Co-Condensation Reactions of Substituted Aromatic Compounds with Lithium Atoms at 77 K

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Lithium atoms were co-condensed with +I-substituted benzene derivatives like trimethyl(phenyl)silane and *tert*-butylbenzene in the presence of THF at 77 K, which resulted in C–H bond activation, to produce the aryllithium compound as well as the coupling of the substituted phenyl radicals. Other +I-substituted benzene derivatives like xylene and mesitylene failed to react with lithium atoms in the presence of THF. Oxygen and nitrogen donor substituted benzene derivatives (anisole, *N*,*N*-dimethylaniline, and *N*,*N*-dimethylbenzylamine) showed activation of the *ortho* C–H bond when co-condensed with lithium atoms in the presence of THF. However, when thioanisole was co-condensed with lithium atoms and THF, a C–S bond cleavage occurred instead. These results were interpreted with the aid of DFT calculations, which show π- and σ-complexes between the lithium clusters and benzene derivatives as reactive intermediates.
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Introduction

The activation of carbon−hydrogen bonds has been a major topic of research for the last 30 years.[1−3] Numerous methods have been developed to perform these reactions. Most of these have centred on the oxidative addition of the hydrocarbon moiety to a highly sub-coordinated metal complex as shown in Figure 1,[4,5] however, C−H bond activation is not limited to transition metal chemistry. Another commonly used method is σ-bond metathesis using extremely electrophilic lanthanide centres as outlined below.[6]

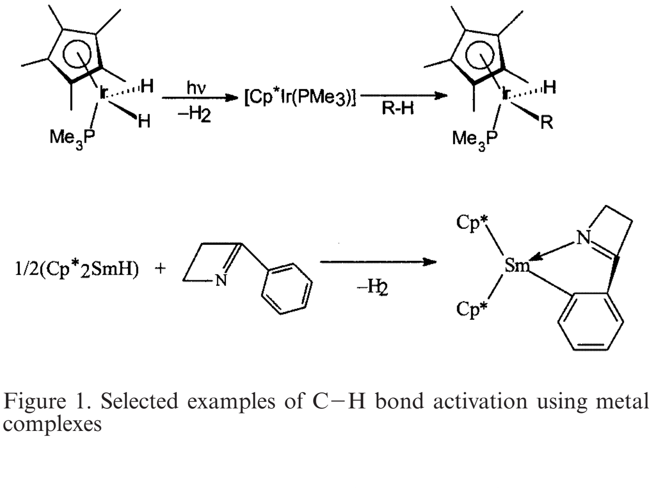
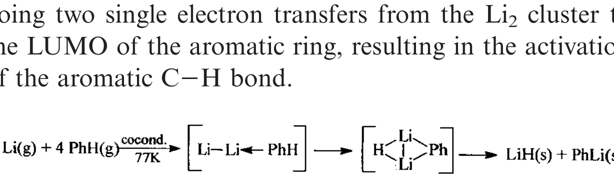


Figure 1. Selected examples of C−H bond activation using metal complexes

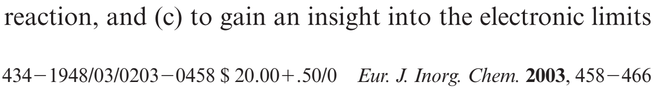
To date there has been very little preparative-scale work using metal atoms to perform oxidative addition reactions. Many metals are known to activate methane in a matrix under photochemical conditions,[3,7] but these types of reactions are of no use for preparative scale chemistry. For example, iron atoms when photolysed react with methane to form CH_3FeH at 10 K in an argon matrix.[8]

$$Fe + CH_4 \xrightarrow[\text{Ar, 10K}]{h\nu} HFeCH_3$$

Work performed by this group in the 1990s showed that lithium atoms could selectively activate the C−H bond of benzene and toluene in the presence of THF without the need for further photochemical excitation.[9−11] This resulted in the direct synthesis of aryllithium compounds on a synthetic scale.



One of the key intermediates in this reaction is an Li_2−benzene π-complex. This complex is capable of undergoing two single electron transfers from the Li_2 cluster to the LUMO of the aromatic ring, resulting in the activation of the aromatic C−H bond.



$$2\,Li(g) + 4\,PhH(g) \xrightarrow[77K]{cocond.} \left[Li{-}Li \leftarrow PhH\right] \longrightarrow \left[H \genfrac{}{}{0pt}{}{<Li>}{<Li>} Ph\right] \longrightarrow LiH(s) + PhLi(s)$$

The aim of this paper was to (a) expand the number of aromatic substrates for this C−H bond activation, (b) to study how different substituents alter the selectivity of the reaction, and (c) to gain an insight into the electronic limits

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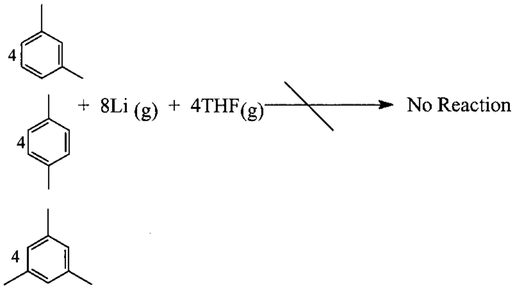
of this reaction. For this purpose the following +I-substituted [$C(CH_3)_3$, $SiMe_3$, *p*- and *m*-xylene] benzene derivatives were chosen, as well as a series of donor-substituted (OMe, NMe_2, CH_2NMe_2, SMe) benzene derivatives.

