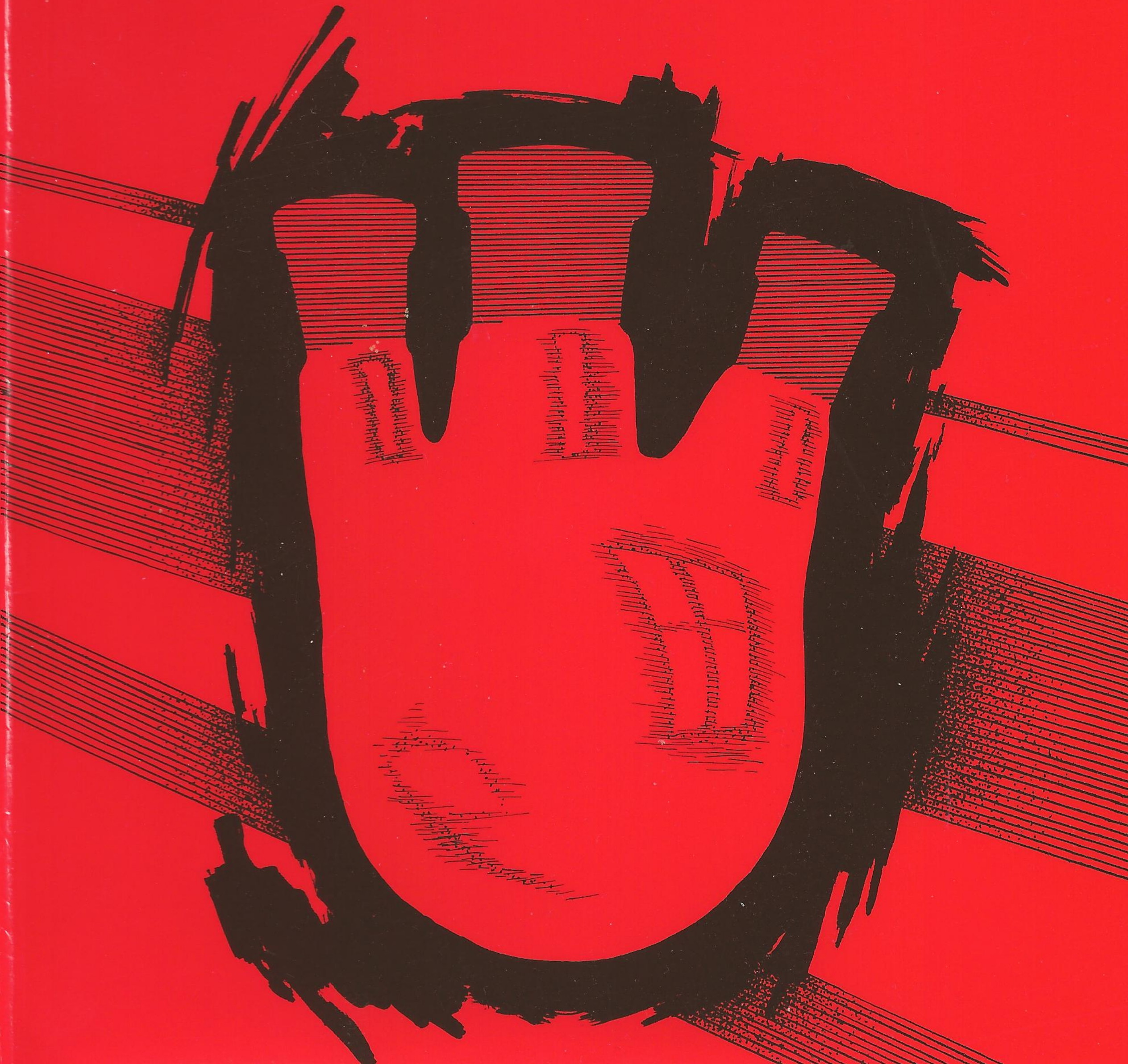
New Applications of Super Bases in Organic Synthesis

Marco Fossatelli



New Applications of Super Bases in Organic Synthesis - Marco Fossatelli

New Applications of Super Bases in Organic Synthesis

Nieuwe Toepassingen van Superbasen in de Organische Synthese
(met een samenvatting in het Nederlands)

Proefschrift ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. J. A. van Ginkel
ingevolge het besluit van het College van Decanen
in het openbaar te verdedigen
op 18 mei 1994 des middags te 2.30 uur.

door

Marco Fossatelli

geboren 23 september 1966, te Zeist.

Promotor: Prof. dr. L. Brandsma,

verbonden aan de faculteit der scheikunde van de Universiteit Utrecht.

ISBN 90-393-0532-3
Druk: Ponsen & Looijen BV, Wageningen.
Omslagtekening: Bert Swevels, Veldhoven.

Het onderzoek beschreven in dit proefschrift werd mogelijk gemaakt met financiële steun van de Stichting Scheikundig Onderzoek Nederland (S.O.N.) en de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (N.W.O.).

Aus den zusammengetragenen Ergebnissen und den angestellten Überlegungen zeichnet sich der Aspekt ab, daß auch in der präparativen Chemie grundsätzlich Neues noch zu finden ist. Um die im Verborgenen ruhenden Schätze zu heben, muß man experimentieren und dabei die Hemmungen, die uns die allmächtig gewordene theoretische Chemie auferlegt, gelegentlich über Bord werfen. Selbstverständlich soll der Chemiker theoretische Zusammenhänge beherrschen, da der Ökonomisch Denkende mehr und weiter sieht. Aber er darf nicht umgekehrt einem Dogmatismus verfallen, der ihn dazu verführt, in vorgefaßter Meinung der Versuch zu scheuen. Denn die den Fortschritt bedingenden Impulse gehen im Entscheidenden vom Experiment aus, an dessen Resultate die sich wandelnde Theorie anzupassen hat.

Georg Wittig   Angewandte Chemie **69** (1957) 245

'What do we know,' he had said, 'of the world and the universe about us? Our means of receiving impressions are absurdly few, and our notions of surrounding objects infinitely narrow. We see things only as we are constructed to see them, and can gain no idea of their absolute nature. With five feeble senses we pretend to comprehend the boundlessly complex cosmos, yet other beings with a wider, stronger, or different range of senses might not only see very differently the things we see, but might see and study whole worlds of matter, energy, and life which lie close at hand yet can never be detected with the senses we have. I have always believed that such strange, inaccessible worlds exist at our very elbows, *and now I believe I have found a way to break down the barriers.*'

H. P. Lovecraft   From beyond (1920)

Contents

Preface 1

Chapter 1:
The Dimetallation of Compounds Containing a Conjugated Enyne system 5

Chapter 2:
New Syntheses of Functionalized Conjugated Diynes and Enynes Containing a Terminal Acetylenic Group 21

Chapter 3:
The Generation of *ortho*-Potassiofluorobenzene and Its Functionalization Reactions of Other Halobenzenes with Super Base Mixtures 39

Chapter 4:
The Stability of *ortho*-Metallated Halobenzenes 45

Appendix: The Crystal Structure of 3-Bromo-2-lithio-thiophene·TMEDA 63

Chapter 5:
An Efficient Synthesis of Triphenylene 71

Chapter 6:
The Influence of the Alkali Metal on the Stability of Carbenoïds A Preliminary Investigation 75

Chapter 7:
On the Halogen-lithium Exchange Reaction of Some Polybromothiophenes and -benzenes and Corresponding Iodium Compounds 87

Chapter 8:
Dimetallation of Benzene 105

Chapter 9:
Influencing the Reactivity of Super Base Mixtures by Addition of an Excess of a *tertiary*-Alkoxide 111

Summary 131
Samenvatting 133

Preface

Before 1960 organoalkalimetal chemistry was mainly the monopoly of a few pioneers such as Gilman and Wittig, who mastered the relatively difficult preparation of important reagents like butyllithium. Although the preparation of the corresponding alkylsodium and -potassium reagents was already known at that time, their application in organic synthesis was limited. One of the most important reasons for this was the rather troublesome preparation from dispersed metals and alkylchlorides in inert solvents and the requirement of special apparatus (high speed stirrers for example). Efficient working with alkylsodium and -potassium, prepared in this way, was not possible, because it was difficult to take from a stock amount of a suspension just the quantity needed for a particular synthesis. For each synthesis the preparation of the reagent has to be repeated on the required scale.[1]

After 1960 the chemistry of organoalkali compounds received three important impulses, *viz.* i) the commercial availability of *n*-butyllithium as a stable solution in hexane, ii) the commercial availability of tetrahydrofuran, a solvent which is more polar than the previously used diethyl ether and in which deprotonation and halogen-lithium exchange reactions proceed much more smoothly[2], iii) the finding of Lochmann and Schlossser, almost at the same time, that alkylsodium and -potassium compounds could be prepared in hexane simply by metal-metal exchange[3]:

$$^{n}\mathrm{BuLi} \quad + \quad \mathrm{KO}\,^{t}\mathrm{Bu} \quad \longrightarrow \quad {}^{n}\mathrm{BuK}\downarrow \quad + \quad \mathrm{LiO}\,^{t}\mathrm{Bu}$$

Scheme 1: Transmetallation between *n*-butyllithium (^{n}BuLi) and potassium *tert*-butoxide (KO^{t}Bu) in hexane yielding butylpotassium (and lithium *tert*-butoxide).

After the papers of Seebach *et al.* on the lithiation of S,S-acetals[4], $CH_2(SR)_2$, with ^{n}BuLi in a THF/hexane mixture the organolithium chemistry was dramatically accelerated. In the same period Schlosser and coworkers published a number of applications of the superbase system generated from *n*-butyllithium and potassium *tert*-butoxide.[5]

A serious draw-back for a broader use of the original superbase·solvent system in organic synthesis was the insolubility of the so generated alkylsodium and -potassium in alkanes. A consequence of the heterogenicity was that in general a large excess of the substrate was needed to guarantee complete conversion of the basic reagent. With relatively cheap substrates, such as benzene and toluene, this is no serious obstacle, but for the cases of more exclusive, and hence more expensive, substrates economic motives will give rise to reluctance with regard to application. The finding in our laboratory in 1976 that in the presence of tetrahydrofuran as a co-solvent the system ^{n}BuLi·KO^{t}Bu became homogeneous, opened the way to synthetically more interesting applications of this superbase as deprotonating reagent.[6] A large number of interesting and useful applications followed.[7] Somewhat later the scope was extended by the discovery of the system ^{n}BuLi·KO^{t}Bu·*N,N,N',N'*-tetramethylethylenediamine in hexane with which substrates with a very low kinetic acidity such as ethene and hydrogen, could be metallated at temperatures in the range between -20 and -30°C.[8]

It was further found in our laboratory that also the 'strenght' of bases other than *n*-butyllithium, could be increased by the addition of equivalent amounts of heavier metal alkoxide. Isoprene, for example was succesfully metallated with a 1:1 molar mixture of lithium di-*iso*-propylamide and potassium *tert*-butoxide.[9] In the absence of the latter auxiliary reagent metallation occured not at all. Some applications have been described in the thesis of P. A. A. Klusener.[10] The present dissertation describes several subjects which are a continuation of the investigations in this laboratory in the field of strongly basic reagents and polar organometallic chemistry.

In this thesis one can find how fluorobenzene can be metallated efficiently and subsequently functionalized (chapter 3) and how 1,3-diynes RC≡C-C≡CH and enynes R'CH=CH-C≡CH (R'= aryl and hetaryl) with high stereochemical purity (either *E* or*Z*) can be prepared in a more simple way (chapter 2). An unexpected influence of the various alkali metal ions on the stability of *ortho*-metallated fluorobenzene is the subject of chapter 4. A valuable 'by product' of this investigations is an efficient synthesis of triphenylene (chapter 5). Investigations on the stability of some representatives of the class of reactive species carbenoïds are described in chapter 6. Chapter 8 describes how benzene can be dimetallated with surpisingly high yield under largely heterogeneous conditions, while in chapter 9 one can find how a number of substrates with low thermodynamic and kinetic acidity can be metallated more completely than possible thus far. Chapter 7 warns chemists to be cautious when drawing conclusions with regard to the extend of metallations from the results obtained from functionalization experiments with the various electrophiles. This warning which has general significance for chemists working in the field of polar organometallic chemistry is based on the possibility that under certain conditions the metallating reagent and the functionalization reagent tolerate each others presence in the reaction medium. Chapter 1 is devoted to dimetallations of a number of compounds with a conjugated enyne system. Some of these dimetallations have synthetic significance.

References

1 For reviews on the organoalkali chemistry in the early years: Gilman, H.; Morton Jr., J. W. *Org. React.* **8** (1954) 258; Benseker, R. A.; Foster, D. J.; Sauve, D. M.; Nobis, J. F. *Chem. Rev.* **57** (1957) 867.

2 The benefit of THF was first discovered by Gilman *et al.*: Gilman, H.; Gaj, B. J. *J. Org. Chem.* **22** (1957) 1165, and references cited therein.

3 Lochmann, L.; Pospísil, J. *Tetrahedron Lett.* (1966) 257; Schlosser, M. *J. Organomet. Chem.* **8** (1967) 9.

4 Seebach, D. *Synthesis* (1969) 17; Seebach, D.; Beck, A. K. *Org. Synth.* **51** (1971) 76; Seebach, D.; Erickson, B. W.; Singh, G. *J. Org. Chem.* **31** (1966) 4303; Seebach, D., Corey, E. J. *J. Org. Chem.* **40** (1975) 231.

5 Schlosser, M. *Pure & Appl. Chem.* **60** (1988) 1627, and references cited therein.

6 Everhardus, R. H.; Gräfing, R.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **97** (1978) 69.

7 Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag, Heidelberg (1987); Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol II* Springer-Verlag, Heidelberg (1990).

8 Klusener, P. A. A.; Brandsma, L.; Verkruijsse, H. D.; von Ragué Schleyer, P.; Friedl, T.; Pi, R. *Angew. Chem.* **98** (1986) 458 (*Angew. Chem., Int. Ed. Engl.* **25** (1986) 465); Brandsma, L.; Verkruijsse, H. D.; Schade, C.; von Ragué Schleyer, P. *J. Chem. Soc., Chem. Commun.* (1986) 260.

9 Klusener, P. A. A.; Hommes, H. H.; Verkruijsse, H. D.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* (1985) 1677.

10 Thesis P. A. A. Klusener *Synthetic Applications of Strongly Basic Reagents.* Department of Preparative Organic Chemistry, University of Utrecht, The Netherlands (1989).

