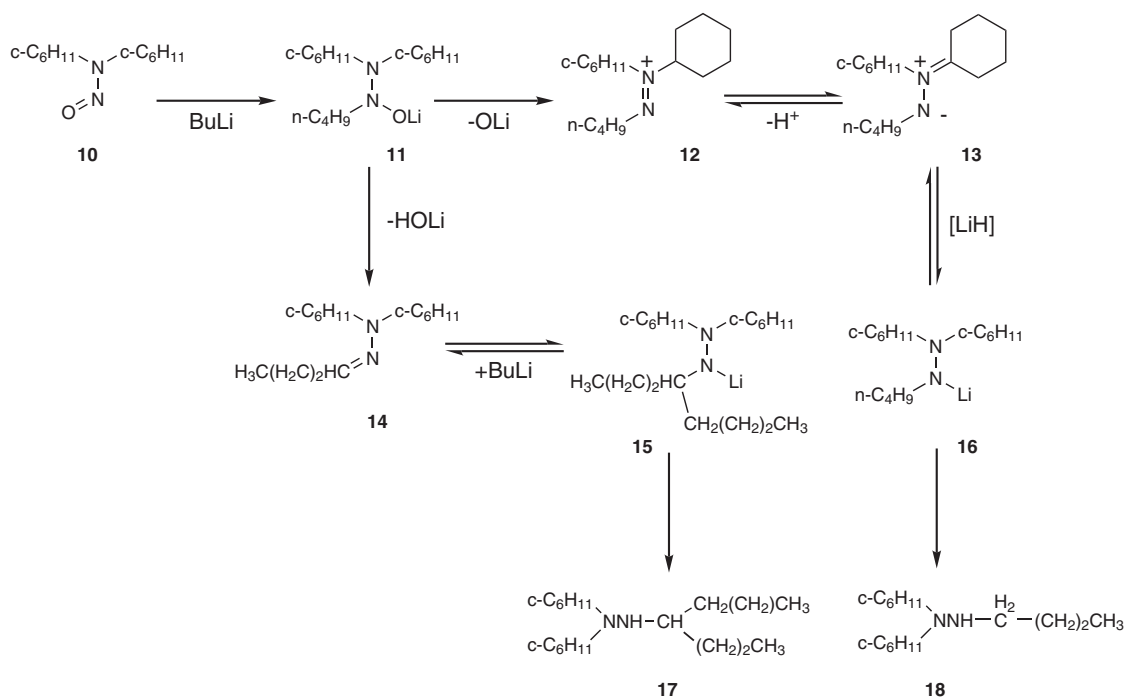
Scheme 2.

the almost quantitative conversion of dialkyl amines into the corresponding dialkyl nitrosamine.^[31] Although nitrosamines are being actively studied, especially on their relationship with carcinogenic and mutagenic properties,^[32] there are scarce synthetic methods. In an attempt to extend the synthetic utility of the new reaction, a further detailed survey of the reaction of nitrosamines with organolithium compounds, under different reaction conditions, allowed the development of another synthetically useful methodology for the preparation of substituted hydrazones and trialkyl hydrazines.^[33]

The product distribution observed under different reaction conditions, and some kinetic determinations, are consistent with the complex mechanism depicted in Scheme 3.^[34] The first step involves attack by the organolithium reagent on the nitroso moiety to give adduct **11** which by elimination of the elements of $\text{HO}^- \text{Li}^+$ produces the hydrazone **14**. In smaller amount, **11** could undergo similar elimination but involving the proton of the α -carbon of one of the cyclohexyl moiety, producing the azomethine **13**, (presumably through a diazenium salt **12**). In the presence of tiny amounts of LiH (an undesirable side product usually formed in the reactions of organolithium compounds) intermediate **13** could undergo *reduction* of the double bond forming **16** that on hydrolysis would produce the hydrazine **18** which was isolated in small amounts. By addition of a second molecule of RLi to the $\text{C}=\text{N}$ bond the adduct **15** is formed, which after quenching produces the trialkylhydrazines **17**. Under these conditions, dimerization of the azomethine is avoided and several

trialkylhydrazines could be obtained in good yields. Similarly to the findings described in part (a), in the study of the reaction of nitrosamines with organolithiums, the isolation and characterization of minor side-products suggested mechanistic hints. In the present case, the involvement of some denitrosation processes, likely occurring through a nitrosiminium ion intermediate.