Results

Experimental Study

The +I-substituted benzene derivatives mesitylene and (*meta*- or *para*-)xylene failed to react with lithium atoms at 77 K in the presence of THF as shown in Scheme 1. However, when an $SiMe_3$ substituent was placed on the aromatic ring [as for trimethyl(phenyl)silane] a reaction with lithium atoms was observed at 77 K. The yield for this reaction was 32%, based on the amount of lithium vapourised. A broadened set of signals corresponding to the species 4,4′-bis(trimethylsilyl)biphenyl was observed in the ^{13}C NMR spectrum. However, the ^{7}Li NMR spectrum showed a broad peak at $\delta = -2.99$ ppm, which indicates the presence of an $Li^+(THF)_4$ solvent-separated ion-pair species. These NMR spectroscopic data in conjunction with the dark red/black colour of the solution indicates that the broadened ^{13}C NMR signals are actually of the 4,4′-bis(trimethylsilyl)biphenyl radical anion. It is formed by the reduction of 4,4′-bis(trimethylsilyl)biphenyl by excess lithium metal, as shown in Scheme 2. When the co-condensation product was redissolved in THF and treated with dimethyl disulfide a full characterisation was achieved (Scheme 2). This showed that the major product is 4,4′-bis(trimethylsilyl)biphenyl (80%) and the minor product trimethyl[4-(methylsulfanyl)phenyl]silane (20%), identified by NMR spectroscopy and GC MS.[12,13]



Scheme 1. Failed reaction of lithium atoms with +I-substituted benzene derivatives

A similar reaction series is seen when *tert*-butylbenzene was co-condensed with lithium atoms and THF at 77 K as outlined in Scheme 2. The yield for this reaction was lower (1% based on the amount of lithium metal vapourised) than the trimethyl(phenyl)silane co-condensation. When the co-condensation product was treated in situ with Me_2S_2, NMR spectroscopic and GC-MS data identified the major product (70%) as 4,4′-di-*tert*-butylbiphenyl[14] and a minor product (30%) as 1-*tert*-butyl-4-(methylsulfanyl)benzene.[15]

When a donor-substituted aromatic compound was used the observed direction of lithiation changed from *para* to *ortho*. Co-condensation of anisole with lithium atoms and THF at 77 K, led to the observed lithiated compound 2-methoxyphenyllithium, shown by NMR spectroscopy (as shown in Scheme 3). The *ipso*-carbon signal at $\delta = 169.6$ ppm and a singlet at $\delta = 1.56$ ppm in the ^{7}Li NMR spectrum, as well as the integration in the ^{1}H NMR spectrum clearly indicate a tetrameric structure in C_6D_6.[16] The yield of this reaction increased to 30% compared to 12% when toluene was used.[9,10] As in previous co-condensations, a further confirmation of the regiochemistry was gained by the reaction of 2-methoxyphenyllithium with dimethyl disulfide. The observed product of this reaction was 1-methoxy-2-(methylsulfanyl)benzene in a quantitative yield, which was identified from NMR spectroscopic data and GC MS data[17,18] as shown in Scheme 3.

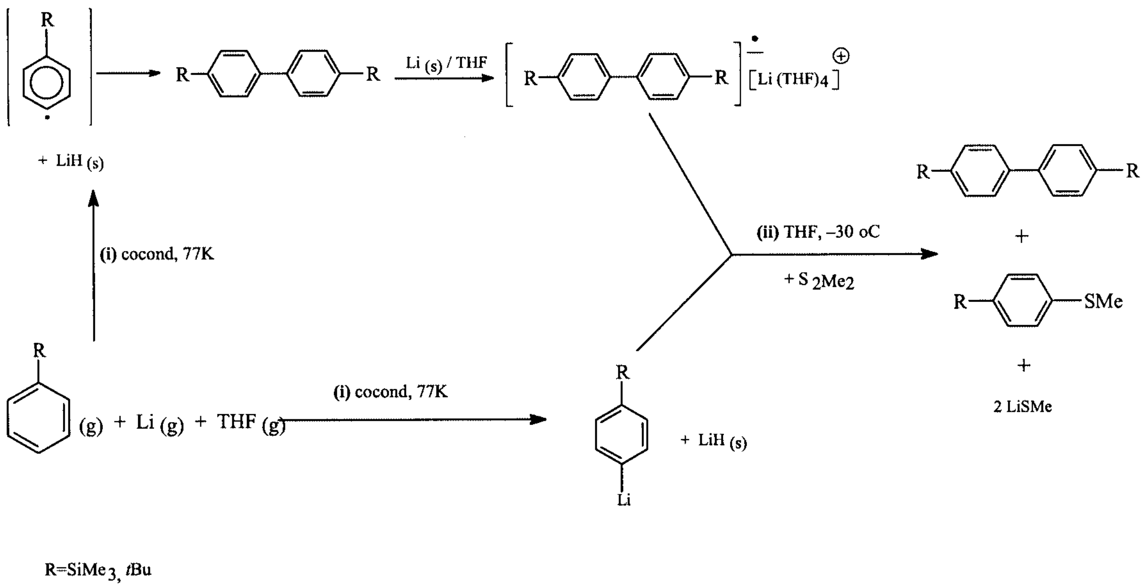
When the sulfur donor thioanisole was used, a different reaction occurred, resulting in a cleavage of the C−S bond instead of C−H bond activation. This time the major product was diphenyl disulfide as shown in Scheme 4. When the co-condensation product was washed with pentane, it yielded a white air-sensitive product. This was shown to be MeLi by treating it with benzaldehyde to produce 1-phenylethanol upon an aqueous work up (as outlined in Scheme 4). When the pentane solution was treated with chlorotrimethylsilane (Scheme 4), the lithiated product identified by NMR spectroscopy and GC MS measurements was shown to be trimethyl(phenylsulfanyl)silane.[19]