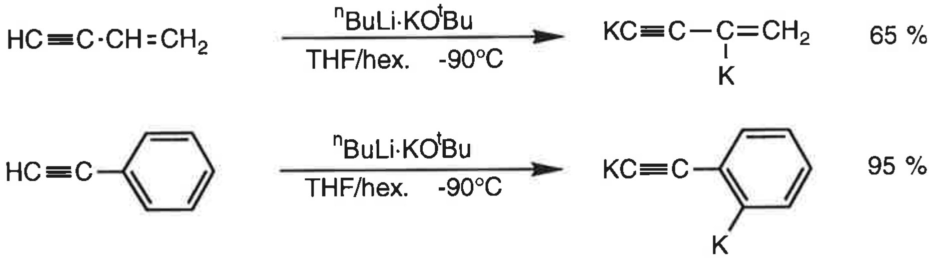
Chapter 1

The Dimetallation of Compounds Containing a Conjugated Enyne System

Introduction

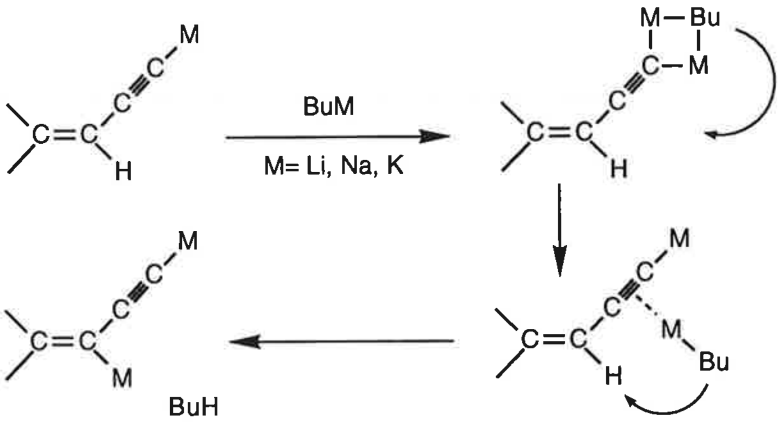
Metallations of vinylic systems with strongly basic systems have received ample interest in organometallic chemistry.[1] Substituents on vinylic systems can show (de-)activating and/or coordinating effects, thus influencing the kinetic and thermodynamic acidity of the vinylic protons and determining the outcome of metallation experiments.

Whereas vinylacetylene can be metallated with a 1:1 molar mixture of *n*-butyllithium and potassium *tert*-butoxide in THF at low temperatures, ethene does not react at all.[2] The succesful *ortho* metallation of vinylacetylene with the same base mixture in THF stands in contrast to the very sluggish metallation of benzene under the same conditions.[3] The investigations of Klusener showed that the acetylide group (-C≡CK) has both directing and activating properties.[3]



Scheme 1: Reported metallations of vinylacetylene and phenylacetylenes.

The directing properties of the acetylide group might be explained by assuming precoordination of the base with the acetylide group and subsequent attack of the base on the vinylic or aromatic proton (see scheme 2). This precoordination and attack are favored by the high electron density on the acetylide-group, making interaction of the alkali metal ion of the base with the π-system energetically advantagous. The effect of the acetylide group seems however not merely a kinetic one, as calculations on metallated vinylacetylenes indicated that the acetylide group also stabilizes the dimetallated species.[2] An acetylide group increases both the kinetic and thermodynamic acidity of protons.



Scheme 2: Possible mechanism of activation of a vinylic proton in a deprotonation reaction by an actylide group.

The previous results mentioned led us to investigate the dimetallations of the enynes **1a-1h**:

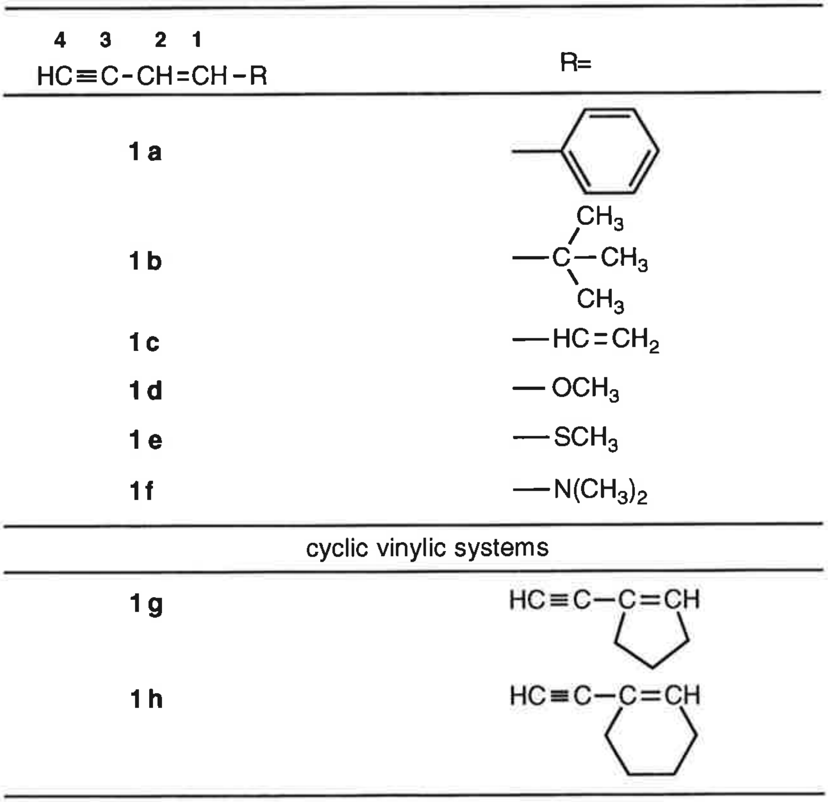


Figure 1: Numbering of enynes and investigated compounds (**1a** - **1f** can have either the *E* or *Z* configuration).

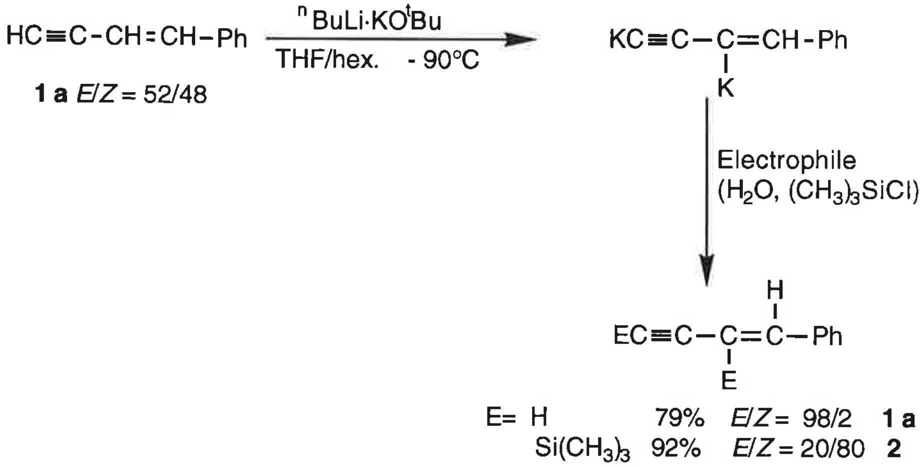
After the first, very fast, deprotonation of the terminal acetylenic group the second metallation can occur either at C-atom 1 or at C-atom 2 (figure 1), depending upon the activating and directing properties of the substituents R and -C≡CM in the monometallated enyne MC≡C-CH=CH-R. Interaction between a strongly basic reagent and an unsaturated system, in principle, can give rise to addition as well as to deprotonation. In order to promote the latter, desired reaction, resulting in the formation of dimetallated products, mixtures of *n*-butyllithium and potassium *tert*-butoxide were used.[4] The enynes were treated with two equivalents of the base mixture, after which an electrophile, in most cases chlorotrimethylsilane, was added. Products were isolated by distillation and analysed by GLC and ^{1}H- and ^{13}C-NMR spectroscopy. In the following schemes only the dimetallated species and their functionalizations are shown. The major side product was, in most cases, the monometallated product, which is omitted for clarity.

Results and discussion

The dimetallation of 1-phenylbut-1-ene-3-yne.

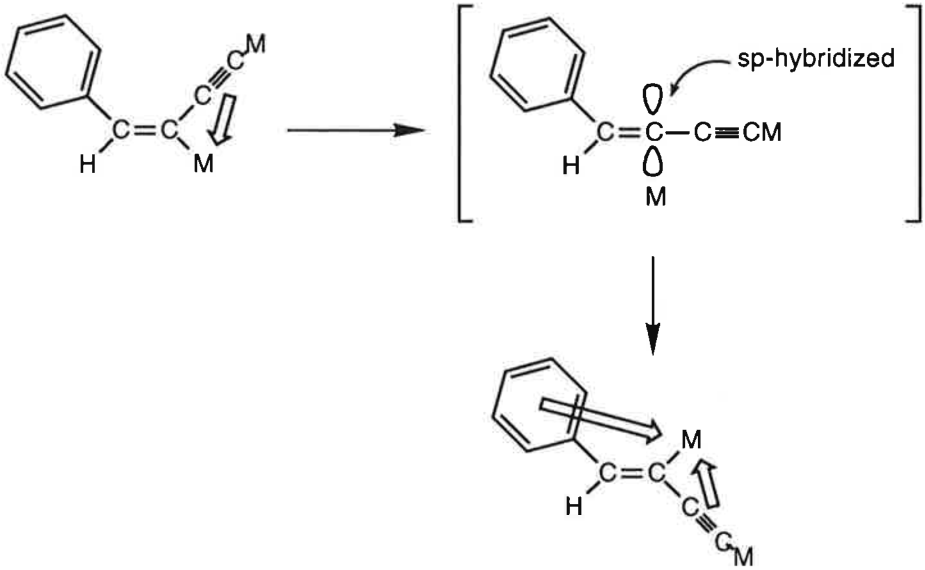
Treatment of 1-phenylbut-1-ene-3-yne (**1a**, *E*/*Z*= 52/48) with ^{n}BuLi·KO^{t}Bu in THF/hexane at -80°C and subsequent quenching with chlorotrimethylsilane afforded the difunctionalized enynes in high yield. The reaction proceeded completely regiospecifically, metallation occurred exclusively at the 2- and 4-positions as a result of the directing properties of the acetylide group.[5] No metallation of the phenyl group was observed.

During metallation the enyne was converted for the greater part to one stereoisomer, the species depicted in scheme 3 being mainly formed. When, after treatment with the base, water was added to the mixture, the enyne **1a** was obtained in an *E*/*Z* ratio of 20/80.



Scheme 3: Dimetallation and subsequent functionalization of **1a** (Ph= phenyl).

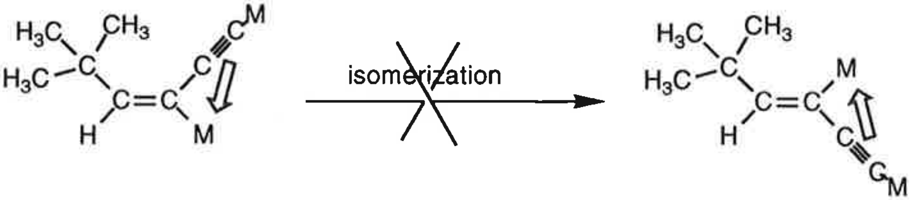
The isomerization is shown best when using the *pure* Z-enyne **1a** as a starting material. After treatment of **1a** (*E*/*Z*= 0/100) with the base and quenching with water **1a** was obtained in an *E*/*Z*-ratio of 84/16 (yield 78%). This inversion of configuration around the double bond is probably energetically advantageous as the anionic species formed after isomerization is more stabilized by internal coordination by both the acetylide and phenyl group to the alkali metal ion (see scheme 4).[6] The isomerization presumably proceeds *via* an intermediate in which the vinylic system adopts an sp-hybridized structure as shown in scheme 4.[7] Isomerizations of metallated vinylic systems have been reported in literature on a number of occasions.[8]



Scheme 4: Proposed mechanism for isomerization of metallated **1a**. Arrows represent stabilizing interactions.

The dimetallation of 3-hexene-5,5-dimethyl-1-yne.

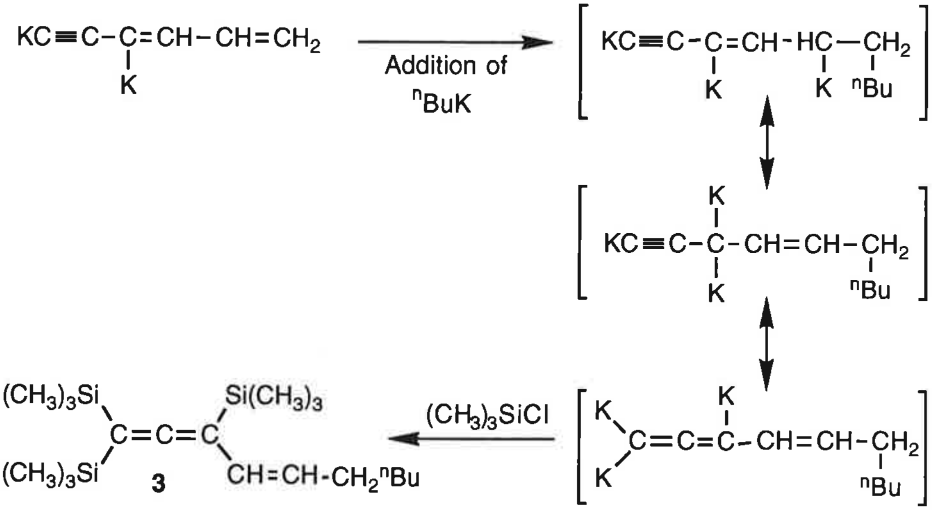
Treatment of the *tert*-butyl substituted enyne 3-hexene-5,5-dimethyl-1-yne (**1b**, *E*/*Z*= 80/20) with $^nBuLi \cdot KO^tBu$ in THF/hexane at -80°C followed by quenching with chlorotrimethylsilane afforded the pure 1,3-disilyl compound in 48% yield (*E*/*Z*= 14/86) (see scheme 5). The yield of dimetallated product could be increased to 59% (*E*/*Z*= 15/85) by using the base system $^nBuLi \cdot KO^tBu \cdot TMEDA$ in hexane at -25°C or the $^nBuLi \cdot KO^tBu$ mixture in pentane at room temperature. Yields are somewhat lower than in the case of vinylacetylene (see scheme 1). This may be explained by less complete dimetallation due to steric hindrance and/or the positive inductive effect exhibited by the *tert*-butyl group. The metallation proceeded with retention of the configuration around the double bond. This is in accordance with the mechanism proposed for the dimetallation of **1a** in scheme 4 as isomerization in this case would not result in better stabilization of the anionic species, as shown in scheme 5:



Scheme 5: Possible explanation of configurational stability of dimetallated **1b.**

The dimetallation of 1,3-hexadiene-5-yne.