In the insertion of CO into C—Li bonds of organolithium compounds, that we have previously studied, EPR determinations revealed that the first (rate determining) step is an ET.^[35] Nevertheless, such a technique cannot be applied to the study of the insertion of NO, since this is a paramagnetic molecule. Searching to shed some light into the intimate mechanism of the reaction, some theoretical calculations were carried out. Similar to the previous theoretical studies that we reported on the reaction of CO with lithium amides, the geometries of the starting lithium amides were calculated, as well as that of NO.^[19] Then, different approaches were applied to the finding of the likely transition state structures. In the grid's finding methodology,^[36] the coordinates are gradually varied to generate a set of structures, for each of which the energy is calculated, obtaining a potential energy surface, of which the transition structure (corresponding at the saddle point of this surface) is then determined. For example, for the case of the diisopropyl lithium amide, the N—Li length was varied in the range 1.5–2.3 Å, and the N—N length in the range 1.55–2.15 Å; the saddle point was found with a N—Li = 2.0 Å and N—N = 1.9 Å. The transition state was localized from the autovalue finding, frequency calculations



Scheme 3.

showed that its structure has only one negative autovalue corresponding at the vibration of the bonds involved in the reaction pathway.^[37]

The Mulliken charge distribution of the transition state for the reaction of dimethyl lithium amide with NO is shown in Fig. 1. It could be observed an excess of spin density at the NO motifs, while an excess of opposite spin density is observed in the amide portion.

The asymmetric charge distribution determined in the calculated transition state suggest that likely an ET is involved in the first step of the reaction, yielding a NO nitrogen with two unpaired electrons with the same spin, Scheme 4. (For the sake of simplicity, the lithium amide is written as a monomeric species, though it is well known that these reagents are present as

oligomeric aggregates). ET from lithium amides has been previously reported, in the reaction of LDA with heteroaromatic π -deficient compounds, an electron transfer from LDA to the heteroaromatic is proposed, yielding a LDA radical cation intermediate.^[38]

Once the ET has occurred, a paramagnetic tetrahedral intermediate, I, is formed. Lithium departure from I (likely assisted by the presence of NO) renders the dialkyl nitrosamine. A tetrahedral zwitterionic intermediate is proposed in the nitrosation of several amines with alkyl nitrites and with *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide (analogue to other intermediates, proposed for aminolysis of carboxylic esters in similar solvents).^[39] In the present case, where the transient intermediates prevent experimental determinations, theoretical calculations could provide some insight into the mechanism up to more sophisticated techniques could be developed to gain experimental evidence.

Conjugate addition of heteroaryl cyanocuprates to α,β -unsaturated carbonyl compounds

Conjugate addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds via organocuprates is an essential C—C bond forming process in synthetic organic chemistry.^[40–42] It is remarkable the broad field in which the conjugated addition reactions are currently applied, they usually represent a key step in the synthesis of valuable compounds, and every day a new progress is achieved.^[43–48] In spite of its enormous synthetic potential, the mechanisms by which reaction occurs and even the structures of the Cu species involved are far from being elucidated. A recent review summarizes the 'state-of-the-art' of the organocuprates structures in solution.^[9]

The general objective of the present study was to contribute to the elucidation of the conjugate addition mechanism via

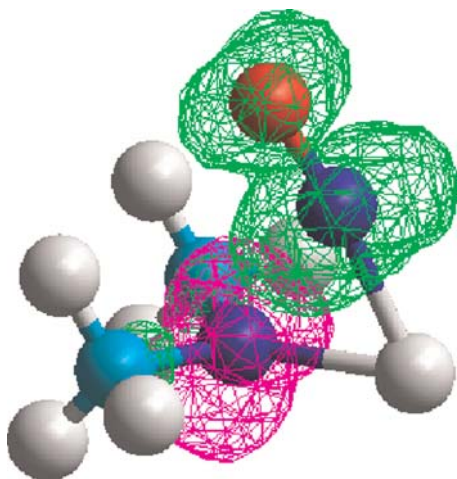
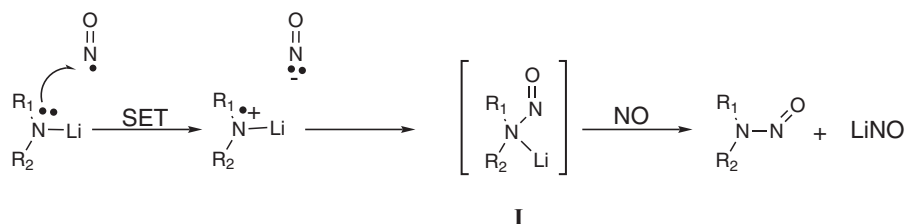