Changing the donor substituent to a nitrogen donor like *N*,*N*-dimethylaniline resulted in the formation of 2-(dimethylamino)phenyllithium as identified by NMR spectroscopy in a low yield of 1% as shown in Scheme 3. In the ^{13}C NMR spectrum in C_6D_6 an *ipso* carbon signal $\delta = 171.6$ ppm, in conjunction with the integration of the ^{1}H NMR peaks indicates a tetrameric structure with four coordinated THF molecules resulting in a species of the composition $Ar_4Li_4{\cdot}THF_4$. It was not possible to determine if the dimethylaniline group was intramolecularly coordinated to Li from the NMR spectroscopic data. The reaction of 2-(dimethylamino)phenyllithium with S_2Me_2 resulted in the formation of dimethyl[(2-methylsulfanyl)phenyl]amine, thus confirming that the regiochemistry is *ortho* to the NMe_2.[20,21]

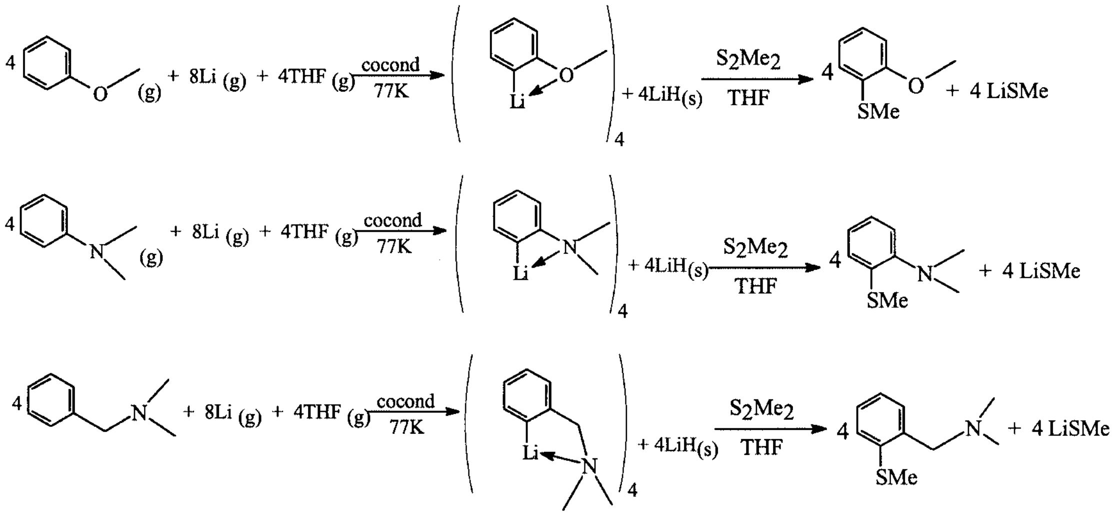
When *N*,*N*-benzylamine was co-condensed with lithium atoms and THF, it yielded a pyrophoric beige solid in 36% yield that was only sparingly soluble in aromatic solvents. NMR spectroscopy in C_6D_6 confirmed the *ortho* activation and the formation of 2-[(dimethylamino)methyl]phenyllithium.[21,22] Examination of the NMR spectroscopic data indicates a tetrameric structure of the composition Ar_4Li_4 in benzene, with no coordinated THF being present as outlined in Scheme 3. The reaction of 2-[(dimethylamino)methyl]phenyllithium with Me_2S_2 confirmed the regiochemistry as being *ortho* to the benzyl group. The isolated product was identified as dimethyl[2-(methylsulfanyl)benzyl]amine by GC-MS and NMR spectroscopic techniques as shown in Scheme 3.[23]

Theoretical Study

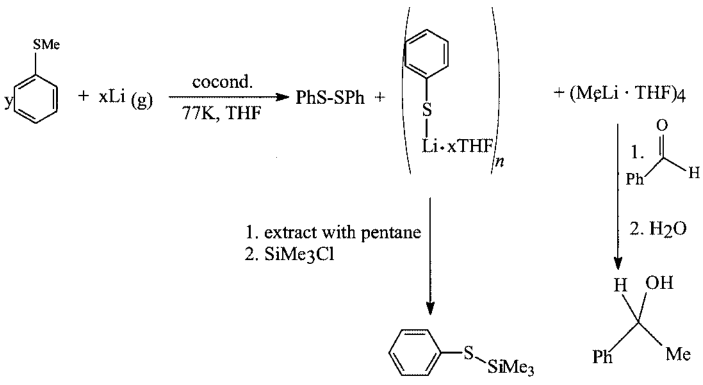
The previously reported mechanism for the reaction of lithium atoms with benzene was performed at the



Scheme 2. The reductive coupling of +I-substituted benzene derivatives by lithium atoms



Scheme 3. Reaction of donor-substituted aromatic compounds with lithium atoms in THF



Scheme 4. Co-condensation of lithium atoms with thioanisole in the presence of THF

Hartree−Fock level of theory.[9,10] We report here the recalculation of the key intermediates for this benzene co-condensation, using a DFT method, B3LYP, and the expansion of this mechanism to include other +I- and donor-substituted benzene derivatives. In the benzene system a similar trend is seen using the B3LYP/6-31G** method as was reported earlier.[9,10] The first step of the reaction, the formation of a π-complex (**1a**), resulted in a calculated reaction enthalpy of −8.2 kcal/mol. This is larger than the previously reported value (HF/6-31G**) of −5.9 kcal/mol.[10] The next step is a double electron transfer via the aromatic system, resulting in the insertion of the Li_2 cluster into the C−H bond (the formation of **1b**). This was calculated to be −15.8 kcal/mol. This is also larger than the previously calculated value of −8.0 kcal/mol.[10] These reaction enthalpies are outlined in Figure 2.