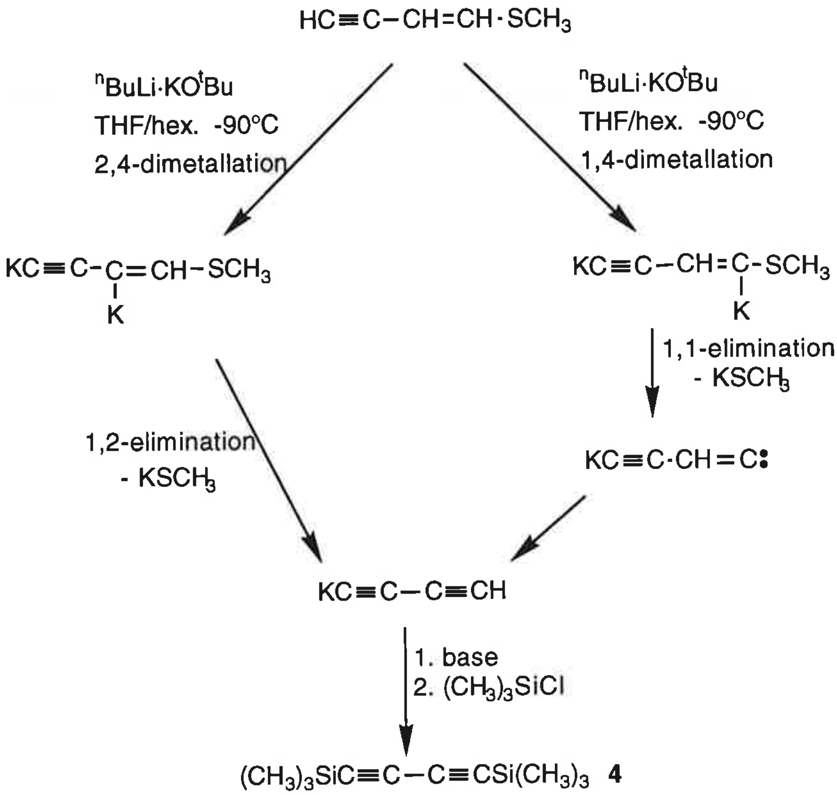
The yield of difunctionalized product obtained by treatment of 1,3-hexadiene-5-yne (**1c**, *E*/*Z*= 45/55) with ^{n}BuLi·KO^{t}Bu in THF/hexane at -80°C and quenching with chlorotrimethylsilane was only 28% (*E*/*Z*= 55/45). Exclusively the 4,6-difunctionalized product was obtained, metallation being directed to the 4-position by the acetylide group. The yield was low due to the occurrence of extensive addition of base to the terminal double bond, yielding compound **3** after isomerisation and quenching with chlorotrimethylsilane. A possible reaction sequence for the formation of **3** is given in scheme 6. Also large amounts of polymer were obtained, possibly formed by an anionic mechanism, initiated by addition of the base to **1c**. Other base systems gave similar poor results. The addition of alkylalkali bases to unsaturated systems is a well known reaction, which is often used as initiation reaction for anionic polymerization of unsaturated systems.[9]



Scheme 6: Addition of base to dimetallated **1c** and subsequent isomerization.

The dimetallation of 1-methoxybut-1-ene-3-yne and 1-methylthiobut-1-ene-3-yne. The main reaction of the heterosubstituted enynes 1-methoxybut-1-ene-3-yne (**1d**, *E*/*Z*= 84/16) and 1-methylthiobut-1-ene-3-yne (**1e**, *E*/*Z*= 10/90) after treatment with 2 equivalents of $^nBuLi \cdot KO^tBu$ in THF/hexane at -80°C was elimination of $KOCH_3$ and $KSCH_3$, respectively, yielding the conjugated diyne-compound **4** in 70-80% yield (see scheme 6). Ziegler *et al.* recently described a similar reaction for the (Z)-enyne-ether with an excess of *n*-butyllithium at -25°C, yielding a diyne compound.[10] The elimination from the potassio compound proceeded at lower temperatures (-80°C).[11] Furthermore, the *thio*ether yielded higher amounts of diyne product, presumably as a consequence of a more facile elimination of the less strongly basic $KSCH_3$.[12] Nothing can be said about the regiospecificity of the metallation as the elimination can proceed *via* a 1,1- or *via* a 1,2-mechanism, see scheme 7. Soderquist *et al.* showed that for the similar elimination reaction of metallated vinylic ethers a 1,2-mechanism was operational.[13]

In the reaction of the enyne ether and thioether the attack of the second equivalent of the base is probably not completely regiospecific as we isolated small amounts of 1,4- and 2,4-disilylated enyne compounds. The activating effect of the acetylide-group accounts for the formation of the 2,4-difunctionalized product, whereas the α-activating properties of the methoxy and thiomethoxy substituents gives rise to the formation of 1,4-difunctionalized product.[13] Since it appeared to be impossible to prevent elimination, no conclusions can be drawn with respect to competitive activating effects of the acetylide and methoxy or thiomethoxy group. However, it may be assumed that the acetylide group is an activator, comparable in strenght or stronger than the methoxy or thiomethoxy group.[14] The metallation-elimination sequence is shown for **1e** in scheme 7.

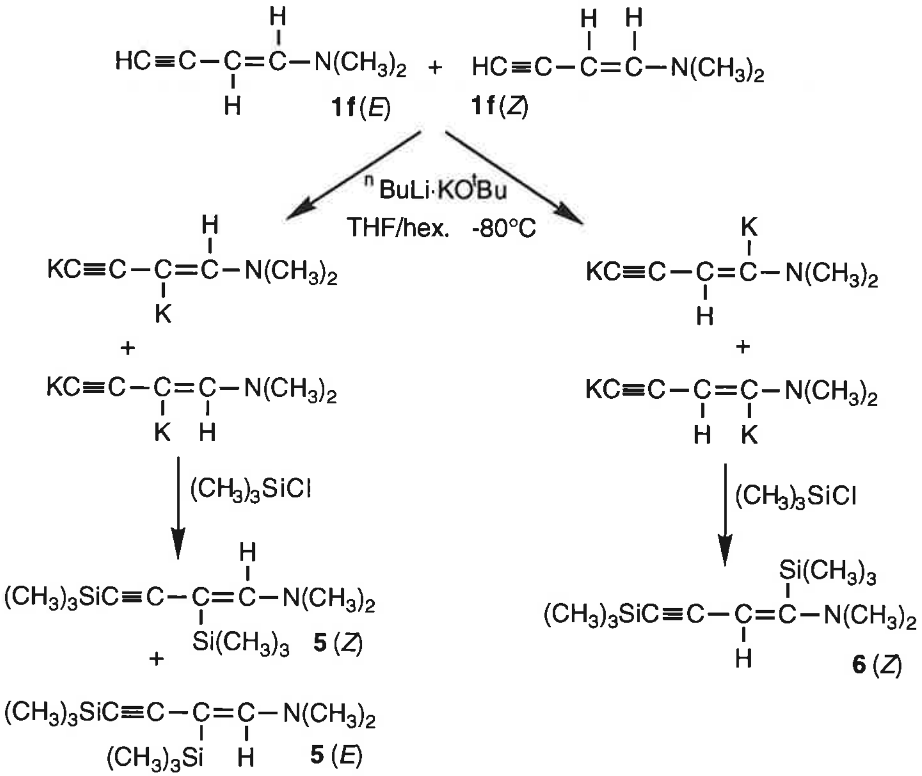


4

Scheme 7: Metallation-elimination sequence for **1e**.

Dimetallation of 1-(*N,N*-dimethylamino)but-1-ene-3-yne.

Treatment of 1-(*N,N*-dimethylamino)but-1-ene-3-yne (**1f**) with ^{n}BuLi·KO^{t}Bu in THF/hexane at -80°C and subsequent quenching with chlorotrimethylsilane afforded a mixture of the 2,4- and 1,4-disilylated enyne (respectively **5** and **6**). The dimethylamino group is known to direct metallations to the α-position.[15] The two substituents in **1f** activate different vinylic protons which accounts for the formation of a mixture of 1,4- and 2,4-dimetallated species. The selectivity was not improved by applying other base mixtures, such as ^{n}BuLi·KO^{t}Bu·TMEDA, or ^{n}BuLi·KO^{t}Bu, in hexane. Remarkable was the difference in results after treatment of the enyne with ^{n}BuLi·KO^{t}Bu in THF/hexane and subsequent quenching with $(CH_3)_3SiCl$ when the *E*/*Z*-ratio of the starting compound was varied. See scheme 8 and table 1.[16]



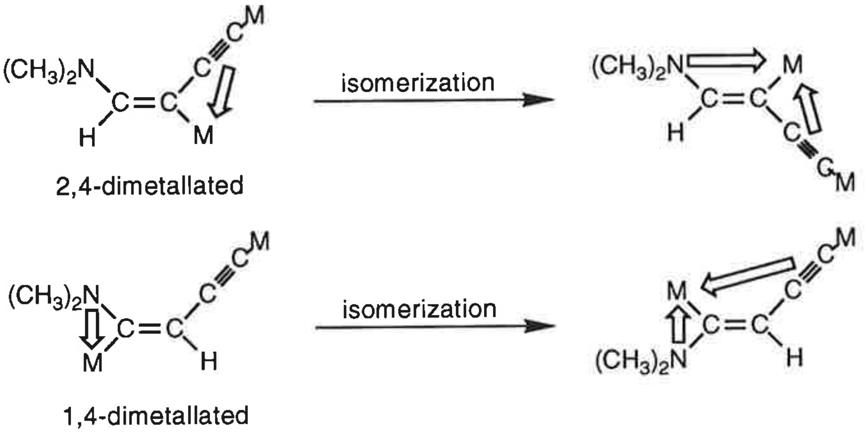
Scheme 8: Dimetallation and functionalization of **1f**.

Table 1: Results of dimetallation and functionalization of **1f**.

Starting material (*E*/*Z*)	2,4-disylilated product (**5**) yield (%)	(*E*/*Z*)	1,4-disylilated product (**6**) yield (%)	(*E*/*Z*)
18/82	48	50/50	19	0/100
100/0	25	20/80	48	0/100

It is remarkable that although the substituents are the same in both cases the product distribution is largely determined by the geometry (*E* or *Z*) of the starting compound. These results indicate that, as can be expected, not only the substituents but also the geometry of a compound influences the acidity of the different protons. It was not possible to isolate both the *E*- and *Z*-isomer of the substrate in a pure form, therefore we could not investigate the influence of the geometry upon the acidity in detail. Furthermore, little is known about structure-dependent differences in acidities of protons in isomeric compounds or differences in stabilities of metallated isomeric compounds. It seems, however, that the acetylide and dimethylamino group are activators of comparable strenght.

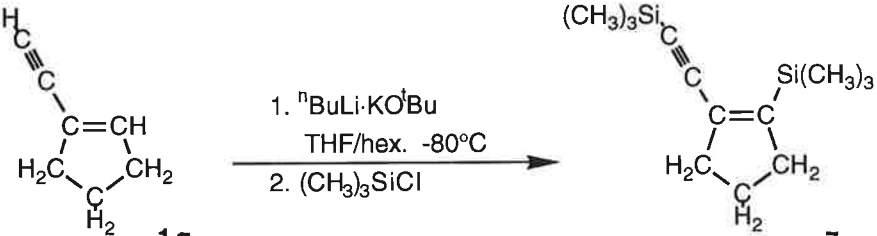
Similar to the phenyl-substituted enyne, dimetallated species of **1f** isomerize for a large part to one isomer. Presumably a mechanism as depicted for **1a** in scheme 4 is operative. Major products are **5** (Z) and **6** (Z) as the dimetallated species from which they are formed (see scheme 8) are more stabilized by internal coordination than the other isomers, as is shown in scheme 9. Remarkable is the fact that no **6** (*E*) was obtained at all.



Scheme 9: Interactions leading to the isomerization of dimetallated **1f**. Arrows represent stabilizing interactions.

The dimetallation of 1-ethynyl-cyclopentene and 1-ethynyl-cyclohexene.

In the cyclic enyne sysyems 1-ethynyl-cyclopentene (**1g**) and 1-ethynyl-cyclohexene (**1h**) no α-protons are present. It seemed interesting to investigate whether an acetylide system is also capable of activating a vinylic proton at the β-position towards abstraction. Treatment of **1g** with ^{n}BuLi·KO^{t}Bu in THF/hexane at -80°C and subsequent quenching with chlorotrimethylsilane afforded of the disilylated product **7** in 26% yield (see scheme 10).



1g **7**

Scheme 10: Dimetallation and functionalization of **1g**.

Cyclopentene is not metallated at all under the same conditions, so the acetylide group indeed activates the β-protons, as it does in the case of phenylacetylene.[3] In addition to the activating effect of the acetylide substituent, the ring-strain in **1g** may account for its regiospecific metallation. Metallation at the vinylic system diminishes the ring strain to some degree.[17] Lenghtening of the reaction period for the dimetallation of **1g** from 1 to 3 hours increased the yield to 38%. A further improvement to 59% was attained by reacting ethynylcyclopentene with the mixture ^{n}BuLi·KO^{t}Bu·TMEDA in hexane for 1 hour at -25°C.

As the cyclohexene system in **1h** does not have ring strain, protons in this enyne will be activated only by the acetylide system. Treatment of **1h** with ^{n}BuLi·KO^{t}Bu in THF/hexane and subsequent quenching with chlorotrimethylsilane afforded 18% of disilylateded products, but metallation took place at an allylic as well as at the vinylic position (ratio ~ 1:1).[18] Cyclohexene is not metallated under similar conditions. It may therefore be concluded that the acetylide-group activates both the vinylic and an allylic proton in **1h** to some degree. When a large excess of cyclohexene is treated with ^{n}BuLi·KO^{t}Bu metallation proceeds only at the -most acidic- allylic position.[19] Introduction of an acetylide substituent on the vinylic system shifts the preference for metallation partially to the vinylic position. The use of TMEDA in stead of THF did not result in higher yields. By using the mixture ^{n}BuLi·KO^{t}Bu in pentane at room temperature an improvement of the yield of dimetallated product to 28% was attained, but the regiochemistry remained unchanged.