Figure 1. Reaction of dimethyl lithium amide with NO. Spin density distribution in the transition state



Scheme 4.

organocuprates and to examine its potentiality in tandem reactions involving heterocyclic compounds, which are interesting moieties but methods for their synthesis are scarce. First of all, several copper precursors were studied by preparing a series of furylcuprates and comparing the results in their conjugate addition to E-cinnamaldehydes and also to 2-cyclohexen-1-one, the so-called higher-order cyanocuprate gave the better results.^[49]

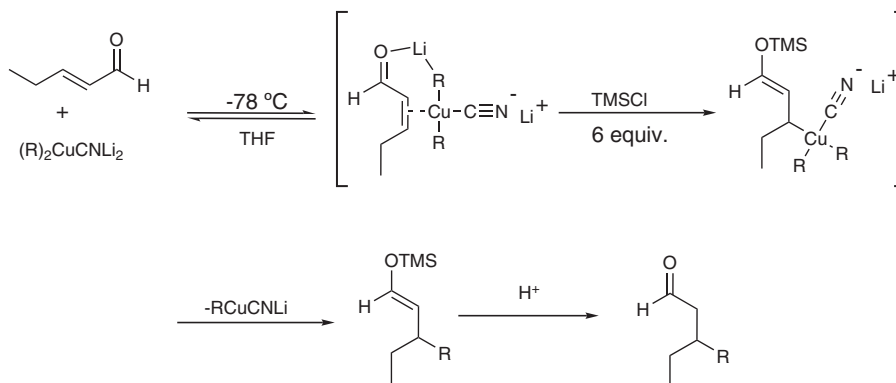
Similarly to the preceding studies, a careful optimization of variables, such as temperature and time of reaction, order of addition and isolation of lateral products, was carried out. Variable overall yields and 1,2:1,4 ratios, as well as the isolation of unexpected products were observed. Corey and Boaz^[50–52] reported the remarkable observation that TMSCl could change both the rate and the stereochemistry of organocuprate reactions, and several groups throughout the world studied this effect. Nevertheless, TMSCl as additive had not been reported in additions using heteroarylcuprates. The addition to both cinnamaldehyde and 2-cyclohexen-1-one was carried out using 6 equiv. of TMSCl at -78°C , TMSCl was added to the reaction mixture after the formation of the organocuprate but previous to the aggregate of the α,β -unsaturated substrate, as recommended in the literature.^[53,54] Several reaction conditions were tested, for the case of cinnamaldehyde, the overall yield was around 85% with variable 1,2:1,4 ratio and minor by-products, for reaction times between 30–60 min. Increasing the time up to 3 h results in an increase of the 1,2:1,4 ratio and also the % of bifurane, (the major by-product), 2-TMS-furan and cinnamic alcohol (in yields of 10 and 4%, respectively), increased with the reaction time. On the other hand, it is worthwhile to mention that in the reaction with 2-cyclohexen-1-one, the 1,4-addition product was formed in yields ranging from 80–95.8% depending on the reaction conditions, without any contamination with the 1,2-addition product or other by-lateral products. Thus, optimization of the reaction conditions, afforded an excellent methodology for the

synthesis of the 3-(2-furyl)-1,3-cyclohexanone, which is isolated from the reaction mixture as a pure compound.

To explore the scope of this methodology, the behaviour of thiophene derivatives was also examined. The thiophenyl cyanocuprate was prepared from thiophene, similarly as done with furyl derivatives. The reactions with aldehydes such as: 2-pentenal, 2-methyl-2-pentenal, and substituted aromatic aldehydes (2-methyl-cinnamaldehyde and 2-bromo-cinnamaldehyde) were tested. For the case of aromatic aldehydes, in the absence or presence of additives no 1,4-addition products were detected, while the 1,2-addition products showed variable yields and the effects of the substituent were unexpected. In the reactions with 2-pentenal and 2-methyl-2-pentenal aldehyde non-conjugated addition product were detected in the absence of additive. On the other hand, when the reactions were carried out in presence of additive, a very good selectivity of the conjugate addition product with an excellent overall yield of the reaction was observed, something that it had not been achieved before.

