Discovering new arene-catalyzed lithiations

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Resum. La litiació catalitzada per hidrocarburs aromàtics és una metodologia útil i versàtil que promou els processos de litiació en condicions de reacció molt suaus. Aquest informe presenta els resultats recents en l'aplicació d'aquesta tecnologia, principalment en els camps següents: *a*) carbolitiació intramolecular *vs*. obertura d'anells en litiometilcicloalcans, *b*) la generació de sintons de diliti com a precursors dels èters bicíclics i espiroèters, les principals unitats de productes naturals biològicament actius, *c*) desprotecció general dels diversos compostos protegits que contenen oxigen, sofre i nitrogen en condicions no hidrolítiques, i *d*) la preparació de nanopartícules de níquel i la seva aplicació en reaccions de formació d'enllaços carboni-carboni i carboni-nitrogen.

Paraules clau: litiació · compostos organolítics · carbociclització · èters bicíclics · desprotecció · nanopartícules de níquel.

Summary. Arene-catalyzed lithiation is a useful and versatile methodology that promotes lithiation processes under very mild reaction conditions. This report presents recent results in the application of this technology, mainly in the following fields: (a) intramolecular carbolithiation vs. ring-opening in lithiomethylcycloalkanes; (b) the generation of dilithium synthons as precursors of bicyclic and spiro ethers, major units in biological active natural products; (c) general deprotection of different oxygen-, sulfur-, and nitrogen-containing protected compounds under non-hydrolytic conditions; and (d) the preparation of nickel nanoparticles and their application in carbon-carbon and carbon-nitrogen bond formation reactions.

Keywords: lithiation · organolithium compounds · carbocyclization · bicyclic ethers · deprotection · nickel nanoparticles

Introduction

Carbon-carbon bond formation is one of the most important reactions in synthetic organic chemistry, as it is the mechanism by which the backbone of any organic molecule is formed. To that end, organolithium compounds, as a source of carbanionic components, play a pivotal role by reacting with carbon electrophiles [44,59]. Different methods are used to generate an organolithium intermediate, including: (i) deprotonation of compounds bearing activated hydrogen atoms, using a lithium base (a lithium amide or an organolithium reagent); (ii) halogen/lithium exchange, mainly starting from brominated or iodinated materials and using either lithium metal or an organolithium compound. Other procedures, such as carbon-heteroatom (heteroatom: oxygen, nitrogen, or sulfur) bond reductive cleavage, the addition of lithium or an organolithium compound to carbon-carbon multiple bonds, tin- or mercury-lithium transmetalations, or the Shapiro reaction, are far less commonly employed [44]. However, the use of chlorinated starting materials and lithium metal may offer the best combination for preparing an organolithium, considering the stability and price of the substrates and the source of the metal. However, chlorine/lithium exchange is problematic, especially at low temperatures, due to the low reactivity of the carbon-chlorine bond; therefore, it is usually necessary to activate the metal in order to obtain the corresponding lithiation. Among the different procedures to activate lithium, arene-promoted lithiation [59] is probably the most effective from a preparative point of view, as it can be performed either stoichiometrically [45] or catalytically [61]. In the first case, an arene [naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most commonly used] and lithium metal are dissolved in equimolecular amounts in tetrahydrofuran and used in solution [60]. In the catalytic version, a substoichiometric amount (<10%) of the arene is used in the presence of an excess of lithium in the same solvent [58,63]. The catalytic reaction has been shown to be more effective than the stoichiometric one, the probable reason being the participation in the first case of an arene dianion instead of the corresponding arene radical-anion, widely accepted as the electron-transfer agent for the stoichiometric reaction. The arene dianion is a much more potent electron-transfer agent than the corresponding radical anion, transferring electrons to the substrate in a single-electron transfer (SET) process [52,53].