Experimental methods

General remarks

All metallation reactions were performed under an atmosphere of nitrogen in a 250 ml three-necked round-bottomed flask, equipped with a thermometer-gasinlet combination, mechanical stirrer and dropping funnel-gasoutlet combination. Solvents were dried before use. *n*-Butyllithium and potassium *tert*-butoxide were obtained commercially and used as such. Reaction mixtures were cooled with a liquid nitrogen bath. Products were analyzed by GLC, using a Varian 4400 gas chromatograph with a silica-coated capillary column, and NMR. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker WP200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50 MHz) in deuteriochloroform, which was also used as internal reference. In some cases NMR spectra were too complex due to the formation of mixtures of products (mono-functionalized, 1,4- and 2,4-difunctionalized, and *E* and *Z* isomers). Essential NMR data are given where possible. A trimethylsilyl group linked to a triple bond can be removed by treatment with a 10% KOH solution in methanol for 30 minutes at room temperature, which is useful for assignment of NMR signals.

Starting materials.

Starting compounds **1a** (*E/Z*= 52/48), **1c** (*E/Z*= 45/55), **1d** (*E/Z*= 84/16), **1f** (*E/Z*= 18/82), **1g** and **1h** were prepared as described in literature.[20] Short describtions of the syntheses of **1a** (*E/Z*= 0/100), **1b** (*E/Z*= 80/20), **1e** (*E/Z*= 10/90) and **1f** (*E/Z*= 100/0) are given below.

Z-**1a** (*E/Z*= 0/100) was prepared in three steps. A Cadiot-Chodkiewicz coupling between 2-bromo-1-phenyl-acetylene and trimethylsilylacetylene gave 1-phenyl-4-trimethylsilyl-diacetylene. Treatment of this compound with activated Zinc powder and CuBr/LiBr in refluxing ethanol gave the enyne 1-phenyl-4-trimethylsilyl-but-1-ene-3-yne (*E/Z*= 0/100). The trimethylsilyl group was removed by treatment with KOH in methanol. Work-up afforded the enyne, bp. 89-91°C (20 mm Hg).

1b (*E/Z*= 80/20) was prepared in two steps. First the Grignard reagens propargylmagnesiumbromide was reacted with pivaldehyde. The thus formed alcohol was mixed with pyridine and fosforyl chloride and the mixture stirred for one hour at 100°C. After addition of water **1b** was isolated by extraction with diethyl ether and distillation, bp. 40-50°C (40 mm Hg).

1e (*E/Z*= 10/90) was synthesized by addition of a slight excess of methanethiolate to a solution of sodium diacetylide in liquid ammonia. The latter was obtained from the reaction between 1,4-dichloro-2-

butyne and three equivalents of sodium amide. After addition of ammonium chloride work-up was carried out by extraction with ether and subsequent distillation, bp. 48-54°C (17 mm Hg).

1f (*E*/*Z*= 100/0) was obtained from 1-(*N*,*N*-dimethylamine)-3-buten-1-yne (*E*/*Z*= 18/82, prepared according to a literature procedure, see ref[20]). After treatment with KO^{t}Bu and HMPT at 60°C, distillation afforded the pure *E*-isomer at 56-70°C (15 mm Hg).

Typical metallation procedure:

Metallation with ^{n}*BuLi·KO*^{t}*Bu in THF.*

In the reaction flask were placed 7.0 g (0.06 mol) of KO^{t}Bu and 50 mL of THF, after which the stirred mixture was cooled to -90°C. To the clear solution was added 40 mL of a 1.6 M (0.06 mol) solution of *n*-butyllithium in hexane within one minute, while maintaining the temperature at *ca.* -90°C. After stirring for some minutes a mixture of 0.025 mol of the enyne and 10 mL of THF was added dropwise over 10 minutes at -75 to -90°C. The mixture was stirred for one hour at -80°C after which the temperature was allowed to rise to room temperature, in order to allow the excess base to react with THF. The mixture was then cooled to -40°C and excess (0.075 mol) of an electrophile was added in one portion. After stirring vigorously for 30 minutes water was added, and the product was extracted three times with pentane or diethyl ether, dried over magnesium sulfate (for reactions of **1f** the crude product was dried over potassium carbonate) and carefully distilled through a short Vigreux column in a water- or oil-pump vacuum. In all cases a more volatile fraction of the monofunctionalized enyne was obtained besides the difunctionalized product.

Metallation with ^{n}*BuLi·KO*^{t}*Bu·TMEDA in pentane.*

To a mixture of 14.0 g (0.12 mol) of TMEDA and 50 mL of pentane in the reaction flask was added 7.0 g (0.06 mol) of KO^{t}Bu at room temperature after which the stirred mixture was cooled to -30°C. To the suspension was added 40 mL of a 1.6 M (0.06 mol) solution of *n*-butyllithium in hexane within one minute, while maintaining the temperature at *ca.* -30°C. After a few minutes a mixture of 0.025 mol of the enyne and 10 mL of pentane was added dropwise over 10 minutes at -30 to -25°C. Stirring at -25°C was continued for one hour after which the temperature was raised to room temperature. The mixture was cooled to -40°C and excess (0.075 mol) of an electrophile was added in one portion. After stirring vigorously for 30 minutes water was added, and the product was extracted three times with pentane or diethyl ether, dried over magnesium sulfate and carefully distilled over a short Vigreux column on a water or oil-pump vacuum. In all cases a more volatile fraction of the monofunctionalized enyne was obtained besides the difunctionalized product.

Metallation with ^{n}*BuLi·KO*^{t}*Bu in pentane.*

In the reaction flask were placed 7.0 g (0.06 mol) of KO^{t}Bu and 50 mL of pentane at room temperature. The stirred mixture was cooled to *ca.* -10°C. To the suspension was added 40 mL of a 1.6 M solution of (0.06 mol) *n*-butyllithium in hexane within one minute, while cooling with an ice bath. The temperature was subsequently raised to room temperature. After some minutes a mixture of 0.025 mol of the enyne and 10 mL of pentane, was added dropwise in 10 minutes. Stirring at room temperature was continued for one hour. The mixture was cooled to -30°C and an excess (0.075 mol) of an electrophile was added in one portion. After stirring for 30 minutes water was added, and the product was extracted three times with pentane or diethyl ether, dried over magnesium sulfate and carefully distilled over a short Vigreux column on a water or oil-pump vacuum. In all cases a more volatile fraction of the monofunctionalized enyne was obtained besides the difunctionalized product.

Metallation of 1a (*E*/ *Z*= 52/48).

Reaction of 1-phenylbut-1-ene-3-yne with ^{n}*BuLi·KO*^{t}*Bu in THF/hexane and quenching with water.*

Product **1a** (*E*/ *Z*= 98/2)was obtained in a yield of 79% (2.54 g), bp. 85-92°C (20 mm Hg.).

1a (*E*) ^{1}H-NMR ($CDCl_3$): δ= 3.18 (d, 1H, C(4)H, *J*= 2.4 Hz), 6.24 (dd, 1H, C(2)H, *J*=16.4, 2.4 Hz), 7.15 (d, 1H, C(1)H, *J*= 16.4 Hz), 7.37-7.52 (m, 5H, phenyl); ^{13}C-NMR ($CDCl_3$): δ= 79.4 (C(4)), 82.2 (C(3)), 106.9 (C(2)), 134.0 (C(1)).

1a (Z) ^{1}H-NMR ($CDCl_3$): δ= 3.46 (d, 1H, C(4)H, *J*= 2.7 Hz), 5.79 (dd, 1H, C(2)H, *J*=12.1, 2.7 Hz), 6.80 (d, 1H, C(1)H, *J*= 12.1 Hz), 7.37-8.02 (m, 5H, phenyl); ^{13}C-NMR ($CDCl_3$): δ= 81.9 (C(3)), 84.2 (C(4)), 106.2 (C(2)), 140.5 (C(1)).

Reaction with $^nBuLi\cdot KO^tBu$ in THF/hexane and quenching with chlorotrimethylsilane.

Disilylated product **2a** (*E*/ Z= 20/80) was obtained in a yield of 92% (6.30 g), bp. 88-95°C (0.1 mm Hg.).

2a (*E*) ^{1}H-NMR ($CDCl_3$): δ= 0.31 (s, 9H, Me_3Si), 0.32 (s, 9H, Me_3Si), 6.88 (1H, C(1)H), 7.25- 8.09 (m, 5H, phenyl); ^{13}C-NMR ($CDCl_3$): δ= 145.0 (C(1)), other data are not known as only small amounts were obtained.

2a (Z) ^{1}H-NMR ($CDCl_3$): δ= 0.16 (s, 9H, Me_3Si), 0.32 (s, 9H, Me_3Si), 7.82 (1H, C(1)H), 7.25- 7.45 (m, 5H, phenyl); ^{13}C-NMR ($CDCl_3$): δ= 96.8 (C(4)), 109.3 (C(3)), 138.6 (C(2)), 152.3 (C(1)).

Metallation of 1b (*E*/ Z= 80/20).

Reaction of 3-hexene-5,5-dimethyl-1-yne with $^nBuLi\cdot KO^tBu$ in THF/hexane and quenching with chlorotrimethylsilane.

The 1,3-disilylated product was obtained in a yield of 48% (3.00 g) (*E*/ Z= 14/86), bp. 110-120°C (20 mm Hg.)

Disylilated product (*E*) ^{1}H-NMR ($CDCl_3$): δ= 1.19 (s, 9H, CCH_3), 5.99 (s, 1H, C(4)H)); ^{13}C-NMR ($CDCl_3$): δ= 29.6 (CCH_3), 36.0 (CCH_3), (121.9 (C(3)), 160.4 (C(4)) (not all data known as only small amounts of the*E*-isomer were obtained).

Disylilated product (Z) ^{1}H-NMR ($CDCl_3$): δ= 1.11 (s, 9H, CCH_3), 6.91 (s, 1H, C(4)H)); ^{13}C-NMR ($CDCl_3$): δ= 30.7 (CCH_3), 35.0 (CCH_3), 92.5 (C(1)), 111.3 (C(2)), 120.9 (C(3)), 167.3 (C(4)).

Reaction with $^nBuLi\cdot KO^tBu\cdot TMEDA$ in pentane and quenching with chlorotrimethylsilane.

Yield of disilylated product 59% (3.75 g) (*E*/ Z= 15/85).

Metallation of 1c (*E*/ Z= 45/55).

Reaction of 1,3-hexadiene-5-yne with $^nBuLi\cdot KO^tBu$ in THF/hexane and quenching with chlorotrimethylsilane.

Disilylated product (*E*/ Z= 55/45) was obtained in 28% yield (1.55 g), bp. 53-120°C (0.1 mm Hg.) (the product consisted of a mixture of disilylated product and addition product **3** (configuration of double bond unknown), which were very difficult to separate by distillation)

Disilylated product (*E*) ^{1}H-NMR ($CDCl_3$): δ= 5.28 (d, 1H, HC=CHH, *J*= 10.0 Hz), 5.37 (d, 1H, HC=CHH, *J*= 17.0 Hz), 6.56 (bd, 1H, C(3)H, *J*= 10.6), 6.96 (ddd, HC=CH_2, *J*= 10.0, 10.6, 17.0 Hz); ^{13}C-NMR ($CDCl_3$): δ= 121.6 (HC=CH_2), 135.3 (HC=CH_2), 151.3 (C(3)).

Disilylated product (Z) ^{1}H-NMR ($CDCl_3$): δ= 5.28 (d, 1H, HC=CHH, *J*= 10.0 Hz), 5.32 (d, 1H, HC=CHH, *J*= 16.5 Hz), 6.63 (ddd, HC=CH_2, *J*= 10.0, 11.6, 16.5 Hz), 7.10 (d, 1H, C(3)H, *J*= 11.6 Hz); ^{13}C-NMR ($CDCl_3$): δ= 120.1 (HC=CH_2), 135.6 (HC=CH_2), 147.4 (C(3)).

Addition product **3**: ^{1}H-NMR ($CDCl_3$): δ= 5.44 (dt, 1H, HC=CH, *J*= 15.6, 6.8 Hz), 5.73 (dt, 1H, HC=CH, *J*= 15.6, 1.3 Hz), 0.80-2.50 (m, 11H, CH_2Bu); ^{13}C-NMR($CDCl_3$): δ= 14.1 ($CH_2CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_2CH_3$), 29.6 ($CH_2CH_2CH_2CH_2CH_3$), 31.4 ($CH_2CH_2CH_2CH_2CH_3$), 33.3 ($CH_2CH_2CH_2CH_2CH_3$), 80.0 (C=C=C), 126.1 (HC=CH), 128.3 (HC=CH), 209.8 (C=C=C).

Metallation of 1d (*E*/ Z= 84/16).

Reaction of 1-methoxybut-1-ene-3-yne with $^nBuLi\cdot KO^tBu$ in THF/hexane and quenching with chlorotrimethylsilane.

The disilylated diyne product **4** was obtained in a yield of 70% (*ca.* 3.40 g), as a white solid at room temperature, bp. 80-100°C (20 mm Hg.) Small amounts of 1,4- and 2,4-disilylated products were also obtained, bp. 50-60°C (0.1 mm Hg.).

4: ^{1}H-NMR ($CDCl_3$): δ=0.18 (Me_3Si). ^{13}C-NMR($CDCl_3$): δ= 85.9 ($Me_3SiC{\equiv}C$-), 88.0 ($Me_3SiC{\equiv}C$-), -0.5 (Me_3Si).

Metallation of 1e (*E*/ *Z*= 18/82).

Reaction of 1-methylthiobut-1-ene-3-yne with $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane.*

The disilylated diyne product **4** was obtained in a yield of 80% (*ca.* 3.90 g), as a white solid at room temperature, bp. 80-100°C (20 mm Hg.) Small amounts of 1,4- and 2,4-disilylated products were also obtained, bp. 50-60°C (0.1 mm Hg.).

Metallation of 1f (*E*/*Z* = 18/82).

Reaction of 1-(N,N-dimethylamino)but-1-ene-3-ynewith $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane.*

The disilylated product (4.00 g) was obtained as a mixture of **5** (yield 48%) (*E*/ Z= 50/50) and **6** (yield 19%) (*E*/ Z= 0/100), bp. 85-100°C (1 mm Hg.)

5 (Z): ^{1}H-NMR ($CDCl_3$): δ= 2.84 (s, 6H, $N(CH_3)_2$), 7.07 (s, 1H, C(1)H).