The calculated reaction enthalpies shown in Figure 2 for the intermediate species, from the reaction involving toluene with lithium atoms, agreed with the proposed mechanism reported earlier.[9,10] From these calculations it can be seen that the Li_2 cluster forms a π-complex (**1c**) with toluene resulting in a reaction enthalpy of −9.1 kcal/mol. This is larger than in the benzene experiment (−8.2 kcal/mol). The intermediate **1c** then undergoes a double electron transfer via the aromatic system in an exothermic step of −15.0 kcal/mol. However, this enthalpy is slightly lower in energy than that of the benzene system (−15.8 kcal/mol). In the resultant species **1d** the Li_2 cluster has inserted into the *para* C−H bond. When the CH_3 group of toluene was replaced by a *tert*-butyl group as in *tert*-butylbenzene, an identical series of reaction enthalpies was found.

When the aromatic compound is trimethyl(phenyl)silane, the energies for each step in the mechanism change slightly as described in Figure 2. For the first step, the coordination of the lithium cluster to the aromatic system to form the π-complex **1e**, the reaction enthalpy is −8.6 kcal/mol. This value is larger than it is in the benzene system but lower than it is for toluene or *tert*-butylbenzene. The second step, which is the formation of the insertion product **1f**, has a reaction enthalpy of −15.4 kcal/mol. This is larger than the reaction enthalpies for the benzene and toluene/*tert*-butylbenzene systems.

When *p*-xylene is used, the energies for each step in the mechanism also differ slightly compared to the previous cases. For the first step, the formation of **1i**, the reaction enthalpy (−9.8 kcal/mol) is the most exothermic of the +I-substituted benzene derivatives. The second step, the formation of **1j** is the lowest of the reaction enthalpies (−14.6 kcal/mol) of all the +I-substituted benzene derivatives.

When the substituent on the aromatic ring is a Lewis base (e.g. O, N, P, S donors) the reaction pathway is more complicated. Now there are two possibilities for coordination of the lithium cluster as shown in Figure 3. The first possibility is the formation of a π-complex (**2a**), as in the previous compounds (**1a−1j**). The second possibility is coordination of the Li_2 cluster to the donor moiety in an η^1-fashion (**2b**). When an oxygen donor is involved, e.g. anisole, the preferred pathway is via the η^1 complex. The energy difference between complex **2a** and **2b** is −2.6 kcal/mol, showing that the η^1 complex **2b** is more stable than the π-complex. As in the previous mechanism the next step is a double single-electron transfer step from the Li_2 cluster to the LUMO of the aromatic ring. However, for the anisole co-condensation this step has a larger reaction enthalpy of −24.7 kcal/mol, compared with the +I-substituted derivatives shown in Figure 2. In the η^1 species **2b** there is an agostic interaction between the *ortho* C−H bond and the coordinated Li_2 cluster, with an Li−H distance of 2.586 Å as detailed in Table 1. This explains the experimentally observed *ortho* activation of the C−H bond.

If the donor atom is changed from an oxygen to a nitrogen donor, for example *N*,*N*-dimethylbenzylamine as outlined in Figure 4, the formation energy for **3b**, the η^1-coordinated Li_2 species, is −15.5 kcal/mol, while for the π-com-

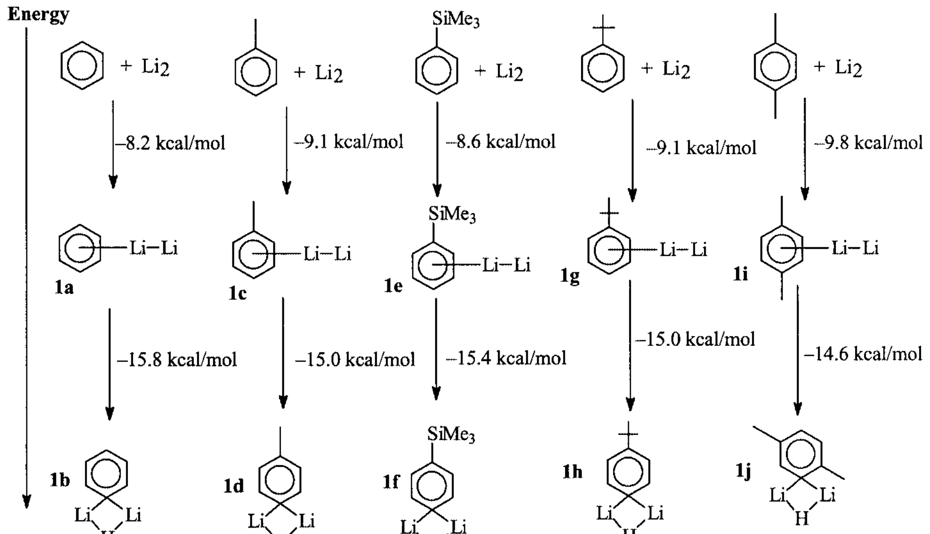


Figure 2. Calculated reaction enthalpies for +I-substituted benzene derivatives and Li_2

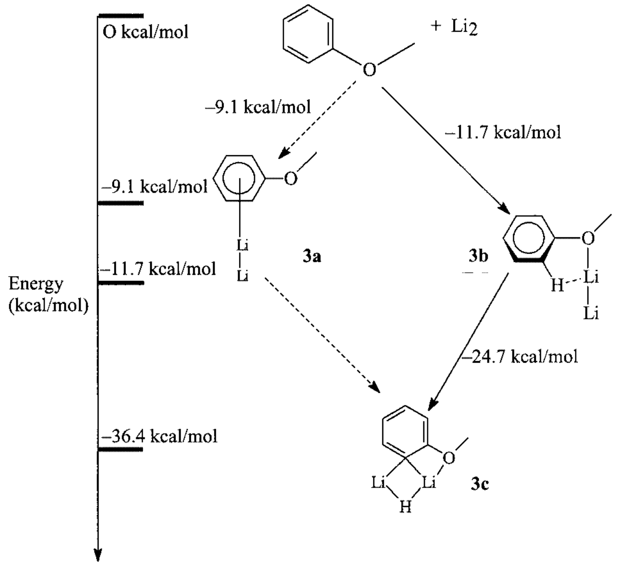


Figure 3. Calculated reaction mechanism for the co-condensation of lithium atoms with anisole