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Arene-catalyzed lithiation has been successfully used in the following reactions: (i) the preparation of simple organolithium compounds starting from non-halogenated precursors (alcohols, ethers, silyl ethers, thioethers, sulfoxides and sulfones, sulfonates, sulfonamides, carbonates, carbamates, and ureas) [48]; (ii) preparation of very sensitive functionalized organolithium compounds by chlorine/lithium exchange [43,54,55], sulfur/lithium exchange [47] or reductive ring opening of heterocycles [62,65]; (iii) generation of dilithiated synthons [46]; and (iv) activation of transition metals [18,36].

In this report, achievements made during the last few years using the arene-catalyzed lithiation methodology are discussed.

Intramolecular carbolithiation vs. ring opening

The carbolithiation of a carbon-carbon double bond consists of the addition of an organolithium reagent to an olefin, yielding a new organolithium intermediate having at least two more carbon atoms [50]. A significant advantage of this process is that the new organolithium can then react with an electrophile, such that in only one synthetic operation profound changes can take place in the starting material. Carbolithiation can take place in two ways, inter- or intramolecularly, with the latter of special interest in the preparation of functionalized cyclic compounds. We explored the possibility of effecting an intramolecular carbolithiation in which the initial organolithium compound was generated by the arene-catalyzed lithiation of a chlorinated precursor. Thus, lithiation of 6-chloro-1-hexene (**1**) in the presence of DTBB (5%) led to the intermediate **2** which is stable at –78°C and which reacted with different electrophiles to yield the unsaturated products **3** (Fig. 1). However, if the reaction was allowed to warm to –30°C, a carbolithiation took place that yielded exclusively the new organolithium **4** and the final cyclic compounds **5** by treatment with an electrophile (Fig. 1) [64,67].

Although the reaction shown in Fig. 1 was successfully applied to other terminal alkenes (such as compounds **6** and **7**) to yield acyclic or cyclic compounds, for substituted substrates **8** and **9**, only the corresponding cyclic products were isolated.

However, for small rings, carbolithiation is not a favored process; instead, ring opening is preferred. This process was studied with cyclopropyl- and cyclobutylmethyllithium (**12** and

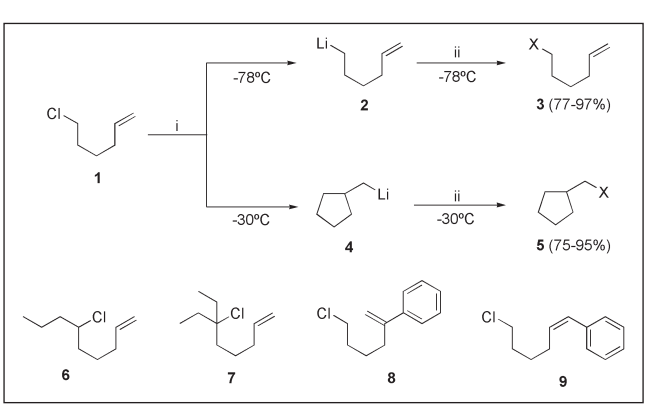


Fig. 1. Reagents: (i) Li, DTBB (5%), THF; (ii) electrophile = Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, then $HCl\text{-}H_2O$.

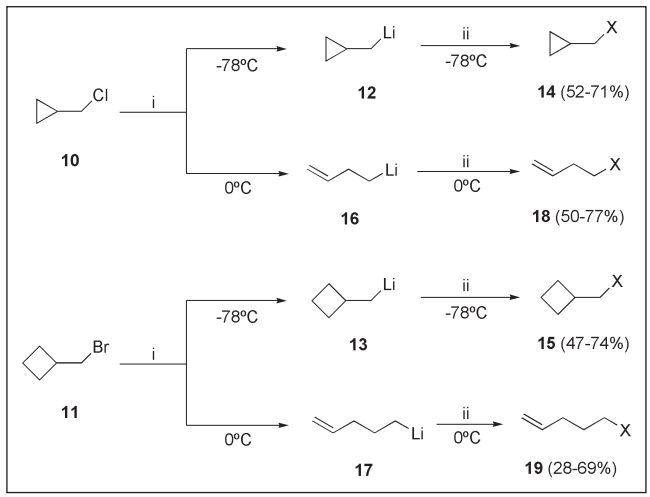


Fig. 2. Reagents: (i) Li, DTBB (for **10**) or $C_{10}H_8$ (for **11**) (5%), THF; (ii) electrophile = Pr^iCHO, Bu^tCHO, PhCHO, Et_2CO, $Pr^n{}_2CO$, $(c\text{-}C_3H_5)_2CO$, $(CH_2)_5CO$, PhCOMe, then H_2O.

