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NOTE

Mixed main-group metal alkyls and alkoxides in synthesis and catalysis†

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The organic derivatives of sodium and potassium are generally insoluble in hydrocarbons while their instability in ethers, for example, precludes long-term storage of solutions and thus restricts their wider application. Addition of magnesium 2-ethoxyethoxide produces hydrocarbon-soluble reagents with reactivity comparable with that of the simple organometallics. The organoalkali-metal reagents in the presence of magnesium 2-ethoxyethoxide in tetrahydrofuran become almost inert towards cleavage of the solvent while retaining organoalkali-metal-like metallation characteristics. The metallating ability of organolithium reagents can be modified by addition of suitable metal alkoxides. Mixed alkali-metal dialkylaminoalkoxides combine the activating properties of an alkoxide with those of a tertiary amine, while magnesium 2-ethoxyethoxide greatly reduces the metallating ability and unwanted side reactions can be avoided. Certain allylic or benzylic organolithium reagents, in the presence of mixed lithium potassium dialkylaminoalkoxides, and in some cases also of magnesium 2-ethoxyethoxide, add either stoichiometrically or catalytically to ethylene to produce mono- or poly-ethylated derivatives. In this way substantial quantities of interesting sterically demanding aromatic derivatives have been produced in good yield. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords: alkali metal; metal alkyls; lithium; sodium; potassium; metal alkoxide; magnesium; barium; metallation; ethylene

This is an account of a research project which was initiated in the early 1970s and concerns the synthesis and application of *s*-block bimetallic carbanion and alkoxide complexes.

Our original aim was the synthesis of hydrocarbon-soluble organomagnesium reagents by reaction of a hydrocarbon-insoluble organoalkali reagent with a magnesium alkoxide, e.g. according to Eqn [1].

$$\mathrm{PhNa} + \mathrm{Mg(OnBu)_2} \longrightarrow \mathrm{PhMgOnBu} + \mathrm{NaOnBu} \quad [1]$$

The organosodium was generated *in situ* from the corresponding chloride and sodium dispersion in toluene. However, this attempt met with failure and as the reaction was progressing an insoluble product formed instead. The only parameter that could be varied in this system was the nature of the alkoxy moiety. Thus, by choosing the 2-methoxy- or ethoxyethoxide of magnesium, or other alkaline-earth metals, it became possible to prepare hydrocarbon-soluble compounds. These products were of unknown composition but were qualitatively shown to contain an alkali metal and magnesium or another alkaline earth metal, and exhibited what is considered to be 'normal organometallic reactivity', i.e. they were mild metallating agents, and gave the expected reaction products with the usual electrophiles (e.g. Eqns [2] and [3]).

$$\mathrm{R(Mg,Na,OR)_?} + \mathrm{CO_2} \longrightarrow \mathrm{RCOOH} \quad [2]$$

$$\mathrm{Ph(Mg,Na,OCH_2CH_2OCH_3)_?} + 1\text{-}\mathrm{C_{10}H_7CH_3} \longrightarrow \underset{73\%}{1\text{-}\mathrm{C_{10}H_7CH_2Na}} \quad [3a]$$

$$\mathrm{Bu(Ba,Li,OCH_2CH_2OCH_3)_?} + \mathrm{PhCH_3} \longrightarrow \underset{80\%}{\mathrm{PhCH_2BaOCH_2CH_2OCH_3}} \quad [3b]$$

With insoluble organolithium reagents, such as cyclohexyl-lithium generated *in situ*, solubilization could be effected by ordinary magnesium alkoxides, such as magnesium n-butoxide, even in

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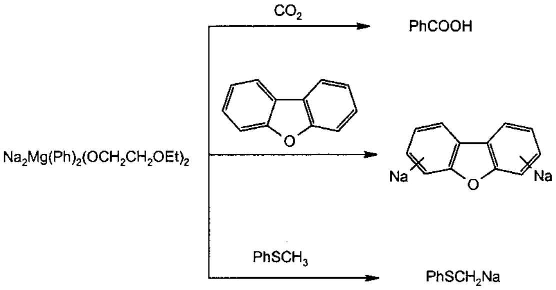
pentane (Eqn [4]).

$$\text{c-C}_6\text{H}_{11}\text{Cl} + 2\text{Li} + \text{Mg(OnBu)}_2 \longrightarrow \underset{\text{soluble in pentane}}{\text{c-C}_6\text{H}_{11}\text{(Li,Mg,OnBu)}_?} \quad [4]$$

At this stage we applied for a patent,[1] which was issued in January 1976, and described systems containing organosodium or organolithium reagents and alkoxides of magnesium, calcium, strontium and barium.