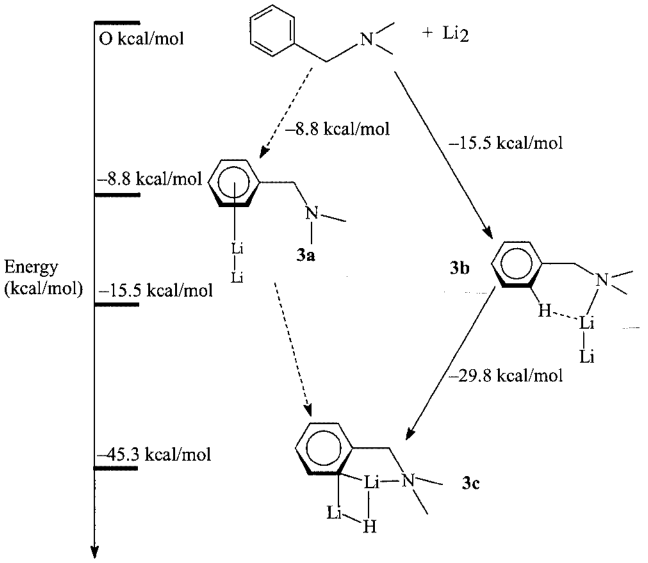


Figure 4. Calculated reaction mechanism for the co-condensation of lithium atoms with benzylamine

Table 1. Agostic H_{ortho}−Li interaction in η^1 complexes

	Li_a−H_{ortho} [Å]
Anisole	2.586
N,*N*-Dimethylaniline	2.777
N,*N*-Dimethylbenzylamine	2.669
Thioanisole	3.001
Dimethylphenylphosphane	3.109

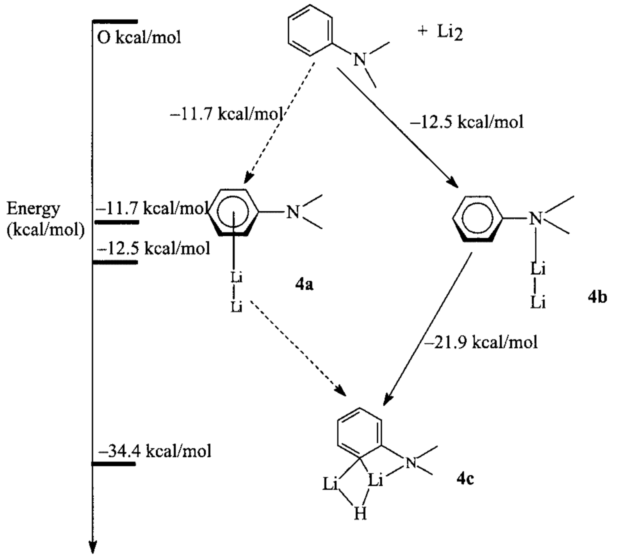


Figure 5. Calculated reaction mechanism for the co-condensation of lithium atoms with *N*,*N*-dimethylaniline

plex **3a** the reaction enthalpy (−8.8 kcal/mol) is less exothermic. It is clear from this difference of −6.7 kcal/mol that the preferred pathway is by coordination to the donor moiety. As in the anisole case the energy for the insertion of the Li_2 cluster into the C−H bond (**3c**) is higher (at −23.1 kcal/mol) than via the π-complex types listed in Figure 2. In the calculated structure **3b** there is also an agostic-type interaction between the *ortho* C−H bond and the coordinated Li_2 cluster as detailed in Table 1. However, in this case the Li−H distance is longer (2.669 Å) than it is in the anisole species **2b** (2.586 Å).

A different preference is seen when the N-donor is *N*,*N*-dimethylaniline. In this reaction there is no clear preference between the η^1-coordination mode (**4b**) and the formation of a π-complex (**4a**) as shown in Figure 5. The difference in energy between these two species is small (−0.8 kcal/mol) and is in favour of an η^1 complex (**4b**). As in the previous two systems, there is an interaction between the *ortho* C−H bond and the coordinated Li_2 cluster **4b** with a long Li−H interaction of 2.777 Å compared to 2.586 Å in the anisole example **2b** (outlined in Table 1). The energy for the insertion into the *ortho* C−H bond of the aromatic ring is −21.9 kcal/mol, which is lower than it is in the other donor species (anisole and *N*,*N*-dimethylbenzylamine).

For soft donor atoms like phosphorus and sulfur, as defined by the Pearson concept, we see a different trend, outlined in Figure 6. When a similar theoretical study is performed on a phosphorus donor like dimethylphenylphosphane, the η^1-coordination mode (**5b**) is preferred over a π-complex (**5a**) with a calculated energy difference of −1.6 kcal/mol (shown in Figure 6). Unlike previous examples outlined above, there is no interaction between the *ortho* C−H bond and the coordinated Li_2 cluster as shown in Table 1. This can be seen from an extremely long Li−H distance of 3.109 Å. The reaction enthalpy for the insertion of the Li_2 into the C−H bond is −20.6 kcal/mol. This is smaller (compared to −21.9 kcal/mol and −24.7 kcal/mol for the anisole system) than the other reaction enthalpies for this step.