13, respectively), generated using the above-mentioned methodology by chlorine- or bromine-lithium exchange and starting from materials **10** and **11**, respectively (Fig. 2). At –78°C and with DTBB as the catalyst (5%), only cyclized products **14** and **15** were isolated, whereas when the reaction was carried out at 0°C or at ambient temperature, with naphthalene as the electron carrier catalyst (5%), the corresponding open-chain products **18** and **19** were obtained through the intermediates **16** and **17**, respectively (Fig. 2) [56]. Organolithiums **16** and **17** are formed by ring opening of the firstly generated intermediates **12** and **13**, respectively, proving that, for small rings, ring opening is preferred over the corresponding carbolithiation (transformation of **16** to **12** or **17** to **13**).

Bicyclic and spiro ethers through dilithium synthons

Many natural products with important biological activity contain a bicyclic [16] or spiro ether [28] moiety as a key structural motive. In an alternative approach, we have used ditlithium synthons [46] to prepare polyfunctionalized molecules in only a single synthetic operation by reaction with electrophiles. An example is the synthesis of the spiro compounds **22** synthesized from the dichloroalkene **20** in two steps: (a) lithiation with DTBB (5%) as catalyst in the presence of a carbonyl compound (Barbier-type conditions) [4] followed by hydrolysis to yield diol **21**, and (b) successive treatment with sodium hydride and iodine, both steps at 0°C (Fig. 3) [13]. In addition, compound **22** can be easily oxidized to yield spiro lactone **23**, a structural unit frequently present in many biologically active natural products.

Spiro ethers having two five-membered cyclic ethers were also prepared using arene-catalyzed lithiation as the key step. In this case, the starting material was the chloro ether **24**, which by lithiation with naphthalene as catalyst (2.5%) in the presence of a carbonyl compound followed by treatment with an epoxide generated, after hydrolysis, the corresponding diol **25** (Fig. 4). These compounds were treated with iodine and silver oxide to afford

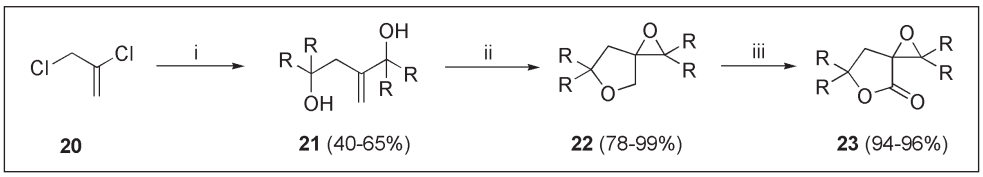
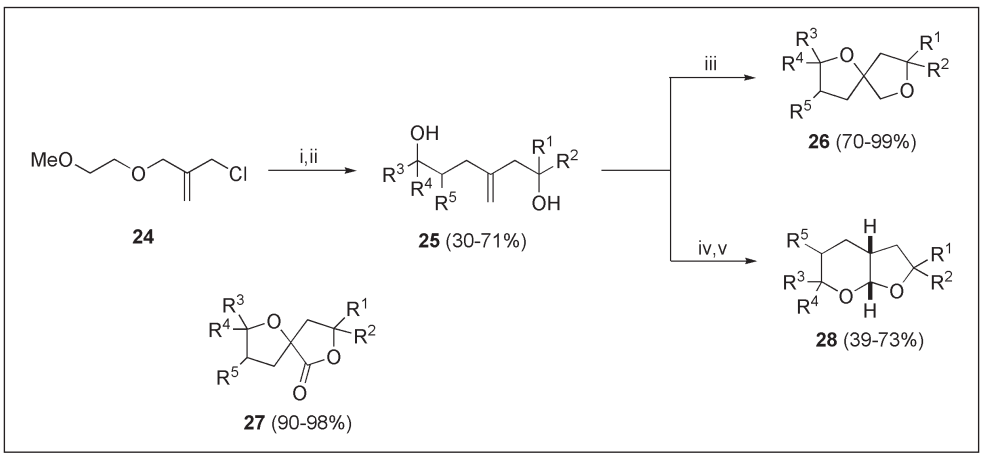