5 (*E*): ^{1}H-NMR ($CDCl_3$): δ= 3.05 (s, 6H, $N(CH_3)_2$), 5.80 (s, 1H, C(1)H).

6 (Z): ^{1}H-NMR ($CDCl_3$): δ= 3.10 (6H, $N(CH_3)_2$), 5.00 (1H, C(2)H).

Metallation of 1f (*E*/*Z* = 100/0).

Reaction with $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane.*

The disilylated product (4.35 g) was obtained as a mixture of **5** (yield 25%) (E/ Z= 20/80) and **6** (yield 48%) (E/ Z= 0/100), bp. 85-100°C (1 mm Hg.).

Metallation of 1g.

Reaction of 1-ethynyl-cyclopentene with $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane.*

The disilylated product **7** was obtained in a yield of 26% (1.54 g), bp. 60-70°C (0.1 mm Hg.)

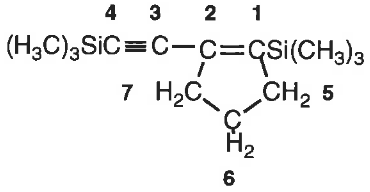


Figure 2: Numbering of 7.

7: ^{1}H-NMR ($CDCl_3$): δ= 1.73- 1.88 (m, 2H, C(6)H), 2.43- 2.56 (m, 4H, C(5)H, C(7)H). ^{13}C-NMR ($CDCl_3$): δ= 24.0 (C(6)), 38.3 (C(5)), 39.9 (C(7)), 97.5 (C(4)), 104.3 (C(3)), 132.7(C(2)), 153.1 (C(1)).

Reaction with $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane, reaction time 3 hours.*

The metallation mixture was stirred for 3 hours instead of 1 hour. Yield of disilylated product 2.25 g (38%).

Reaction with $nBuLi\cdot KO^{t}Bu\cdot TMEDA$ *in pentane and quenching with chlorotrimethylsilane.*

The disilylated product **7** was obtained in a yield of 59% (3.50 g).

Metallation of 1h.

Reaction of 1-ethynyl-cyclohexene with $^{n}BuLi\cdot KO^{t}Bu$ *in THF/hexane and quenching with chlorotrimethylsilane.*

The disilylated product was obtained in a yield of 18% (1.14 g), bp. 80-90°C (1 mm Hg.), as a mixture of 1,4-disilylated product and 4,5- or 4,8-disilylated product in a *ca.* 1:1 ratio (for numbering see below), the last two products are the result of allylic deprotonation. We were unable to establish whether the 4,5- or 4,8-disilylated product was formed.

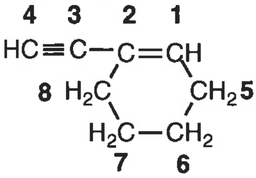


Figure 3: Numbering of **1h.**

1,4-Disylilated product: ^{1}H-NMR ($CDCl_3$): δ= 1.53-1.59 (m, 4H, C(6)H, C(7)H), 2.02- 2.09 (m, 4H, C(5)H, C(8)H). 4,5 or 4,8-disilylated product: ^{1}H-NMR ($CDCl_3$): δ= 2.75 (m, 1H, C(1)H).

Reaction with ^{n}*BuLi·KO*^{t}*Bu in pentane and quenching with chlorotrimethylsilane, reaction time 3 hours.*

The metallation-mixture was stirred for 3 hours instead of 1 hour. Yield of disilylated product 1.77 g (28%), as a mixture of 1,4-disilylated product and 4,5- or 4,8-disilylated product.

References

1 Brandsma, L.; Verkruijsse, H. D.; Schade, C.; Von Ragué Schleyer, P. *J. Chem. Soc., Chem. Commun.* (1986) 260.

2 Brandsma, L.; Hommes, H.; Verkruijsse, H. D.; Kos, A. J.; Neugebauer, W.; Baumgärtner, W.; von Ragué Schleyer, P. *Recl. Trav. Chim. Pays-Bas* **107** (1988) 286.

3 Thesis P. A. A. Klusener, Department of Preparative Organic Chemistry, University of Utrecht (1989); Hanekamp, J. C.; Klusener, P. A. A.; Brandsma, L. *Synth. Commun.* **19** (1989) 2691; Klusener, P. A. A.; Hanekamp, J. C.; Brandsma, L. *J. Org. Chem.* **55** (1990) 1311.

4 For examples of metallations with superbase mixtures: Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer- Verlag, Heidelberg (1987); Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol II* Springer-Verlag, Heidelberg (1990).

5 A phenyl substituent does not activate α- or *ortho* -protons neither directs metallations towards these protons. Biphenyl for example is metallated in 12% yield with *n*-butyllithium in diethyl ether of which only 8% at the 2- position, metallation mainly occurs at the 3- (58%) and 4-positions (34%). Shirley, D. A.; Johnson Jr., J. R.; Hendrix, J. P. *J. Organomet. Chem.* **11** (1968) 209.

6 Interaction between a lithium ion and the π-system of a phenyl ring is energetically advantageous. van Eikema Hommes, N. J. R.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **31** (1992) 755.

7 Knorr, R.; Lattke, E. *Tetrahedron Lett.* **45** (1977) 3969; Panek, E. J.; Neff, B. L.; Chu, H.; Panek, M. G. *J. Am. Chem. Soc.* **97** (1975) 3996; Bauer, W.; Feigel, M.; Müller, G.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **110** (1988) 6033.

8 Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **108** (1986) 3402; Mulvaney, J. E.; Carr, L. J. *J. Org. Chem.* **33** (1968) 3286; Kessler, H. *Tetrahedron* **30** (1974) 1861; Bauer, W.; Feigel, M.; Müller, G.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **110** (1988) 6033.

9 Mulvaney, J. E.; Carr, L. J. *J. Org. Chem.* **33** (1968) 3286; Mulvaney, J. E.; Newton, D. J. *J. Org. Chem* **34** (1969) 1936; Miginiac, L. *J. Organomet. Chem.* **238** (1982) 235.

10 Zweifel, G.; Rajagopalan, S. *J. Am. Chem. Soc.* **107** (1985) 700; Stracker, E. C.; Zweifel, G. *Tetrahedron Lett.* **47** (1990) 6815.

11 The vinylic ethers $H_2C=CH\text{-}OMe$ and $H_2C=CH\text{-}SMe$ are both metallated specifically at the α-position: Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **44** (1979) 303; Verkruijsse, H. D.; Brandsma, L.; von Ragué Schleyer, P. *J. Organomet. Chem.* **332** (1987) 99. *Lithiated* vinyl ethers and vinyl thioethers can be functionalized in high yield at temperatures from -70°C to -20°C: Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **95** (1973) 2694; Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **43** (1978) 1595; Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **102** (1980) 1577.

12 The pK_a value of CH_3SH is 11, the pK_a value of CH_3OH is 16 (in water). March J. *Advanced Organic Chemistry 3rd ed.* John Wiley and Sons, New York (1985).

13 Soderquist, J. A.; Hsu, G. J-H. *Organometallics* **1** (1982) 830.

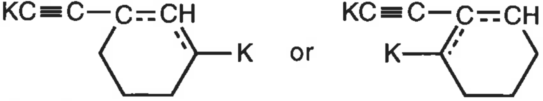
14 Results from Yamaguchi *et al.* on the metallation of *p*-methoxy- phenylacetylene with $^{n}BuLi{\cdot}KO^{t}Bu$ in THF/hexane at -78°C lead to the same conclusion: metallation occurred for 75 % at the 2-position and for 16 % at the 3-position. Yamaguchi, M.; Ikeura, C.; Nakamura, S.; Minami, T. *Chem. Lett.* (1991) 1259.

15 Stork, G.; Polt, R. L.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **110** (1988) 8360.

16 The same results were obtained when the mixture was quenched with mono- deuterioethanol or when $HC{\equiv}C\text{-}CH{=}CH\text{-}N(CH_2CH_3)_2$ was used as starting compound.

17 Schlosser, M *Struktur und Reaktivität Polarer Organometalle* Springer- Verlag, Berlin (1973).

18 We were unable to establish which of the two possible isomers was formed during metallation:



19 The order of acidity of the protons in cyclohexene and cyclopentene is reported to be as follows: cyclohexene allylic position > cyclopentene vinylic position > cyclopentene allylic position ≈ cyclohexene vinylic position. Schröder, G. *Chem. Ber.* **96** (1963) 3178.

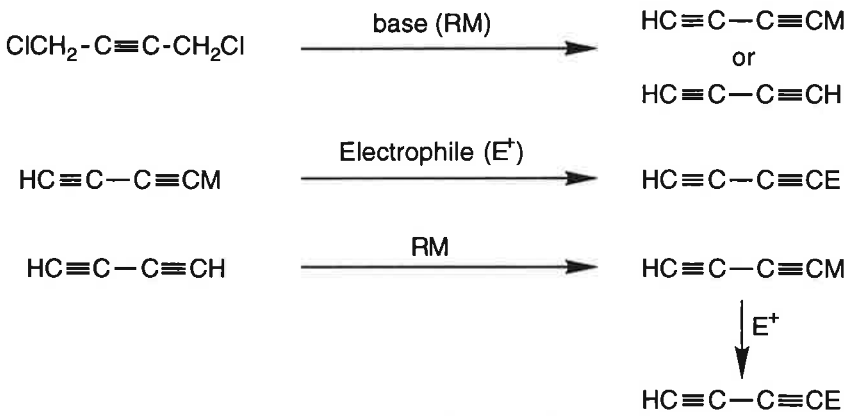
20 Brandsma L. *Preparative Acetylenic Chemistry* Elsevier, Amsterdam (1971).

Chapter 2

New Syntheses of Functionalized Conjugated Diynes and Enynes Containing a Terminal Acetylenic Group

Introduction

A number of methods has been developed for the preparation of conjugated diyne and enyne systems. A brief overview of these methods is given below, for each type of reaction an example is given.[1,2,3]

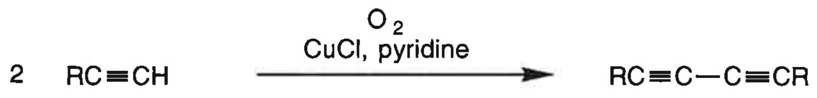


$$ClCH_2\text{-}C{\equiv}C\text{-}CH_2Cl \xrightarrow{\text{base (RM)}} HC{\equiv}C{-}C{\equiv}CM \text{ or } HC{\equiv}C{-}C{\equiv}CH$$

$$HC{\equiv}C{-}C{\equiv}CM \xrightarrow{\text{Electrophile } (E^+)} HC{\equiv}C{-}C{\equiv}CE$$

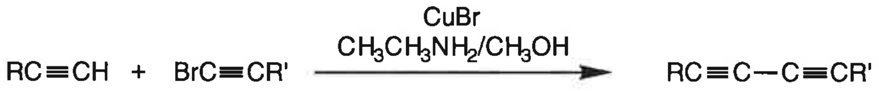
$$HC{\equiv}C{-}C{\equiv}CH \xrightarrow{RM} HC{\equiv}C{-}C{\equiv}CM \xrightarrow{E^+} HC{\equiv}C{-}C{\equiv}CE$$

Scheme 1: Dehydrohalogenation, followed by functionalization.



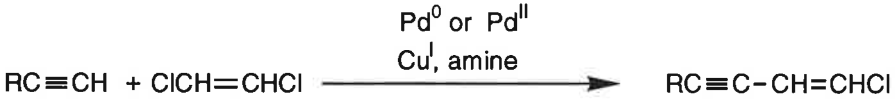
$$2 \quad RC{\equiv}CH \xrightarrow[\text{CuCl, pyridine}]{O_2} RC{\equiv}C{-}C{\equiv}CR$$

Scheme 2: Oxidative coupling, known as the Glaser reaction.



$$RC{\equiv}CH + BrC{\equiv}CR' \xrightarrow[CH_3CH_3NH_2/CH_3OH]{CuBr} RC{\equiv}C{-}C{\equiv}CR'$$

Scheme 3: Cadiot-Chodkiewicz cross-coupling.



$$RC{\equiv}CH + ClCH{=}CHCl \xrightarrow[\text{Cu}^{I}\text{, amine}]{\text{Pd}^{0} \text{ or } \text{Pd}^{II}} RC{\equiv}C\text{-}CH{=}CHCl$$

Scheme 4: Transition-metal catalyzed cross-coupling (also applicable for diynes).

$$HC{\equiv}C{-}C{\equiv}CH + ROH \xrightarrow{\text{base}} HC{\equiv}C\text{-}CH{=}CH\cdot OR$$

Scheme 5: Addition of nucleophiles to diynes.

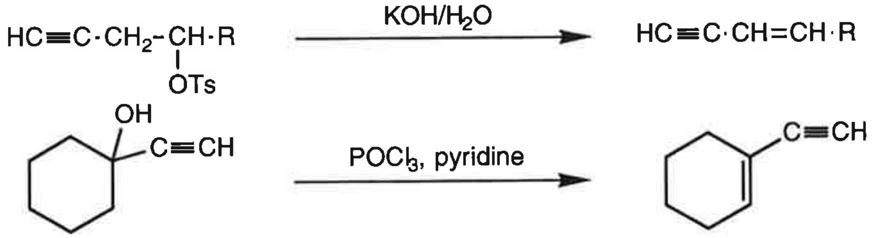
$$RCH_2C\equiv CCH_2OR' \xrightarrow{\text{base}} RCH{=}CH{-}C\equiv CH$$

$$RSCH_2C\equiv CCH_2SR' \xrightarrow{\text{base}} RSC\equiv C{-}CH{=}CH_2$$

Scheme 6: 1,4-Elimination of ethanol or ethanethiol.

$$HC\equiv C\cdot CH_2\cdot CH{=}CH_2 \xrightarrow{\text{base}} HC\equiv C\cdot CH{=}CH\cdot CH_3$$

Scheme 7: Base-catalyzed isomerization of separated diyne or enyne systems.