In the early 1980s we returned to this project, wanting this time to take a closer look at the composition of these reagents.[2] We focused our attention on the phenyl derivatives of sodium and, to a lesser extent, of potassium and lithium. We added a limited amount of magnesium 2-ethoxyethoxide to phenylsodium, either preformed or prepared *in situ*, and analysed the clear supernatant for total alkalinity and magnesium content. Thus we could determine the Na/Mg ratio in the soluble species. This ratio could be very readily reproduced; 23 determinations all gave a ratio of Na/Mg = 2:1. With phenylpotassium the ratio of K/Mg in the soluble species was 1:1, whereas with unsolvated, preformed phenyl-lithium the Li/Mg ratio was 3:1. However, when phenyllithium was generated *in situ* from diphenylmercury and lithium metal, a process which requires long reaction times, the ratio of Li/Mg in the soluble species was 4:1. Thus the trend that seems to emerge is that the M/Mg ratio decreases with increasing atomic number of the alkali metal. On the basis of the above information it was concluded that the 'unit composition' for the phenylsodium case was $\text{Na}_2\text{MgPh}_2(\text{OCH}_2\text{CH}_2\text{OEt})_2$. It appeared then reasonable to ask whether this apparently novel organometallic reagent exhibited organomagnesium- or organosodium-like behaviour. This reagent on carboxylation afforded benzoic acid in a yield close to that corresponding to the sodium content, and it could easily metallate substrates such as dibenzofuran and thioanisole. What is of interest here is that the metallation products (Scheme 1) were the same as those obtained by metallating the same substrates by ordinary, insoluble organosodium reagents. Therefore, the complex appears to exhibit an organosodium-like behaviour.



Scheme 1

Butylsodium also forms hydrocarbon-soluble products with magnesium 2-ethoxyethoxide.[3] Sodium-to-magnesium ratios between 2 and 2.7:1 were determined in the soluble species. These complexes are of moderate thermal stability and only when sufficient magnesium alkoxide is added to the butylsodium to form a 1:1 Na/Mg ratio, does the thermal stability of the soluble complex become substantial and the reactivity low. It is of interest to note that the latter complex reacts with benzophenone, affording benzhydrol as the main reaction product, i.e. the reduction product.

In order to gain further insight into the Na,Mg,Ph,–OR system, we approached the problem from another direction, namely by studying the interaction between Ph_2Mg and $\text{MOCH}_2\text{CH}_2\text{OEt}$, where M = Na, K, Li.[4] One could think several modes of interaction between the diphenylmagnesium and the alkali-metal 2-ethoxyethoxide. Some of these possibilities are shown in Eqns [5a]–[5d]. Equation [5a] represents a metal–metal interchange reaction between sodium and magnesium, leading to the formation of phenylsodium and phenylmagnesium alkoxide. Another possibility (Eqn [5b]) is the complete metal–metal interchange which results in the formation of two molecules of phenylsodium and one molecule of magnesium alkoxide. A third possibility is the formation of a complex between the interacting species (Eqn [5c]). Lastly, Eqn [5d] represents the case in which we have a mixed mode involving complete metal–metal interchange, followed by complex formation by the resulting species.

$$\text{Ph}_2\text{Mg} + \text{NaOCH}_2\text{CH}_2\text{OEt} \longrightarrow \text{PhNa} + \text{PhMgOCH}_2\text{CH}_2\text{OEt} \quad [5a]$$

$$\text{Ph}_2\text{Mg} + 2\text{NaOCH}_2\text{CH}_2\text{OEt} \longrightarrow 2\text{PhNa} + \text{Mg(OCH}_2\text{CH}_2\text{OEt)}_2 \quad [5b]$$

$$\text{Ph}_2\text{Mg} + \text{NaOCH}_2\text{CH}_2\text{OEt} \longrightarrow \text{complex formation} \quad [5c]$$

$$\text{Ph}_2\text{Mg} + 2\text{NaOCH}_2\text{CH}_2\text{OEt} \longrightarrow (\text{PhNa})_2 \cdot \text{Mg(OCH}_2\text{CH}_2\text{OEt)}_2 \quad [5d]$$