Fig. 3. Reagents: (i) Li, DTBB (5%), $R_2CO = Et_2CO$, $(c\text{-}C_3H_5)_2CO$, $(CH_2)_5CO$, $Y(CH_2CH_2)_2CO$ [Y = O, S, Pr^nN], adamantan-2-one, THF, then H_2O; (ii) NaH, THF, then I_2; (iii) $NaIO_4$, RuO_2 (cat.), CCl_4.

Fig. 4. Reagents: (i) Li, $C_{10}H_8$ (2.5%), $R^1R^2CO = Et_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, $O(CH_2CH_2)_2CO$, adamantan-2-one, THF, –78 to 0°C; (ii) $R^3R^4C(O)CHR^5$ = $MeCH(O)CH_2$, $PhCH(O)CH_2$, *n*-$C_6H_{13}CH(O)CH_2$, $Et_2C(O)CH_2$, $PhMeC(O)CH_2$, $(n\text{-}C_5H_{11})_2C(O)CH_2$, cyclopentene oxide, cyclohexene oxide, methylenecyclohexane oxide, methyleneadamantane oxide, 0°C, then H_2O; (iii) I_2, Ag_2O, THF; (iv) BH_3·THF, then H_2O_2-NaOH; (v) PCC or $Ru(PPh_3)_3Cl_2$, CH_2Cl_2.



1,7-dioxaspiro[4.4]nonanes (**26**), also readily oxidized to yield the new bicyclic lactone **27**, which, like the spiro compound, is a structural moiety present in many active natural products [17,20].

Another interesting class of bicyclic ethers is the family of perhydrofuro[2.3-*b*]pyrans (**28**), which are directly accessible from diols (**25**) by successive hydroboration and oxidation [15,17].

More recently [21], we applied the arene-catalyzed technology to prepare a series of bicyclic and spiro compounds, with the key step being a sulfur-lithium exchange [47] starting from dithioethers. The unsaturated material **29** was subjected to the catalytic lithiation protocol in the presence of carbonyl compounds, resulting in the isolation of unsaturated diol **30** after hydrolysis (Fig. 5). These compounds were further treated with iodine and silver triflate, yielding the corresponding 1,7-dioxaspiro[4.5]decanes (**31**), which could be oxidized to the expected bicyclic lactone **32** [24]. Unexpectedly, the treatment described above for compound **28** in this case produced the *cis*-bicycle **33**, which kinetically is the most stable of this group of compounds. In fact, its treatment with a catalytic amount of *p*-toluene sulfonic acid resulted in high yields of the corresponding thermodynamically most stable *trans*-derivative **34** [25]. Finally, direct ozonolysis of diol **30** at low temperature directly afforded the spiro ketal **35** [51].