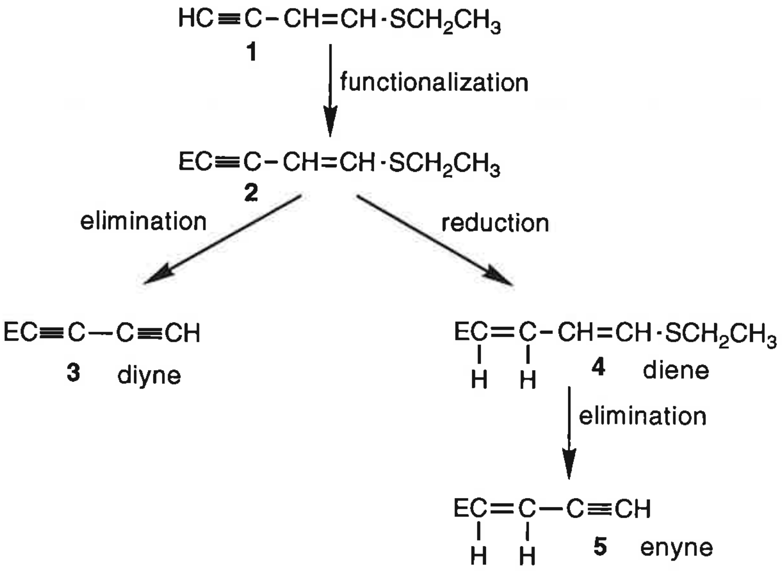


Scheme 8: 1,2-Elimination of *p*-toluenesulfonic acid or water (Ts= *p*-toluenesulfonic acid).

The need for complicated or unstable starting materials puts limits to the use of the methods mentioned above. Furthermore, difficultly to separate side-products are sometimes formed.

Previous work in this laboratory has shown that derivatives $RC\equiv C\text{-}CH{=}CH\text{-}SC_2H_5$ readily lose ethanethiol upon treatment with alkali amides in liquid ammonia.[2] It has also been shown that $HC\equiv C\text{-}CH{=}CH\text{-}SC_2H_5$ is easily reduced by activated zinc powder to give $H_2C{=}CH\text{-}CH{=}CH\text{-}SC_2H_5$.[4] The reduction of internal triple bonds generally proceeded stereospecifically, affording *cis* double bonds.

Based on these findings the following route was designed for a new synthesis of diynes and for the preparation of *cis*-enynes, see scheme 9. Each step will be discussed below.

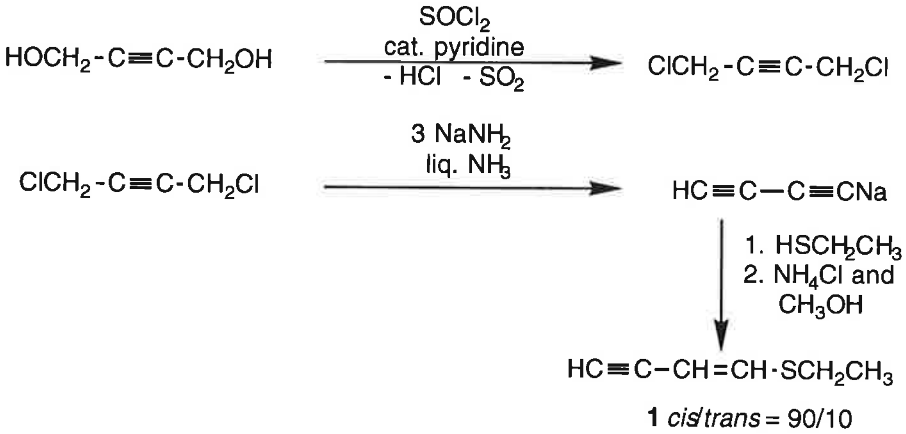


Scheme 9: New synthetic route to diynes and enynes.

Results and discussion

Preparation of starting compound 1.

The starting compound $HC\equiv C\text{-}CH=CH\text{-}SCH_2CH_3$ (**1**) was obtained as a 90/10 mixture of the *cis/trans* isomers along the following scheme:[2]

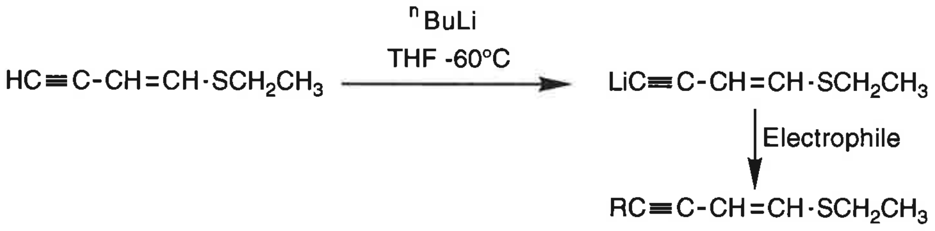


Scheme 10: Preparation of starting material **1**.

The sulfide gradually turned brown upon standing at room temperature, but could be stored without any polymerization for several weeks at -25°C.

Functionalization of the enyne sulfide, formation of 2.

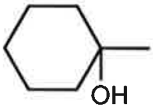
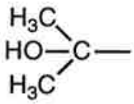
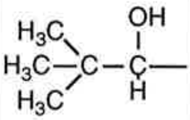
i) following the conventional way of functionalization, a number of couplings with aldehydes, ketones and alkyl halides was succesfully performed:



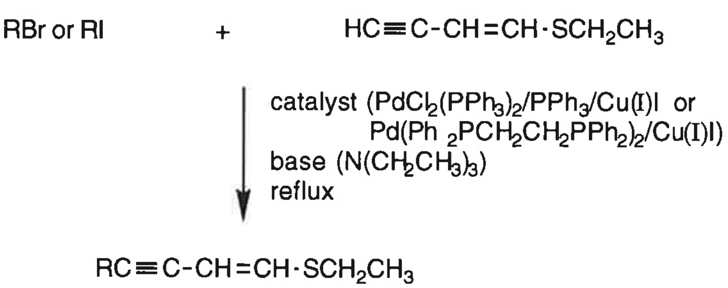
2

Scheme 11: Functionalization of **1** *via* metallated intermediate.

Table 1: Results of functionalization *via* metallated intermediate.

compound	R	electrophile	yield (%)
2a	$CH_3(CH_2)_7$	octyl bromide (+ HMPT)	85
2b		cyclohexanone	85
2c		acetone	85
2d		pivaldehyde	85

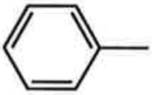
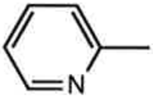
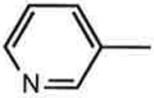
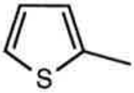
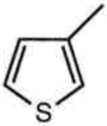
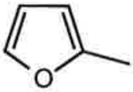
ii) aryl- and hetaryl-substituted enyne sulfides were prepared by Pd/Cu-catalyzed cross-couplings:



2

Scheme 12: Functionalization of enyne sulfide *via* palladium catalyzed reactions.

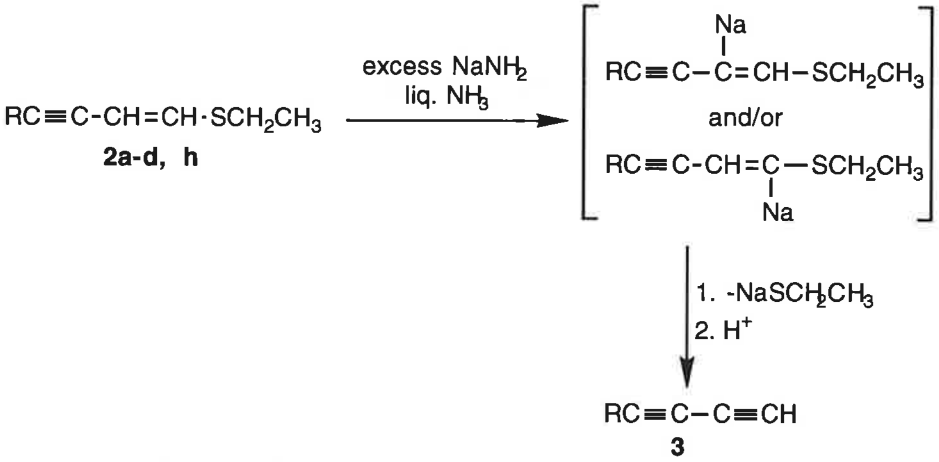
Table 2: Results of functionalizations *via* palladium catalyzed reactions.

compound	R	yield (%)
2e		93
2f		90
2g		80
2h		70
2i		77
2j		74

All of the above mentioned functionalized enyne sulfides are stable over long times, when kept in the refrigerator.

Preparation of conjugated diynes 3.

Diynes can easily be obtained in one step from the functionalized enyne sulfide by treatment with the strong base sodium amide in liquid ammonia:



Scheme 13: Synthesis of diynes.

Table 3: Yields of elimination reaction.

compound	**3a**	**3b**	**3c**	**3d**	**3h**
yield (%)	85	95	80	80	60

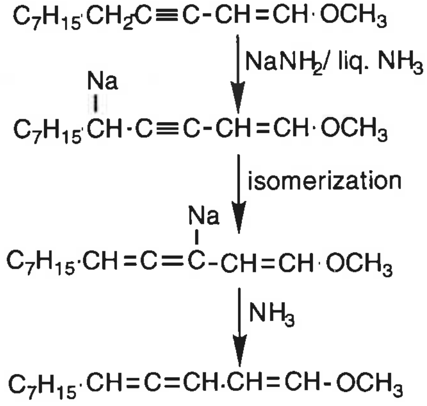
Since compound **2** consisted for ~ 90% of the *cis* isomer, it may be assumed that the greater part of the diyne is formed by the normal *trans*-1,2-elimination, i.e. simultaneous removal of the SCH_2CH_3 group and the proton that is in the β-position to this group. A minor process might be the formation of an α-metallated species, leaving of the SCH_2CH_3 group and rearrangement of the carbene RC≡C-CH=C: to RC≡C-C≡CH.[5]

With bases other than sodium amide the results were less satisfactory. With lithium di*iso*-propylamide (LDA) in THF at -60°C the elimination proceeded more slowly than with sodium amide in liquid ammonia at -33°C. *n*-Butyllithium is not suitable as it adds across the unsaturated system.

Comparison of the enyne thioether with the analogous enyne ether showed that the former is more suitable for the synthesis of **3**:

i) treatment of the coupling product from *cis*-HC≡C-CH=CH-OCH_3 and cyclohexanone with sodium amide in liquid ammonia resulted only in the partial conversion into the *trans* isomer: a 50/50 mixture of the *cis* and *trans* isomers was obtained. Metallation of the vinylic system followed by protonation by ammonia may account for this result.

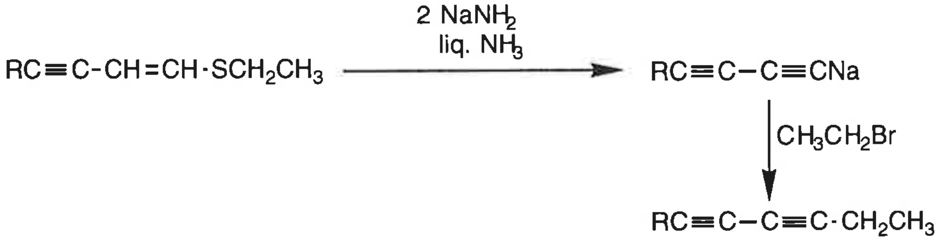
ii) the octyl derivative *cis*-C_8H_{17}C≡C-CH=CH-OCH_3 gave an allenic ether and much of an undistillable product upon treatment with sodium amide in liquid ammonia. The formation of the allenic ether can be explained by the presence of propargylic protons being susceptible for base catalyzed isomerization into an allene:



Scheme 14: Formation of allene from enyne ether.

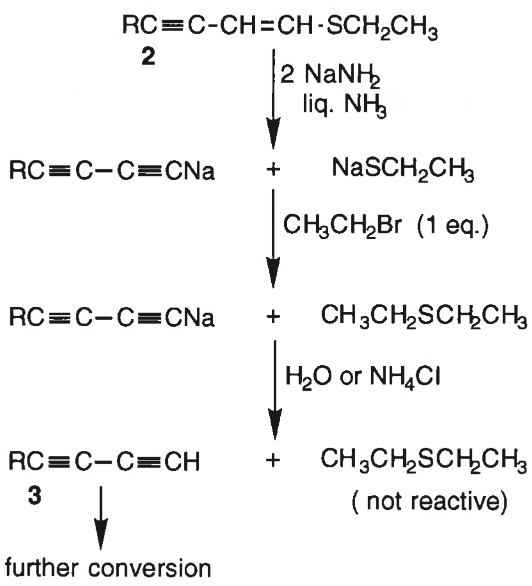
The differences in results of the enyne ether and enyne thioether can be explained by assuming a more facile elimination of the less basic $NaSCH_2CH_3$ compared to $NaOCH_3$ upon treatment with sodium amide in liquid ammonia.[6,7]

A number of products were obtained by the usual procedure of work-up. Especially the diynes **3** with R= aryl or hetaryl were extremely unstable and the crude products (obtained after removal of the solvent) very soon turned black upon standing at room temperature. Attempts to distill them often resulted in an explosive decomposition.[8] For this reason functionalization of the sodium derivative with an excess of alkyl bromide was carried out.[9]



Scheme 15: *In situ* functionalization of diynes.

It is, in principle, also possible to use the etheral extract of the 1,3-diynes **3**, obtained after protonation of the sodium compounds, for further syntheses. However, after protonation with water or ammonium chloride, readdition of thiolate to **3** may occur during the work-up. It is therefore advisable to "neutralize" the thiolate selectively by addition of a reagent that does not easily react with the metallated diyne. Controlled addition of *one equivalent* of an alkyl bromide to the reaction mixture may be considered.



Scheme 16: Procedure for the obtention of etheral solutions of terminal diynes.

The extract obtained then also contains diethyl sulfide, a compound which is not reactive during further syntheses with the diyne.

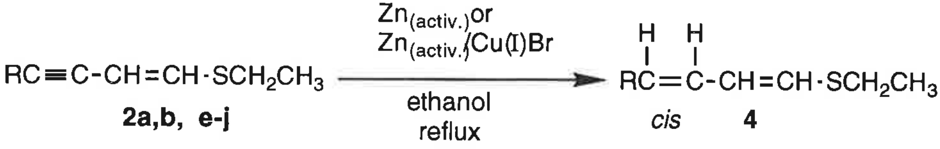
Preparation of enynes.

The synthesis of enynes comprises two steps. First the triple bond of the functionalized enyne sulfide **2** is selectively reduced to a double bond after which the resulting diene sulfide **3** is treated with a strong base, yielding the enyne **4**.

The reduction of the triple bond, synthesis of dienes 3.

As the functionalized enyne contains various groups that are susceptible to reduction the reductive system has to be chosen carefully so that only the triple bond is reduced. The systems zinc/ethanol and zinc/Cu(I)Br/ethanol proved to be suitable for this purpose.[4,10] These reductive systems selectively transform the triple bond to a *cis* double bond.