The mechanism whereby TMSCl influences the rate and stereochemistry of organocuprates reactions is still controversial. Corey *et al.* proposed a mechanism in which the TMSCl directly silylates the O of the enone in a 'd- π^* -complex'. A second scenario invokes that TMSCl activate conjugate addition of copper reagents as a Lewis acid in a TMSCl-substrate interaction,^[53,54] while an opposite interpretation suggest that an interaction between TMSCl and R_2CuLi may exist where TMSCl acts as a Lewis base toward the cuprate giving a cyclic intermediate.^[55] The other salient feature of this last mechanism is that the TMS enol ether (a commonly observed side-product) is formed directly via such a cyclic intermediate.

Scheme 5 depicts an interpretation of the reaction with $\text{R} = \text{thienyl}$. A similar mechanism can be draw for the reaction of 2-cyclohexen-1-one with furyl cuprate. In both cases, the 1,4-addition product is formed in yields $>90\%$, while the silyl ether of



Scheme 5.

the enolate is not observed. The only silylated product found is the heteroaryl-TMS which is expected taking into account that the heterocycle is in excess. The absolute absence of any silyl ether in the present study allows us to rule out a mechanism in which the cyclic intermediate or transition state leads directly to the TMS enol ether, as it was previously proposed. Instead, the effect of the TMSCl additive would be promoting conversion of the initially formed complex to a reactive tetravalent copper species capable of rapid reductive elimination to the product. Thus, formation of the tetravalent copper species enhances the rate of the 1,4-cuprate addition, and this is the only product obtained under the present reaction conditions. Theoretical calculations to enlighten the role of the tetravalent copper species are under progress.

EXPERIMENTAL PART

General remarks

All reactions involving organolithium reagents were carried out by standard techniques for the manipulation of air and water-sensitive compounds, previously described.^[56] Characterization of products was carried out by melting point (when available), mass spectrometry (recorded on a BG Trio-2 spectrometer), ¹H- and ¹³C-NMR spectroscopy (recorded in a Bruker 200 and/or in a Bruker 500 MHz NMR spectrometers). Product quantification was carried out by using a 5890 Series II Plus Hewlett-Packard gas chromatograph (equipped with a DB-5 column), at 70–280 °C programmed temperature.

Hexane and THF (HPLC grade) were distilled from blue solutions of sodium-benzophenone ketyl immediately before using *n*-butyllithium (1 M in *n*-hexane solution) was synthesized as previously described, starting from *n*-butyl-chloride.^[21] All the other alkyl-lithiums used were prepared similarly to *n*-BuLi, starting from the respective alkylbromides. Some general procedures, for the synthesis of different functionalized molecules, are described below as an illustration of the usefulness of each one of the three methodologies herewith discussed.

Synthesis of substituted 2,3-dihydrobenzo[b]furans

A solution of 0.05 mmol of 2-bromophenyl-3-phenylprop-2-enyl ether in 10 ml of THF was cooled to –85 °C under a blanket of dry nitrogen and 1.5 eq. of *n*-BuLi as a solution in hexane was added dropwise via syringe over a 1–2 min period. The temperature was maintained at –80 °C for 5 min, and the electrophile, pure or as a solution in THF, was added rapidly via syringe. The reaction mixture was immediately allowed to reach 0 °C and stand for 5 min before quenching with MeOH. After work-up, the products were isolated by TLC and identified by melting point, ¹H and ¹³C NMR.

Synthesis of dialkylnitrosamines

To a round-bottomed reaction flask (evacuated and filled with dry nitrogen alternatively) capped with a no-air stopper, nitric oxide was added at ca. 1013 mbar. After that, a solution of lithium dialkylamide (1 mmol) in THF (1 ml) was added with vigorous magnetic stirring for 3 h. The reaction was worked out with 0.2 of distilled methanol. Excess NO was removed and distilling the THF under reduced pressure afforded slightly orange crystals in very good to quantitative yields. For the case of dicyclohexylnitro-

samine, crystallization from acetone rendered white crystals of m.p. 104.5–105.5 °C.