A hint of what happens in this system was given by the outcome of the following experiment. On adding triphenylmethane to a solution of diphenylmagnesium in tetrahydrofuran (THF), we observed no reaction. On addition of sodium 2-ethoxyethoxide, however, to the solution, we observed rapid production of sodium triphenylmethide. Even the yellow colour of the benzyl carbanion formed rather rapidly when potassium 2-ethoxyethoxide was added to a solution of Ph_2Mg in THF containing toluene. When this mixture was stirred for 24 h at room temperature and then carboxylated, a 60% yield of phenylacetic acid was obtained. These experiments undoubtedly indicate the involvement of a metal–metal interchange process, leading to the formation of phenylsodium or phenylpotassium, which should be the metallating agents. What is of paramount importance is that both the phenylpotassium formed originally and the resultant benzylpotassium had survived in the THF medium. Therefore, this was our first evidence that an alkali-metal alkyl generated as described above is modified in some way, so that it retains its metallating ability towards methyl aromatics and the like but becomes almost inert towards cleavage of THF.

A decisive NMR spectroscopic experiment provided evidence which enabled us to draw conclusions about the mode of interaction in the system $Ph_2Mg + MOCH_2CH_2OEt$. We recorded the hexadeuterobenzene-soluble species resulting from mixing diphenylmagnesium and sodium 2-ethoxyethoxide in a 1:2 molar ratio and recording the proton and ^{13}C spectra. These spectra were identical to those which were recorded for the soluble species obtained from a 2:1 ratio of PhNa and $Mg(OCH_2CH_2OEt)_2$ (Eqn [6]). We therefore concluded that complete metal–metal interchange takes place between diphenylmagnesium and sodium 2-ethoxyethoxide according to Eqn [5d]. That is, the metal–metal interchange reaction leads to the formation of the alkylmetallic product of the more electropositive metal, just as in the case of BuLi + KOR, for example.[5]

$$Ph_2Mg + 2NaOCH_2CH_2OEt \longrightarrow [?] \longleftarrow 2PhNa + Mg(OCH_2CH_2OEt)_2 \qquad [6]$$

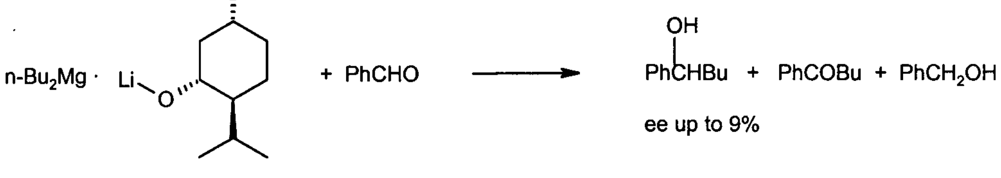
identical NMR spectra for reaction products

Thus the $R_2Mg + 2MOR'$ system appears to be equivalent to the $2RM + Mg(OR')_2$ system. This has been proved for R = aryl, and the diminished metallating ability and the stability towards THF cleavage of the organoalkali reagents is due to their complexation with magnesium alkoxide.

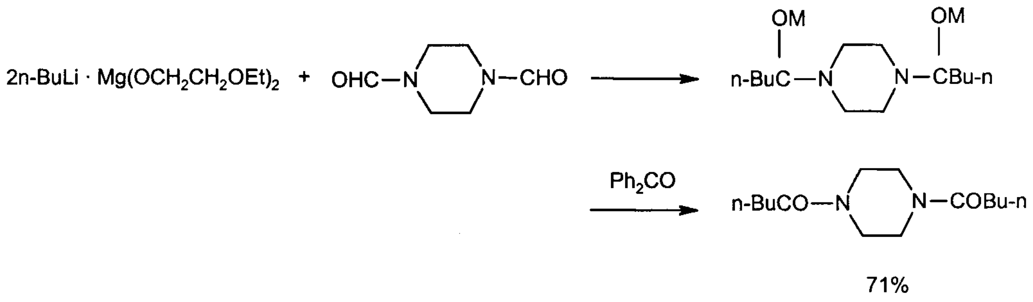
Our next step was to investigate the synthetic potential of these systems.[6]