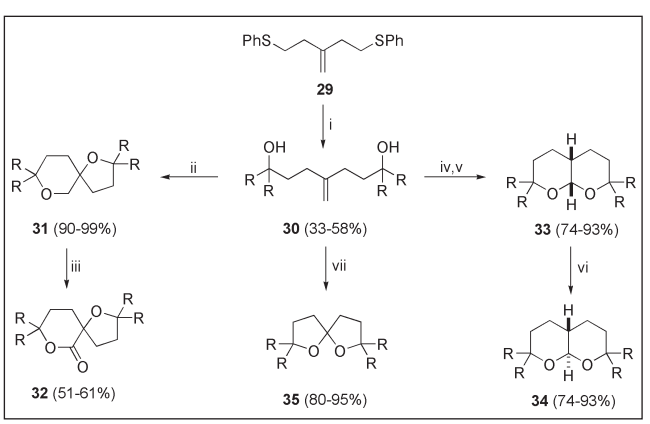


Fig. 5. Reagents: (i) Li, DTBB (2.5%), $R_2CO = Et_2CO$, $Pr^i{}_2CO$, $Bu^t{}_2CO$, $(n\text{-}C_5H_{11})_2CO$, $(c\text{-}C_3H_5)_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, $Y(CH_2CH_2)_2CO$ [Y = O, Pr^nN], adamantan-2-one, THF, 0°C, then H_2O; (ii) I_2, AgOTf, THF; (iii) $NaIO_4$, RuO_2 (cat.), CCl_4; (iv) BH_3·THF, then H_2O_2-NaOH; (v) PCC, CH_2Cl_2; (vi) *p*-TSA, $CHCl_3$; (vii) O_3, CH_2Cl_2, –78°C.

Deprotection of oxygen-, nitrogen- and sulfur-containing compounds

One important operation in total synthesis is the protection of sensitive functionalities during a reaction, which should be deprotected at the end of the process. In this context, arene-catalyzed lithiation has proven to be an efficient methodology for protected alcohols, amines, and thiol derivatives. Thus, allylic ethers and amines **37** [5] as well as benzylic ethers and amines **38** [5] (including the corresponding tritylic derivatives [41,66]) were efficiently deprotected by an arene (naphthalene or DTBB) catalyzed (5–10%) lithiation following by simple hydrolysis,

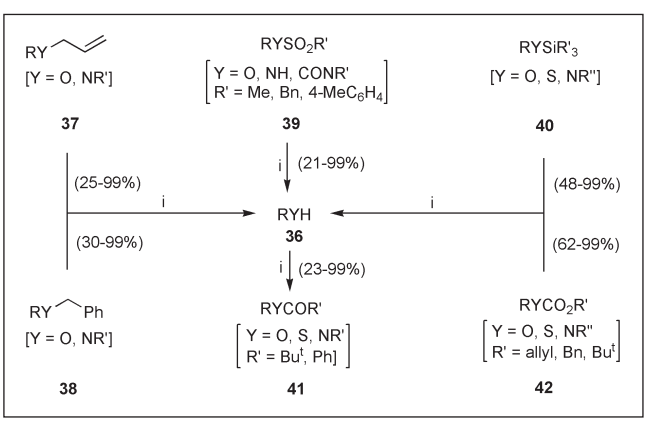


Fig. 6. Reagents: (i) Li, $C_{10}H_8$ or DTBB (5–10%), 0°C, then H_2O.

yielding the expected product **36** (Fig. 6). The same methodology was highly versatile in the desulfonylation of sulfonates and sulfonamides **39** [22], and in the desilylation of several silyl ethers, thioethers, and amines **40** [42]. The deacylation of carboxylates, thiocarboxylates, or carboxamides **41** is an important process that liberates the corresponding alcohols, thiols, or amines, respectively. While it is normally performed under acidic hydrolytic conditions, in our hands in situ catalytic lithiation hydrolysis represents a reasonable alternative [40]. Finally, one important family of protecting groups for carboxylic acids consists of carbonate derivatives, such as the allyloxycarbonyl-, benzyloxycarbonyl-, and *tert*-butyloxycarbonyl- (Boc) derivatives **42**. All these compounds were deprotected in a very general fashion by using the above-described protocol [1,39].