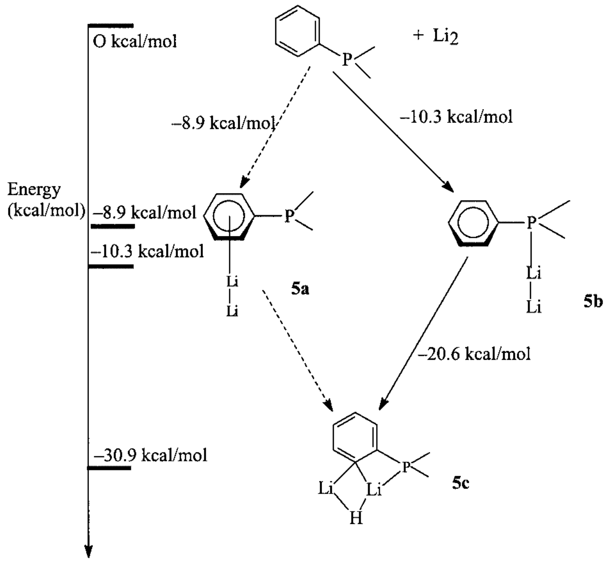


Figure 6. Calculated reaction mechanism for the co-condensation of lithium atoms with dimethylphenylphosphane

However, when the same calculation is performed on a sulfur donor like thioanisole, the situation changes. This time there is no favoured pathway, with the π-complex **6a** being just 0.1 kcal/mol lower in energy than the η^1-species **6b** as shown in Figure 7. Again there is no interaction between the *ortho* C−H bond and the η^1-coordinated Li_2 cluster. In this species the $Li-H_{agostic}$ distance is longer (3.001 Å) than it is in the corresponding η^1 complexes with oxygen and nitrogen donor substituents as outlined in Table 1. However the Li−S distance of 2.452 Å is significantly larger than in the anisole species (Li−O distance of 1.948 Å). This is a clear indication of weaker bonding due to the unfavourable hard/soft donor interaction. When a single electron is placed onto the free thioanisole there is a substantial elongation of the S−Me bond from 1.821 to 1.993 Å and the S−Ph bond length decreases from 1.785 to 1.739 Å. It was possible to predict the experimental observed C−S bond activation from this calculation.

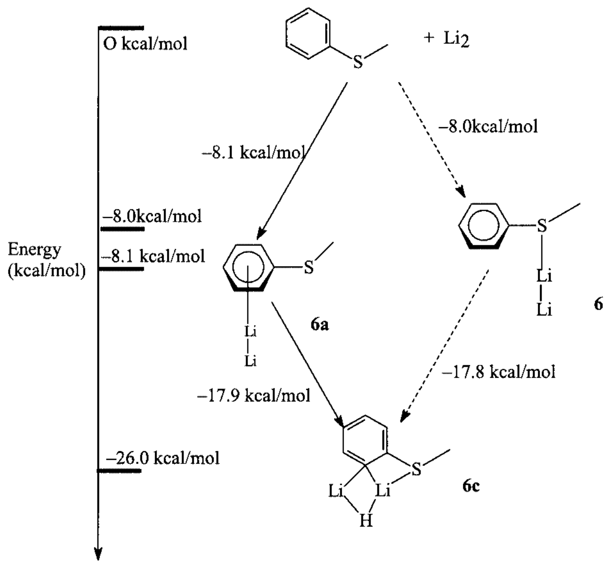
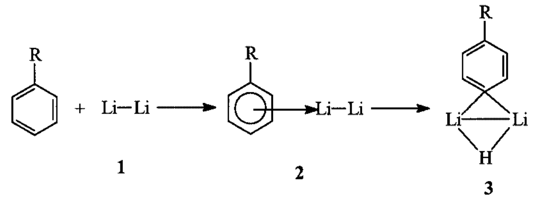


Figure 7. Calculated reaction mechanism for the co-condensation of lithium atoms with thioanisole

Discussion

Previous research in this area showed that toluene reacted with lithium atoms in the presence of THF under co-condensation conditions. The thermodynamic product benzyllithium was not formed; however, the isolated compound was identified as *p*-tolyllithium.[9,10] This interested us in the examination of the effect that other +I substituents have on the reaction. A delicate balance between +I enhancing complex formation ability and LUMO energy, allowing reductive cleavage of the aromatic C−H bond, is needed for successful C−H activation.

The electron-deficient Li_2 cluster **1** as shown in Scheme 5, will accept electron density from the aromatic system to form an unusual main group element π-complex (**2**). When the substituent on the aromatic ring donates electron density to the π-system (the +I effect), the interaction with the lithium cluster will strengthen. This can be observed by the decrease in the calculated Li−C and Li−Li bond lengths shown in Tables 2 and 3. For example in the case of toluene the Li−C distance decreases to 2.610 Å, while for mesitylene the Li−C distance is 2.591 Å compared with the longer Li−C of 2.626 Å for the benzene system. This means that there will be a stronger interaction between the aromatic rings of the +I-substituted benzene derivatives [for example xylene, *tert*-butylbenzene, mesitylene, and trimethyl(phenyl)silane] than benzene. However, the next mechanistic step is crucial. This involves the double single-elec-



Scheme 5. Key mechanistic steps in aromatic C−H bond activation using lithium atoms

Table 2. Selected Li−C bond lengths for the +I-substituted benzene derivatives

	Li−C distance [Å]
Benzene	2.625
Toluene	2.591
p-Xylene	2.570
Mesitylene	2.547
tert-Butylbenzene	2.595
Trimethyl(phenyl)silane	2.601

Table 3. Selected Li−Li bond lengths for all calculated intermediates

Li−Li distance [Å] in:	π complex	D*-η^1 complex	C−H activated species	Free Li_2
Benzene	2.769	N/A	N/A	2.723 Å
Toluene	2.776	N/A	2.281	
Trimethyl(phenyl)silane	2.781	N/A	2.283	
Anisole	2.772	2.746	2.299	
Thioanisole	2.774	2.762	2.299	
N,*N*-Dimethylaniline	2.795	2.767	2.295	
N,*N*-Dimethylbenzylamine	2.781	2.785	2.296	
Dimethylphenylphosphane	2.782	2.769	2.293	

tron transfer from the π-bonded Li_2 cluster **3** to the LUMO of the aromatic ring. The outcome of the reaction depends on how the substituents affect the LUMO, and not its +I ability. If the LUMO energy is increased in relation to toluene and benzene, as it is for mesitylene and xylene (as outlined in Table 4), it is impossible to place electron density into it, thereby preventing the reaction from occurring. This can be seen from the lack of reaction between lithium atoms and xylene or mesitylene (as described in Scheme 1). If the substituent lowers the LUMO energy, as for trimethyl(phenyl)silane and *tert*-butylbenzene (as shown in Table 4) the reaction will proceed quite readily. If the LUMO energy of the aromatic ring is lowered too much, a single electron reduction of the aromatic compound to its stable radical anion will occur instead of C−H bond activation.