Dibutylmagnesium when unsolvated is insoluble in hydrocarbon media, but it could be solubilized by lithium (−)-mentholate. It appeared to us that this combination might be a promising reagent for inducing asymmetry (Scheme 2). The results, however, were quite disappointing. The enantiomeric excess in the expected addition product to benzaldehyde, the butylphenylcarbinol, was rather small; the reason for this became apparent from the other by-products of the reaction, namely valerophenone and benzyl alcohol— the oxidation and reduction products, respectively, of butylphenylcarbinol and benzaldehyde. This then was an indication that the system exhibited some type of Meerwein–Ponndorf–Verley–Oppenauer activity. Since these types of oxidation–reduction reactions are reversible, the cause of the loss of the stereochemical integrity of the butylphenylcarbinol becomes apparent.

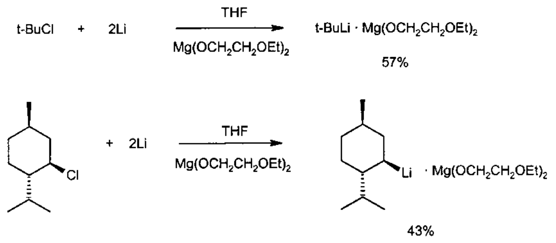
One can, however, take advantage of the above-mentioned property of the $R_2Mg + MOR'$ or $RM + Mg(OR)_2$ system and apply the reagents to synthetically useful reactions. For example, Eqn [7] demonstrates that one can go directly to the ketone from either an alkyl-lithium reagent and a magnesium alkoxide or from a dialkylmagnesium and a lithium alkoxide, simply by using the carbonyl compound in excess, i.e. as both a substrate and an



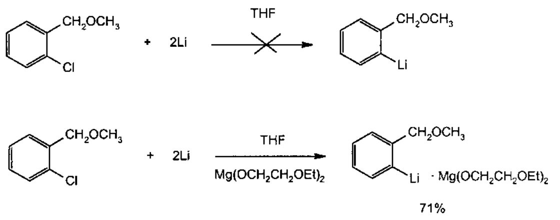
Scheme 2



Scheme 3



Scheme 4



Scheme 5

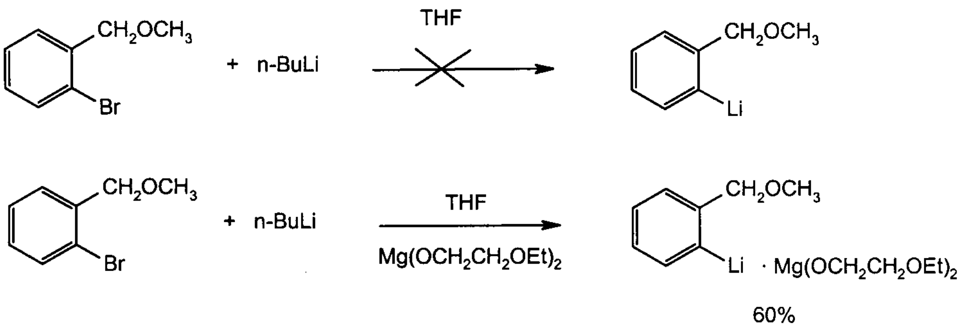
Oppenauer oxidant.

$$nBu_2Mg \cdot LiOCH_2CH_2OEt + xs.\ PhCHO \longrightarrow PhCOnBu \qquad [7]$$

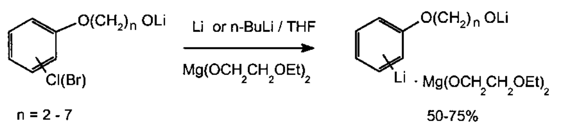
The reaction was extended to the synthesis of amides by reacting a mixed alkyl alkoxide reagent with a formamide and oxidizing the salt of the intermediate hemiaminal by an Oppenauer oxidant such as benzophenone (Scheme 3).[7]