As the reaction most probably takes place at the surface of the zinc it has to be activated prior to use.[11] This can be most easily done by addition of some 1,2-dibromoethane to the zinc/ethanol mixture. If necessary, addition of copper(I) bromide to the activated zinc can be carried out in order to enhance the efficiency of the reductive system.



Scheme 17: Reduction of enyne sulfides.

Table 4: Results of reduction.

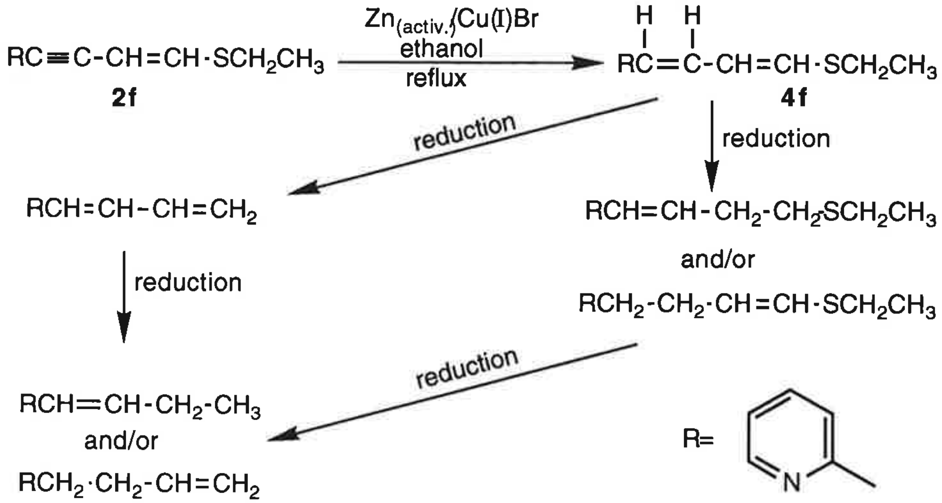
starting material	substituent	reductive system[a]	product[b]	yield (%)
2a	octyl	Zn	-	0[c]
2a	octyl	Zn/Cu(I)Br	**4a**	80
2b	1-cyclohexyl-1-ol	Zn/Cu(I)Br	**4b**	~70[d]
2e	phenyl	Zn	-	0[c]
2e	phenyl	Zn/Cu(I)Br	**4e**	80
2f	2-pyridyl	Zn	**4f**	77
2f	2-pyridyl	Zn/Cu(I)Br	mixture[e]	-
2g	3-pyridyl	Zn	-	0[c]
2g	3-pyridyl	Zn/Cu(I)Br	**4g**	79
2h	2-thienyl	Zn	**4h**	89
2i	3-thienyl	Zn	-	0[c]
2i	3-thienyl	Zn/Cu(I)Br	**4i**	71
2j	2-furyl	Zn	**4j**	94

[a] In refluxing ethanol. [b] The new vinylic bond: *cis/trans* = 100/0. [c] Starting material recovered. [d] Yield of crude product, which was pure however. The product decomposed during distillation. [e] The mixture was shown to consist of the compounds depicted in scheme 18 by GC-MS analysis on a Kratos MS80 GC-MS combination.

The choise of reductive system proved to be decisive for the outcome of the reduction. For starting compounds with a heteroatom in the β-position (i.e. **2f**, **2h** and **2j**) the system zinc/ethanol proved to be effective. For the other enynes further activation of the zinc was necessary.[12] Zinc metal is highly activated by addition of copper(I) (the well known zinc/copper couple is *in situ* formed). Furthermore, copper(I) coordinates to triple bonds, thus activating them towards reduction.

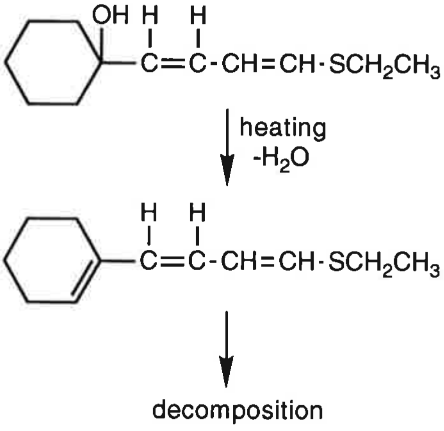
The reduction of the triple bond probably proceeds at the zinc surface. Whereas most reactions were completed in a few hours, the reduction of the octyl substituted enyne sulfide **2a** required prolonged reaction times (~ 6 hours), possibly caused by less strong adsorption.

The reduction of the 2-pyridyl substituted enyne sulfide **2f** with zinc proceeded very efficiently. When, however, this enyne was treated with with zinc/copper(I) bromide further reduction occurred, see scheme 18. The activating effect of the 2-pyridyl group towards reduction, combined with the highly reactive reductive system, can possibly account for this result.



Scheme 18: Side reactions occurring when **2f** was treated with a too active reductive system.

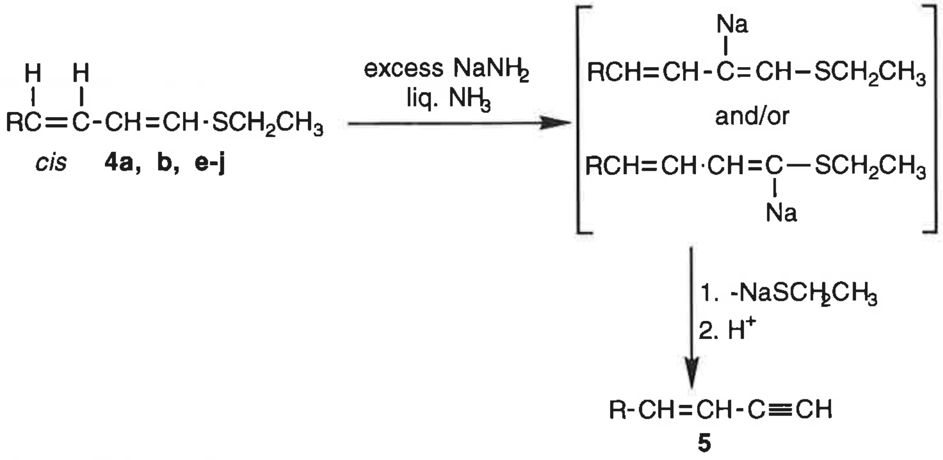
The product obtained after reduction of the hydroxycyclohexyl substituted enyne sulfide **2b** proved to be unstable under the conditions of distillation, possibly water was split off during distillation (see scheme 19). The crude product, after work-up, was sufficiently pure, however, to be used for further reactions. As we expected the same problems for **2c** and **2d**, the reduction was not carried out with these enynes.



Scheme 19: Possible mechanism of decomposition of **4b**.

The elimination reaction from dienes, preparation of **5**.

The diene sulfide was subsequently treated with the strong base sodium amide in liquid ammonia, which resulted in elimination of sodium ethanethiolate with formation of an enyne:



Scheme 20: Formation of enynes.

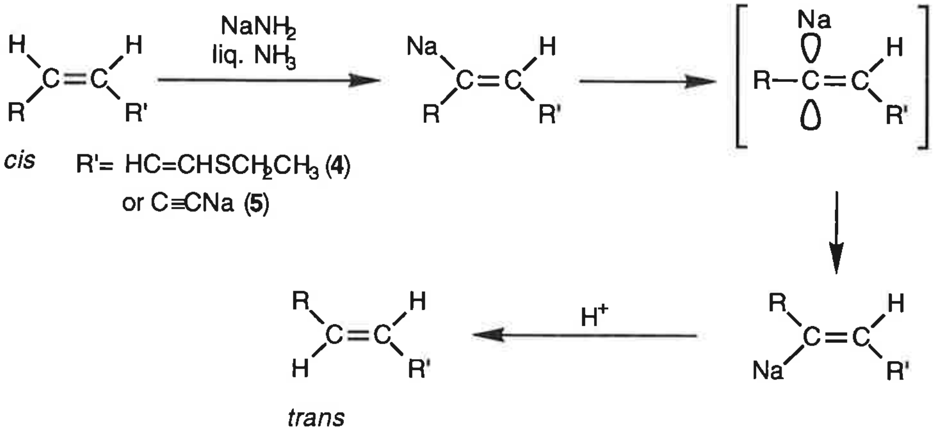
Table 5: Results of the elimination reaction.

compound	yield (%)	*cis/trans*
5a	0[a]	-
5b	0[b]	-
5e	72	~97/3
5f	54	0/100
5g	63	~97/3
5h	66	85/15
5i	65	~97/3
5j	71	~97/3

[a] No elimination occurred, but the product isomerized instead.

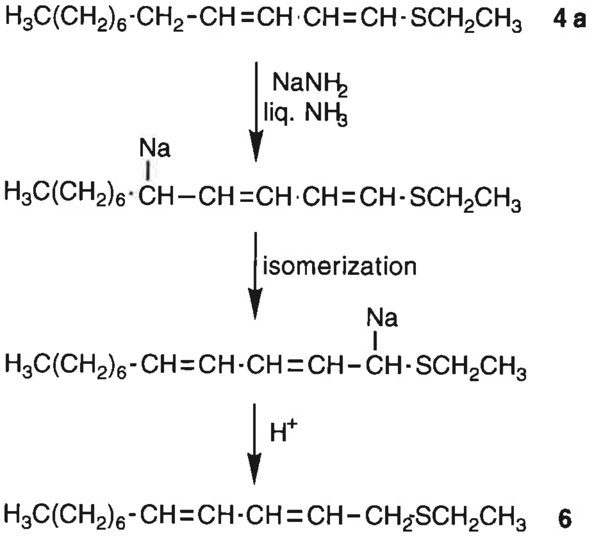
[b] Starting material recovered.

In some cases the elimination reaction afforded not only the expected *cis*-enyne, but also a certain amount of the *trans* isomer. In the case of the 2-pyridyl derivative **5f** only the *trans* isomer was obtained. The *trans*-enynes may be formed either through a *cis* to *trans* isomerization in the diene compound or after the elimination has taken place, so by an isomerization in the enyne.[13,14] As the isomerization presumably is base-induced, this process might be facilitated when acidifying substituents (R in the scheme below) are present, such as 2-pyridyl and 2-thienyl:



Scheme 21: Isomerization of a metallated vinylic system (all reactions are reversible).

The octyl substituted compound **4a** showed a different kind of base-induced isomerization. After treatment with base a mixture of starting material **4a** and isomerized product **6** was obtained (ratio ~ 1:1). The reactions leading to the formation of **6** are shown in the following scheme.



Scheme 22: Base induced isomerization of **4a.**

The same isomerizations took place when using lithium di-*iso*-propylamide in THF.[15]

The hydroxycyclohexyl compound **4b** remained unchanged during treatment with sodium amide, possibly the metallation of the relatively acidic hydroxyl group causes deactivation of the compound towards metallation of the vinylic system.

Experimental methods

General conditions.

Functionalization reactions were performed under an inert nitrogen atmosphere. Solvents were dried before use. All products were isolated by distillation and analyzed by NMR spectroscopy and GLC. ^1H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^1H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn. The purity of all compounds was higher than 96%.

Preparation of sodium amide for elimination reactions.

Sodium amide (0.4 mol) was prepared from 9.2 g (0.4 mol) of sodium in 500 mL of liquid ammonia as described by Brandsma.[16]

Preparation of starting material (1).

Preparation of 1,4-dichlorobutyne.

1,4-Dichlorobutyne was obtained from the 1,4-diol as described by Brandsma.[2]

Preparation of enyne thioether (1).

In a 3 L three-necked round-bottomed flask, equipped with a mechanical stirrer and a dropping funnel, a suspension of 1.5 mol of sodium amide in 2 L of liquid ammonia was prepared. To this suspension was added dropwise over 20 minutes 62 g (0.5 mol) of 1,4-dichlorobutyne. After an additional 10 minutes 34 g (0.55 mol) of freshly distilled ethanethiol was added with vigorous stirring over a period of 25 minutes. 10 Minutes after this addition 50 g of powdered ammonium chloride was added in small portions over 20 minutes with stirring at a moderate rate. After this addition tubes were placed on the flask and the mixture was stirred very vigorously for 5 minutes. The mixture was allowed to stand for 2 to 3 hours (the flask was placed in a water bath of ~ 25°C in order to allow the major part of the ammonia to evaporate). Diethyl ether (300 mL) was added and 300 g of crushed ice was then gradually introduced with stirring. The brown upper layer was separated, after which the water layer was extracted three times with diethyl ether. The combined organic fractions were washed with water and dried over magnesium sulfate. The greater part of the diethyl ether was distilled off at normal pressure through a 40 cm Vigreux column in a nitrogen atmosphere. The bath temperature was kept below 100°C. The residue was distilled in vacuo. The enyne thioether (**1**) (cis/trans= 90/10) was obtained in 89% yield (50 g), bp. 64°C (12 mm Hg). The compound was stored in the refigerator.

Typical functionalization via metallation, preparation of 2a-d.

In a 250 mL three-necked round-bottomed flask equipped with a thermometer-gas inlet combination, mechanical stirrer and dropping funnel-gas outlet combination was placed a mixture of 11.2 g (0.10 mol) of 1 and 70 mL of THF. The mixture was stirred and cooled to -70°C. Subsequently 66 mL of a 1.6 M solution (0.10 mol) of n-butyllithium in hexane was added carefully. After a few minutes 0.11 mol of an electrophile was added at -70°C. Alkylation reactions required the assitance of HMPT (~ 40 mL). The temperature of the well stirred mixture was allowed to rise to -20°C after which 100 mL of water was added. (In the case of alkylations the temperature of the mixture was allowed to rise to 10°C and stirring continued for half an hour.) The layers were separated and the water layer was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate and subsequently concentrated *in vacuo*. Distillation of the remaining liquid gave the functionalized enyne sulfide (**2**).

Table 6: Yields and properties of compounds 2.

comp.	substituent	yield (%)	bp. (°C/mm Hg)	typical ^{1}H-NMR data δ (ppm)(*J* (Hz))
2a	octyl	85	155/1	5.45 (dt, 9.7, 2.2); 6.33 (d, 9.7)
2b	1-cyclohex.-1-ol	85	150/1	5.45 (d, 9.8); 6.42 (d, 9.8)
2c	1,1-dimethyl-1-ol	85	130/1	1.49 (s); 5.42 (d, 9.8); 6.41 (d, 9.8)
2d	1-*tert*butyl-1-ol	85	145/1	0.99 (s); 4.14 (d, 1.7); 5.48 (dd, 9.8, 1.8); 6.46 (d, 9.8)

Typical functionalization *via* paladium catalyzed reaction, preparation of 2e-j.