Table 4. Calculated LUMO energies of selected reactants using B3LYP/6-31G**

	LUMO [eV]
N,*N*-Dimethylaniline	0.387
Mesitylene	0.261
m-Xylene	0.197
o-Xylene	0.194
p-Xylene	0.164
Toluene	0.123
tert-Butylbenzene	0.102
Anisole	0.085
Benzene	0.072
N,*N*-Dimethylbenzylamine	0.057
Thioanisole	−0.041
Trimethyl(phenyl)silane	−0.180
4,4′-Di-*tert*-butylbiphenyl	−0.579
4,4′-Bis(trimethylsilanyl)biphenyl	−0.898

For the reaction of trimethyl(phenyl)silane with lithium atoms in the presence of THF, a reaction sequence different from the toluene co-condensation was observed. This is governed by the ability of the $SiMe_3$ group to stabilise an aromatic radical. The major product identified was 4,4′-bis(trimethylsilanyl)biphenyl. This is the coupled product of the free phenyltrimethylsilyl radical. This indicates that a reduction of trimethyl(phenyl)silane occurs at 77 K, which then couples to form the substituted biphenyl derivative as outlined in Scheme 2. In this case the $SiMe_3$ substituent stabilises the radical long enough to allow it to form the coupled product 4,4′-bis(trimethylsilanyl)biphenyl. On warming in the MVS reactor, excess solid lithium reduces 4,4′-bis(trimethylsilanyl)biphenyl to its radical anion, in an analogous reaction to the reduction in solution of 4,4′-di-*tert*-butylbiphenyl by lithium metal.[14] From the calculated LUMO energies of these two biphenyl species (Table 4) a comparison can be made in relation to the ease of reduction of 4,4′-bis(trimethylsilanyl)biphenyl. The calculated LUMO energies for 4,4′-di-*tert*-butylbiphenyl is −0.579 eV, while 4,4′-bis(trimethylsilanyl)biphenyl has a lower LUMO energy of −0.898 eV. This shows that the reduction of 4,4′-bis(trimethylsilanyl)biphenyl by lithium metal can readily occur in THF solution.

However, a secondary C−H activated product was also identified. This was the *para*-lithiated aromatic 4-(trimethylsilyl)phenyllithium. It could not be identified in solution but treating this species with S_2Me_2 to form trimethyl[4-(methylsulfanyl)phenyl]silane, allowed a further full characterisation of the substitution pattern on the ring as outlined in Scheme 2.

The co-condensation of *tert*-butylbenzene and lithium atoms in the presence of THF was similar to the reaction involving trimethyl(phenyl)silane (as detailed in Scheme 2). The major product was found to be 4,4′-di-*tert*-butylbiphenyl. This is formed from the coupling of the *tert*-butylphenyl radical. On warming in the MVS machine it is believed that 4,4′-di-*tert*-butylbiphenyl is reduced by solid lithium metal to its radical anion. Because of this no direct NMR spectroscopy was attempted, instead the co-condensation product was treated with S_2Me_2. A minor product was observed to be *tert*-butyl-4-(methylsulfanyl)benzene, this corresponds to a secondary reaction occurring at 77 K, the activation of the *para* C−H bond of *tert*-butylbenzene.

When a Lewis base function is used, the +I inductive effect versus LUMO effect is no longer important, because the favoured donation mode to the Li_2 cluster is now via the η^1-coordination mode through the donor moiety as shown by a series of DFT calculations described in Figures 3−7. This mode of bonding is energetically favoured over the formation of a π-complex with the Li_2 cluster. Due to this change in the coordination mode, a change in regiochemistry occurs, resulting in *ortho* C−H bond activation.

When an oxygen donor was used as in the case of anisole, the NMR spectroscopic data, which is in good agreement with the literature data,[16] showed an *ortho*-lithiated product. NMR spectroscopic data indicate a tetrameric structure of the composition Ar_4Li_4. In contrast to the benzene and toluene experiments reported previously,[9,10] the yield was increased to 30% from 12%, which is extremely high for an MVS experiment. As in the trimethyl(phenyl)silane co-condensation, treating it with dimethyl disulfide as outlined in Scheme 3, allowed a further characterisation of the lithiated product. This reaction confirms the *ortho* lithiation by the formation of 1-methoxy-2-(methylsulfanyl)benzene, which was identified from NMR spectroscopic data and GC MS data.[17,18]

When the oxygen donor substituent of anisole is changed to the softer sulfur atom as in thioanisole, a similar result was expected. However, no C−H bond activation was observed, instead NMR spectroscopic data indicated a cleavage of the S−Me bond. This resulted in the formation of the $Ph{-}S^{\cdot}$ radical, which dimerises to form diphenyl disulfide. Secondary products were shown to be $(MeLi{\cdot}THF)_4$ and PhSLi·THF by derivatisation reactions and this is described in Scheme 4. This result is not unexpected since the S−Me bond strength of 69.4 kcal/mol is weaker than that of the C−H bond of 100 kcal/mol. The selectivity for the S−C sp^3 bond is due to its lower bond strength compared with the S−Ph sp^2 bond of 86.5 kcal/mol.[24]

When the donor substituent was a nitrogen donor as in *N*,*N*-dimethylaniline, the observed product was 2-(dimethylamino)phenyllithium (as outlined in Scheme 3). This reaction type is similar to the anisole case, but with a much lower yield of 1%. This is possibly due to the high LUMO energy (0.387 eV) of the *N*,*N*-dimethylaniline, as described in Table 4. This reaction is surprising since some +I-substituted aromatic compounds like mesitylene and xylenes, which have lower LUMO energies, do not react with lithium atoms. Presumably, the change in coordination mode to η^1 facilitates this reaction.