Armed with the knowledge that magnesium alkoxide stabilizes alkali metal alkyls so that they become almost inert towards THF cleavage, we decided to generate t-butyl-lithium from t-butyl chloride and lithium metal in THF and in the presence of magnesium 2-ethoxyethoxide (Scheme 4). A number of other THF-unstable organolithium reagents were prepared in the same way.[8]

The preparation of substituted phenyl-lithium with sensitive functional groups, such as an alkoxymethyl group, became possible according to Scheme 5. Evidently, the *o*-methoxymethylphenyl-lithium generated, modified by magnesium alk-



Scheme 6

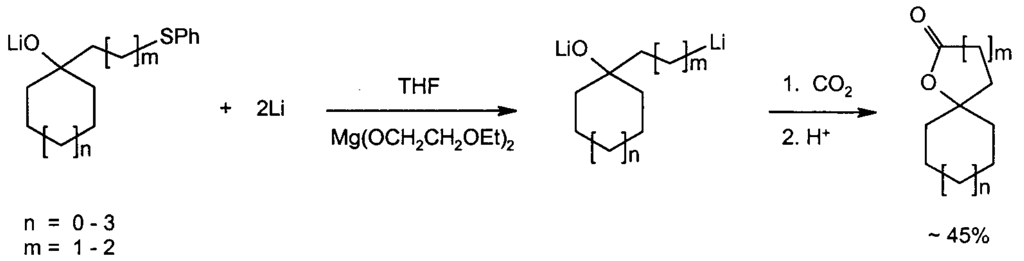


Scheme 7

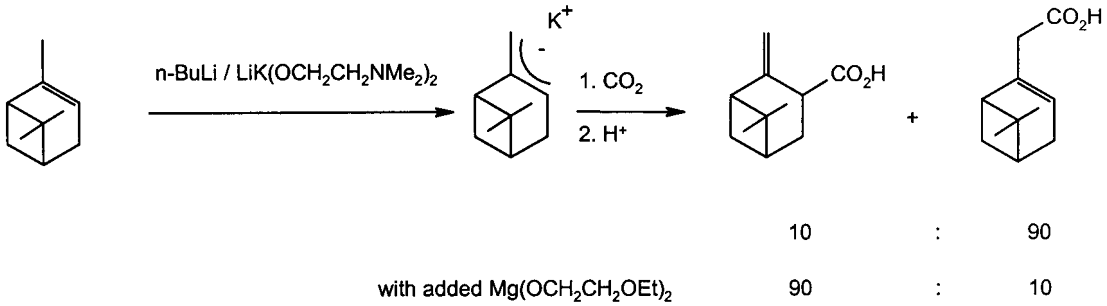
oxide, is incapable of attacking the methoxymethyl group, thus avoiding complications arising from a possible Wittig rearrangement.

The same substituted phenyllithium was prepared from the corresponding bromide (Scheme 6) by bromine-lithium interchange reaction.[8] Here, it is also of importance to note that butyl-lithium modified by magnesium 2-ethoxyethoxide retains its ability to undergo a halogen–metal interconversion reaction.

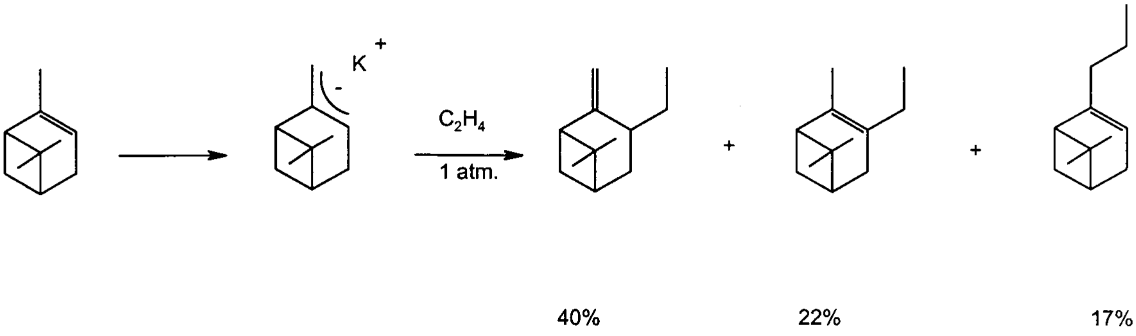
Recently, we have shown that the $LiO(CH_2)_nO$— group on a benzene ring is rather strongly *ortho*-directing in the lithiation reaction.[9] Therefore, if one attempts the preparation of the corresponding *m*- or *p*-substituted phenyl-lithiums from either the corresponding chlorides and lithium metal in THF or from the bromides by halogen–metal interchange with butyl-lithium, one will end up with the *ortho*