Synthesis of substituted hydrazones and hydrazines

One millimole of the corresponding *N*-nitrosodialkylamine was put in a 10 ml round bottomed flask, equipped with a magnetic stirrer and protected from light. The flask was tapped with a rubber septum, it was placed in a bath at the desired temperature, and then evacuated and filled with dry N₂, alternatively several times. Two millilitre of anhydrous THF was added to dissolve the nitrosamine. The organolithium solution (1.05–1.2 mmol in *n*-hexane) was added by syringe with vigorous stirring, and allowed to react for 5 min. Then, the flask was placed in a water-ice bath, and distilled methanol (ca. 0.15 ml) was syringed. The solvent was distilled at reduced pressure and the residue was purified by silica-gel column chromatography (when necessary), or dissolved in CH₂Cl₂ prior to GC-analysis. For the synthesis of hydrazines, the procedure is similar but using 4–5 equivalents of organolithium reagent, and allowing to react for 2 h at room temp. When two different organolithiums are used, the first is added in a small excess (1–1.2 mmol), and the second (3–5 equivalents) is added after 5 minutes, allowing to react for 2 h.

Kinetics of the reaction of nitrodicyclohexylamide with *n*-BuLi

The reaction was carried out at three working temperatures (0 °C, 12 °C and room temp.), following the conditions described for the hydrazine synthesis ([*n*-BuLi]:[nitrosamine] = 3). Aliquots of ca. 0.5 ml were withdrawn by a syringe at different time intervals, and quenched with distilled MeOH (30 µl) in small vials that had been previously evacuated and purged with N₂. The resultant solutions were analysed by GC.

Synthesis of 3-heteroaryl substituted compounds by 1,4-addition to α,β-unsaturated carbonyl compounds

The heterocycle (2.5 mmol in 3 ml THF) was added to a purged septum-capped round-bottomed flask, protected from light, under argon atmosphere and cooled to –78 °C. After 5 min BuLi (2 mmol) was added dropwise under stirring. After 10 min the mixture was heated at 0 °C and held for 30 min. The mixture was transferred via canula to a purged septum-capped round-bottomed flask containing 1 mmol of copper cyanide in 3 ml THF at –78 °C under stirring condition, and it was stirred until the complete dilution of the salt (30–60 min). After the formation of organocuprate, 6 equiv. of TMSCl were added to the reaction mixture, stirred for 10 min, then it was heated to –40 °C and the carbonyl compound (1 mmol) was added dropwise; the mixture was allowed to warm to r.t. and quenched by the addition of 3 M aqueous NH₄Cl. The reaction mixture was extracted with dichloromethane. The organic extract was dried (anhydrous Na₂SO₄) and the solvent distilled under vacuum.

Methods of calculations

All geometry optimizations, transition state findings, single point and frequency calculations were carried out using the Gaussian 03 software pack, unrestricted Hartree–Fock (UHF), with a 6-31G base was used. For the precise finding of transition states the autovalor finding method was used, starting from initial approximated structures obtained from the potential energy curve build as a function of the N–N and N–Li bond distances.

In all the cases, it was confirmed that these structures had only one negative autovalor, which corresponds to the reaction coordinate.

CONCLUSIONS

The three organometallic reactions described above exhibit a wide mechanistic spectrum.

Evidences have been afforded that in the reaction of aryl halides of one specially designed radical clock, the lithium–halogen exchange occurs through a carbanionic intermediate and no evidences for radical species were found. On the contrary, in the insertion of NO into N—Li bonds of lithium amides, theoretical calculations showed a paramagnetic transition state with a large negative spin density located on the NO motifs, which reasonably indicates that electron transfer from the lithium amide to the NO is the first step of the reaction. For the case of the 1,4-conjugate addition of heteroaryl cuprates, results are consistent with a mechanism involving the initial formation of a d– π complex and its conversion to a tetravalent copper species. The effect of the TMSCl additive would be promoting conversion of the d– π complex to a more reactive tetravalent copper species capable of rapid reductive elimination to the product.

It is relevant to recall that, in the three cases, a detailed study of the effects of changing reaction conditions (temperature, solvent, time of reaction, etc.), a careful search of minor side products, and the characterization of intermediates afforded mechanistic hints. The elucidation of the complex mechanism of these reactions provided clues to lead each reaction toward the production of useful compounds in good to excellent yields. New synthetic tandem routes were developed that are more environmental friendly processes than the conventional ones.

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