In an ether solution *N*,*N*-dimethylbenzylamine is known to react with BuLi to form 2-[(dimethylamino)methyl]phenyllithium. The factors controlling the selectivity are not well investigated.[20,21] It is reported as being tetrameric (Ar_4Li_4) in the solid state with the NMe_2 group intramoleculary coordinated to Li, while in THF solution it is dimeric with the composition $Ar_2Li_2{\cdot}4THF$. When benzylamine is co-condensed with lithium atoms and THF as outlined in Scheme 3, a pyrophoric beige solid is obtained in a larger yield (36%) than in the *N*,*N*-dimethylaniline experiment (1%). ^1H and ^{13}C NMR spectroscopic data show the presence of 2-[(dimethylamino)methyl]phenyllithium with no coordinated THF. This composition is in agreement with the published solid-state structure.[21] No activation was detected in the benzyl position. Confirmation of the regiochemistry was obtained as in previous co-condensations by the reaction with S_2Me_2.

Conclusion

Lithium atoms are able to activate +I- and donor-substituted benzene derivatives. In the case of +I-aromatic compounds like trimethyl(phenyl)silane and *tert*-butylbenzene, two products were observed, the major product was the coupled biphenyl and the minor product the C−H-activated *para*-lithiated aromatic compound. However, other +I benzene derivatives with higher LUMO energies than toluene, like xylenes and mesitylene, failed to react. It appears that this reaction type has a narrow range based on the LUMO energy of the aromatic compound. When donor substituted benzene derivatives like anisole, *N*,*N*-dimethylaniline, and *N*,*N*-benzylamine were co-condensed with lithium atoms in the presence of THF, *ortho* C−H bond activation was exclusively observed. This results from a mechanistic change from a π-bonded Li_2 cluster via the phenyl ring to a η^1-bonded Li_2 via the donor atom. For this reaction type, the LUMO energy is not as important as in the series of reactions using +I-substituted benzene derivatives. For the co-condensation of thioanisole with lithium atoms in THF, an activation of the C−S bond as well as a reductive coupling of thioanisole was observed.

Experimental Section

General: All experimental procedures were performed using standard Schlenk techniques under dry argon. THF, toluene, *m*-, *p*-xylene, anisole, and *tert*-butylbenzene were dried and distilled from sodium benzophenone ketyl under argon. Trimethyl(phenyl)silane, thioanisole, *N*,*N*-dimethylaniline, *N*,*N*-dimethylbenzylamine were dried and distilled from calcium dihydride under argon. All solvents were then degassed by three freeze-pump-thaw cycles. Celite was stored overnight in an oven at 120 °C and was dried under vacuum for 3 h before use. For each filtration layers of approximately 6 cm of Celite were used. ^1H and ^{13}C NMR spectra were obtained using either a Varian 300 MHz or a Varian 500 MHz NMR machine. All chemical shifts are reported in ppm and are referenced to TMS. The ^7Li NMR spectra in this study were obtained with a Jeol 300 MHz machine. The chemical shifts for the ^7Li NMR spectra are reported in ppm and are referenced to an internal standard of LiBr in D_2O. All GC MS samples were run as dichloromethane solutions using a Finnigan Trace GC MS, with an RTX-5MS 15-m column.

Typical Co-condensation Experiment: Lithium metal (0.53 g, 0.076 mol) was vapourised from an aluminium crucible protected by a stainless-steel inlet at around 800 °C over 90 min and co-condensed with a mixture of the aromatic compound (20 mL) and THF (80 mL, 1.12 mol). After removal of the solvent mixture, the residue was dissolved in dry toluene and the solution was filtered through Celite from the solid lithium hydride by-product and unreacted lithium metal. After removal of the toluene in vacuo a dark red solid was isolated and washed with dry pentane (20 mL). The lithiated aromatic compound was identified by ^1H and ^{13}C NMR spectroscopy.

Typical Derivatisation of the Lithiated Aromatic Compound with Me_2S_2: Dimethyl disulfide (0.3 mol/L) was added dropwise with vigorous stirring to a solution of of the lithiated aromatic compound (0.25 g) in THF (20 mL) at room temperature. The reaction was thought to be complete when a colour change from red to yellow occurred. Water (10 mL) was added to this solution and the organic phase separated. The aqueous phase was washed three times with dichloromethane (10 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent was then removed under reduced pressure, affording the derivatised compound as a brown oil. GC MS and ^1H and ^{13}C NMR spectroscopy were used to identify the product.

Theoretical Methods Used in this Study: With a view to determining the structures and reaction enthalpies of intermediates in the reaction mechanism, the application of theoretical methods has proven advantageous. For this purpose the program package used was GAUSSIAN 98[25] implemented on a DEC Alpha work station (500 MHz CPU/256 MB RAM) or an Origin 200 eight-processor cluster (SGI 180 MHz CPU/2 GB RAM). Ab-initio calculations were performed at the DFT level of theory (B3LYP) using the 6-31G** basis set for C, H, O, N, S, P, and Li. Harmonic vibrational frequencies, calculated at the same level, characterised stationary points and gave the zero-point energy. The difference in the sum of the electronic and the zero-point energies were interpreted as reaction enthalpies at 0 K. LUMO energies for each aromatic compound were obtained from geometry-optimised structures using B3LYP/6-31G**.

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