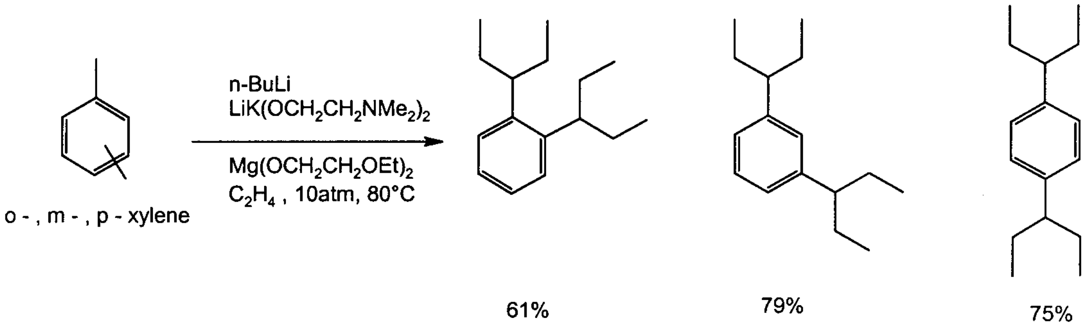
Scheme 8



Scheme 9



Scheme 10

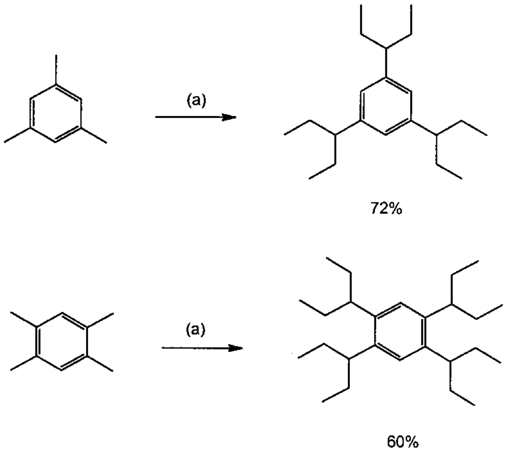


Scheme 11

isomer. If, however, the reaction is carried out in the presence of magnesium alkoxide, the *m*- and *p*-substituted phenyl-lithiums are produced in good yields (Scheme 7).[10]

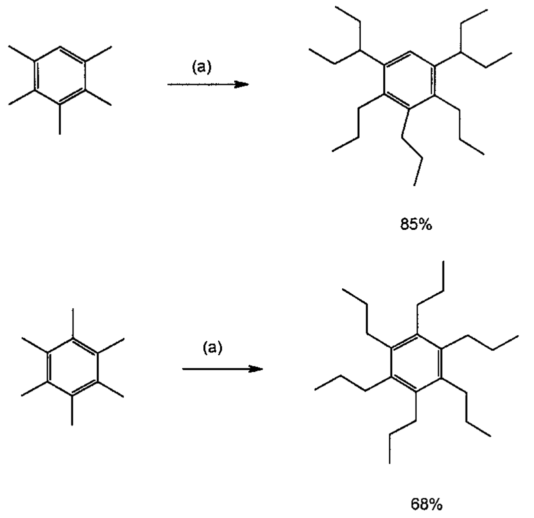
Scheme 8 summarizes the synthesis of a series of 3 and 4-lithio-oxybutyl-lithiums by cleaving the corresponding phenylthio derivatives with a lithium dispersion in THF and in the presence of magnesium 2-ethoxyethoxide. In both types of reagents the ω-carbon atom is shared by a carbocyclic ring. These reagents become storable for several days and perhaps for weeks. On carboxylation and acidification they afford the corresponding spirolactones, some of which are natural products and constitute the aroma of various fruits.[11]