Ni-nanoparticles in carbon-carbon and carbon-nitrogen bond-forming reactions

Nickel nanoparticles [19,23], prepared by reduction of nickel(II) chloride with lithium and a catalytic amount of an arene in combination with a hydrogen source, have been widely use in a versatile and practical methodology to reduce a variety of organic functionalities [18,36]. As hydrogen source, water (or deuterium oxide) [2,3,6,7–10,12,57], molecular hydrogen [11,14], or an alcohol (ethanol [26,27,29] or isopropanol [34,35,37]) have been successfully employed, and the corresponding reduced functional groups being olefins [2,10,11,14,27,29,37], acetylenes [3,11,14,27], halogenated compounds [7,11,12,14], sulfonates [57], aromatic derivatives [11,14,57], carbonyl compounds and their imines [6,26,34,35], and nitrogen-containing compounds (hydrazines, azo and azoxy compounds, amine oxides [8,11,14], and nitrones [9]).

In the last few years, we have also used nickel nanoparticles to induce carbon-carbon or carbon-nitrogen bond formation. In this case, besides the classical homocoupling of aromatic and heteroaromatic iodides to yield diaryl or dihetaryl derivatives, respectively [32], the nickel nanoparticles were used in the four processes shown in Fig. 7. The first is the reductive amination of an aldehyde **43** using a primary amine **44** in the presence of isopropanol, to yield a secondary amine **45**; this reaction involves in situ formation of the corresponding imine followed by its hydrogen-transfer reduction [33]. The second consists of the alkylation of a methyl ketone **46** with a primary alcohol **47** to yield ketone **48** [30,31]; this is an interesting reaction from both a mechanistic (alcohol acts here as an electrophile, its normal reactivity being as a nucleophile) and a practical (this is a good example of "green chemistry" since the only byproduct in the reaction is water) point of view. In the third, an indirect aza-Wittig reaction using a primary alcohol **49** and an iminophosphorane **50** as reagents yields a secondary amine **51**. This reaction is of preparative interest because it includes the use of readily available (inexpensive, stable) alcohols instead of aldehydes as substrates; mechanistically, it belongs to the so-called hydrogen autotransfer reactions [49]. Lastly, the indirect Wittig reaction, again starting from a primary alcohol **49**, uses a typical ylide **52** such that olefins **53** are obtained as a *Z/E* mixture, which can be easily treated with a catalytic amount of iodine under hexane reflux to comprise only the *E*-diastereomer [38]. Using this last methodology, we prepared a family of 5-substituted resorcinols (including resveratrol) of significant biological activity.

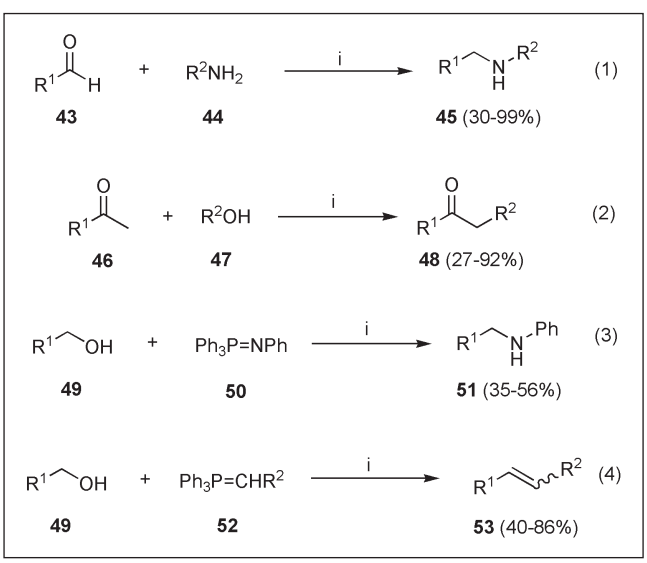


Fig. 7. Reagents: (i) $NiCl_2$, 2Li, DTBB (5%), solvent [Pr^iOH reflux (1) or THF at room temperature (2) or at reflux (3), (4)].

Conclusions

From the chemistry described herein, it can be concluded that arene-catalyzed lithiation is an effective methodology to carry out lithiation processes involving halogen-, oxygen-, sulfur-, and nitrogen-lithium exchange, as well as the reduction of nickel(II) salts to nickel nanoparticles. All of these reactions find a wide application in synthetic organic chemistry.

Acknowledgements

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