Bearing in mind the activating effect on organolithium reagents of potassium alkoxides[5] as well as of tertiary amines of low steric requirements,[12] we decided to prepare potassium 2-dimethylaminoethoxide and use it as a LICKOR reagent, the latter terminology being derived from the organolithium, 'LIC', and potassium alkoxide, 'KOR', components. However, the solubility of $KOCH_2CH_2NMe_2$ in hydrocarbon media is very low and in order to increase its solubility we prepared the mixed lithium potassium 2-dimethylaminoethoxide, $LiK(OCH_2CH_2NMe_2)_2$, which is considerably more soluble in methylcyclohexane than the potassium alkoxide alone. This bimetallic alkoxide in combination with butyl-lithium constitutes a 'higher-order LICKOR reagent'. Its powerful metallating ability was demonstrated in the metallation of α-pinene (Scheme 9), which gives an allylic-type carbanionic species.[13] An interesting selectivity inversion was observed in the



(a) n-BuLi, $LiK(OCH_2CH_2NMe_2)_2$, $Mg(OCH_2CH_2OEt)_2$, C_2H_4 , 20atm, 80°C

Scheme 12



(a) n-BuLi, $LiK(OCH_2CH_2NMe_2)_2$, $Mg(OCH_2CH_2OEt)_2$, C_2H_4 , 20atm, 80°C

Scheme 13

carboxylation reaction of the metallated α-pinene in the absence and in the presence of magnesium 2-ethoxyethoxide. In the former case the ratio of endocyclic to exocyclic olefinic product was 9:1, whereas when magnesium alkoxide was added to the metallated α-pinene prior to carboxylation to form a hydrocarbon-soluble species, the ratio was 1:9. This could be of synthetic value, given that the exocyclic olefinic products are generally more useful than the corresponding endocyclic olefinic isomers.

Metallated α-pinene reacts slowly with ethylene at 1 atm and gives mainly three monoethylated isomeric products (Scheme 10).[13] This prompted us to revisit the reaction of the anionically catalysed addition of methylaromatics to ethylene. This reaction, which has been studied mainly by Pines,[14] usually gives an intractable mixture of products such as indanes, alkylated benzenes and telomers. Our higher-order LICKOR reagent in combination with magnesium 2-ethoxyethoxide provides a catalytic system whereby the addition of methylaromatics to ethylene takes place in a rather chemoselective way. Thus methyl groups attached to a benzene ring are converted to the corresponding 3-pentyl groups, which result from double ethylation of the originally ‘primary benzylic’ carbon. A higher alkylbenzene with a ‘secondary benzylic’ carbon can only be monoethylated; for example, n-butylbenzene is transformed into 3-phenylhexane. The xylenes are ultimately converted to the corresponding bis (3-pentyl) derivatives (Scheme 11) and likewise mesitylene and durene are converted to tris- and tetrakis-(3-pentyl) derivatives, respectively (Scheme 12).

On going, however, to penta- and hexa-methylbenzenes, the reaction becomes strongly dependent on steric factors. Thus in these two cases the methyl groups which are flanked by other methyl groups can only be monoethylated, whereas if the methyl group has a free *ortho* position, like the methyl groups in the 1 and 5 positions in pentamethylbenzene, they can undergo double ethylation (Scheme 13). Despite the simple structure of these compounds, several of them had never been reported in the past, a fact that could indicate the usefulness of this catalytic method.[15]

Lastly, it may be worthwhile to mention the generation of radical anions in hydrocarbon media and their solubilization by lithium alkoxides. For example, sodium stilbene radical anion was generated in 2 M lithium 2-ethoxyethoxide in toluene (Eqn [8]). It should be stressed that the alkoxide, besides its solubilizing effect, also appears to facilitate the electron transfer from the metal to the reducible substrate.[16]

$$\text{Ph-CH} = \text{CH-Ph} + \text{Na} \xrightarrow[\text{toluene}]{2\,\text{M LiOCH}_2\text{CH}_2\text{OEt}} \underset{\text{soluble}}{(\text{Ph-CH} = \text{CH-Ph})^{-\cdot}\text{Na}^{+}} \qquad [8]$$

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