Catalytic system $PdCl_2(PPh_3)_2$, PPh_3, *CuI, triethylamine.*

In a 250 mL three-necked round-bottomed flask equipped with a thermometer-gas inlet combination, mechanical stirrer and reflux condenser-gas outlet combination was placed a mixture of 100 mL of dry triethylamine, 11.2 g (0.10 mol) of enyne sulfide, 0.10 mol of the (hetero)aromatic bromide or iodide, 0.5 g of dichloride-bis(triphenylphosphine) palladium, 0.6 g of triphenylphosphine and 0.4 g of finely powdered copper(I) iodide. The mixture was stirred and heated. At a temperature between 80 and 90°C an exothermic reaction started. When the reaction had ceased the mixture was heated under reflux for an additional 15 minutes. To the mixture was added 100 mL of water and 100 mL of pentane. After separation of the layers the water layer was extracted three times with pentane. The combined organic layers were washed twice with a saturated aqueous ammonium chloride solution. The organic layer was dried over magnesium sulfate (in the case of nitrogen containing compounds potassium carbonate was used) after which it was concentrated *in vacuo*. Distillation of the remaining liquid gave the functionalized enyne sulfide (**2**).

Catalytic system $Pd(Ph_2PCH_2CH_2PPh_2)_2$, *CuI, triethylamine.*

In the flask were placed 100 mL of triethylamine, 0.10 mol of enyne sulfide, 0.10 mol of the (hetero)aromatic bromide or iodide, 0.5 g of $(dppe)_2Pd$ (dppe= diphenylphosphinoethane) and 0.4 g of copper(I) iodide. The further operations were carried out as described above.

The results of the coupling reactions are shown in table 7.

The presence of small amouts of palladium during distillation can give rise to decomposition of the product. Part of the Pd-rests precipitate upon addition of pentane. The remaining traces can be removed by filtering the extract through a layer of neutral Al_2O_3 (3 cm thickness).

Table 7: Yields and properties of compounds 2.

comp.	substituent	yield (%)	bp. (°C/mm Hg)	typical ^{1}H-NMR data δ (ppm)(*J* (Hz))
2e	phenyl	93	120/0.5	6.57 (d, 9.9); 5.73 (d, 9.8)
2f	2-pyridyl	90	140/0.5	6.53 (d, 9.9); 5.68 (d, 9.9)
2g	3-pyridyl	80	160/1	6.44 (d, 9.9); 5.50 (d, 9.9)
2h	2-thienyl	70	125/0.5	6.57 (d, 9.9); 5.72 (d, 9.9)
2i	3-thienyl	77	125/0.5	6.54 (d, 9.9); 5.70 (d, 9.9)
2j	2-furyl	74	110/0.5	6.59 (d, 10.0); 5.68 (d, 10.0)

Typical elimination reaction yielding a diyne.

To a vigorously stirred suspension of 0.40 mol of sodium amide in 500 mL of liquid ammonia in a 1 L three-necked round-bottomed flask, equipped with a mechanical stirrer, was added over some minutes 0.10 mol of functionalized enyne sulfide (**2**) in 50 mL of THF. The mixture was stirred for an additional period (usually ~ 2 hours) until GC showed that the conversion was complete. Subsequently 150 mL of diethyl ether was added and the ammonia was allowed to evaporate (in the last stage of the evaporation the flask was placed in a water bath of about 40°C). To the mixture was added 250 mL of an aqueous solution of ammonium chloride. Work-up was performed as described above. The results of the elimination and properties of **3** are shown in table 8.

Table 8: Yields and properties of compounds **3**.

comp.	substituent	yield (%)	bp. (°C/mm Hg)	typical ^{1}H-NMR data δ (ppm)(*J* (Hz))
3a	octyl	85	95/1	1.93 (s)
3b	1-cyclohex.-1-ol	85	90/1	2.18 (s)
3c	1,1-dimethyl-1-ol	80	75/1	1.44 (s); 1.80 (s)
3d	1-*tert*butyl-1-ol	80	85/1	0.95 (s); 2.16 (d, 1.0); 3.99 (b)
3h	2-thienyl	50	70/1	2.50 (s)[a]

[a] Recorded on a Varian EM90 in tetrachloromethane with tetramethylsilane as internal standard (^{1}H-NMR: 90 MHz).

Typical reduction yielding a diene.

Reduction with zinc/ethanol.

In a 250 mL three-necked round-bottomed flask equipped with a reflux condenser and magnetic stirring bar was placed a mixture of 25 g of analytically pure zinc powder (particle size < 60 μm) and 120 mL of ethanol. Subsequently a few mL of 1,2-dibromoethane were added and the suspension was heated to 50°C. After a few minutes an exothermic reaction started, causing refluxing of the ethanol and evolution of gas (ethene). When this reaction had subsided the mixture was cooled to about 40°C and a mixture of 0.10 mol of the enyne (**2**) and 25 mL of THF was added in one portion. The mixture was heated under reflux until GC showed that the conversion was completed (usually 1 hour). The clear upper layer was decanted into 250 mL of an aqueous saturated ammonium chloride solution. The remaining zinc was rinsed twice with small portions of ethanol and twice with diethyl ether, these portions were added to the water/ethanol layer. To this mixture was added 150 mL of diethyl ether after which the layers were separated. The water layer was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate (in the case of nitrogen containing enynes potassium carbonate was used). The solution was concentrated *in vacuo*. Distillation of the remaining liquid gave the enyne (**4**). Results and properties are shown in table 9.

Reduction with zinc/Cu(I)Br/ethanol.

The reaction was performed as described above. After activation of the zinc powder with 1,2-dibromoethane a mixture of 3 g of Cu(I)Br, 4 g of LiBr and 40 mL of THF was added in one portion at about 40°C. Subsequently the enyne (**2**) was added. Results and properties are shown in table 9.

The presence of small amouts of zinc during distillation can give rise to decomposition of the product. The zinc traces can be removed by filtering the extract.

Table 9: Yields and properties of compounds **4**.[a]

comp.	substituent	reductive system	yield (%)	bp. (°C/mm Hg)
4a	octyl	Zn/Cu(I)Br	80	135/1
4b	1-cyclohexyl-1-ol	Zn/Cu(I)Br	~ 70	-[b]
4e	phenyl	Zn/Cu(I)Br	80	135/1
4f	2-pyridyl	Zn	77	160/1
4g	3-pyridyl	Zn/Cu(I)Br	79	150/1
4h	2-thienyl	Zn	89	120/0.5
4i	3-thienyl	Zn/Cu(I)Br	71	150/1
4j	2-furyl	Zn	94	120/1

[a] All products were pure. NMR-spectra were in accordance with the assumed structure. A complicated pattern of signals was present. [b] Yield of crude product, which was pure. This crude product was used for further reactions. The product was not distilled as product decomposed upon heating.

Typical elimination reaction yielding an enyne.

To a vigorously stirred suspension of 0.40 mol of sodium amide in 500 mL of liquid ammonia in a 1L three-necked round-bottomed flask, equipped with a mechanical stirrer, was added over a few minutes 0.10 mol of functionalized diene sulfide (**4**) in 50 mL of THF. The mixture was stirred until GC showed that the conversion was completed (usually in ~ 2 hours). Subsequently 150 mL of diethyl ether was added and the ammonia was allowed to evaporate (in the last stage of the evaporation the flask was placed in a water bath of about 40°C). To the mixture was added 250 mL of an aqueous solution of ammonium chloride. Work-up was performed as described above.

Table 10: Yields and properties of compounds **5**.

comp.	substituent	yield (%)	bp. (°C/mm Hg)	*cis/trans*	typical ^{1}H-NMR data of main isomer δ (ppm)(*J* (Hz))
5a	octyl	0[a]	-	-	-
5b	1-cyclohexyl-1-ol	0[b]	-	-	-
5e	phenyl	72	60/1	~ 97/3	6.80 (d, 12.1); 5.79 (dd, 12.1, 2.7); 3.46 (dd, 2.7, 1.0)
5f	2-pyridyl	54	80/1	0/100	6.95 (d, 16.0); 6.65 (dd, 16.0, 2.4); 3.12 (dd, 2.4, 0.6)
5g	3-pyridyl	63	90/1	~ 97/3	6.58 (d, 12.0); 5.71 (dd, 12.0, 2.7); 3.37 (dd, 2.7, 1.0)
5h	2-thienyl	66	70/1	85/15	6.97 (d, 11.6); 5.58 (dd, 11.5, 2.6); 3.61 (dd, 2.7, 0.9)
5i	3-thienyl	65	65/1	~ 97/3	6.79 (d, 11.8); 5.64 (dd, 11.8, 2.7); 3.45 (dd, 2.6, 1.0)
5j	2-furyl	71	40/1	~ 97/3	6.69 (d, 11.6); 5.52 (ddd, 12.0, 2.5, 0.3); 3.49 (dd, 2.6, 1.0)

[a] No **5a** was obtained, instead a mixture of **4a** and isomerized product **6** was found (ratio ~ 1:1). **6**: typical ^{1}H-NMR data: δ = 3.16 (bd, $CH_2SCH_2CH_3$, *J*= 7.2 Hz, 2H). [b] No reaction, the starting material was recovered.

References

1 General methods: Shostakovskii, M. F.; Bogdanova, A. V. *The Chemistry of Diacetylenes* John Wiley & Sons, New York (1974); *Houben-Weyl Methoden der Organischen Chemie* Band V/1d (offenkettige und cyclische polyene, en- ine); Band V/2a (alkine, di- und polyine, allene, kumulene) 4^{e} Auflage, Georg Thieme Verlag, Stuttgart (1972).

2 Brandsma, L. *Preparative Acetylenic Chemistry* Elsevier, Amsterdam (1971).

3 Transition-metal catalyzed synthesis of enynes: King, A. O.; Okukado, N.; Negishi, E-I. *J. Chem. Soc., Chem. Commun.* (1977) 683; Negishi, E-I.; Okukado, N.; King, A. O.; van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **100** (1978) 2254; Ohshita, J.; Furumori, K.; Matsuguchi, A.; Ishikawa, M. *J. Org. Chem.* **55** (1990) 3277; Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **32** (1991) 6109.

4 Aerssens, M. H. P. J.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* (1984) 735.

5 Soderquist, J. A.; Hsu, G. J-H. *Organometallics* **1** (1982) 830.

6 In literature the elimination LiOR from intermediary β-lithiated vinyl ethers, with the formation of a triple bond, has been described: Kooyman, J. G. A.; Hendriks, H. P. G.; Montijn, P. P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **87** (1968) 69; Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **43** (1978) 1595; Zweifel, G.; Rajagopalan, S. *J. Am. Chem. Soc.* **107** (1985) 700; Stracker, E. C.; Zweifel, G. *Tetrahedron Lett.* **31** (1990) 6815

7 pK_a (CH_3OH)= 16, pK_a (CH_3SH)= 11 (in water). March, J. *Advanced Organic Chemistry 3rd ed.* John Wiley and Sons, New York (1985).

8 For example, after distillation of a few grams of 2-butadiynal-thiophene the product spontaneously exploded violently after standing at room temperature for a few minutes.

9 Excess alkyl bromide should be added in order to destroy all organometal species (included sodium amide), otherwise metallation of the alkylated product and subsequent isomerization results in the formation of by-products.

10 Although these systems are described as reductive systems of acetylenic groups in literature, their use has been limited. Zn: Morris, S. G.; Herb, S. F.; Magidman, P.; Luddy, F. E.; *J. Am. Chem. Soc.* **49** (1972) 92; Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **60** (1077) 48. Zn/Cu(I)Br: LeGoff, E.; *J. Org. Chem.* **29** (1964) 2048; Sondengam, B. L.; Charles, G.; Akam, T. M.; *Tetrahedron Lett.* **21** (1980) 1069. See also: Clarke, A. J.; Crombie, L. *Chem. Ind.* (1957) 143; Morris, S. G.; Magidman, P.; Herb, S. F. *J. Am. Oil Chem. Soc.* **49** (1972) 505. See also ref[3], Houben-Weyl. The scope and limitations of the use of this reductive system in reductions of unsaturated systems has been investigated in our laboratory: see ref[4].

11 Näff, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **58** (1975) 101.

12 Even the type of zinc used can be of influence upon results. For example Zink Staub (Merck, korngroβe < 60 μm) proved to be more reactive than Zink Pulver (Merck, korngroβe < 60 μm), possibly as a result of differences in particle size.

13 See chapter 1.

14 Knorr, R.; Lattke, E. *Tetrahedron Lett.* **45** (1977) 3969; Panek, E. J.; Neff, B. L.; Chu, H.; Panek, M. G. *J. Am. Chem. Soc.* **97** (1975) 3996; Bauer, W.; Feigel, M.; Müller, G.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **110** (1988) 6033.For other exaples of isomerizations of vinylic systems: Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **108** (1986) 3402; Mulvaney, J. E.; Carr, L. J. *J. Org. Chem.* **33** (1968) 3286; Kessler, H. *Tetrahedron* **30** (1974) 1861; Bauer, W.; Feigel, M.; Müller, G.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **110** (1988) 6033.

15 As LDA in THF is a weaker base then sodium amide in liquid ammonia the elimination reaction with the former was much slower.

16 Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag, Heidelberg (1987).

Chapter 3

The Generation of *ortho*-Potassiofluorobenzene and Its Functionalization

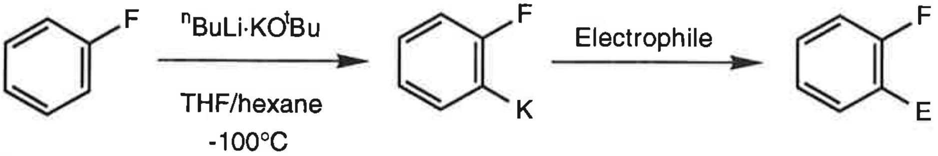
Reactions of Other Halobenzenes with Super Base Mixtures

Results and discussion

The generation and functionalization of *ortho*-metallated fluorobenzene.

Fluorobenzene has been metallated for the first time by Gilman *et al.* in 1957 using a solution of *n*-butyllithium in neat THF. After a period of seven hours at -50°C the metallation mixture was carboxylated to give 2-fluorobenzoic acid in a reasonable yield.[1]

In this chapter we show that a very quick metallation of fluorobenzene can be achieved at -100°C with the superbase combination $^{n}BuLi\cdot KO^{t}Bu$ in a mixture of THF and hexane. The high efficiency of this metallation appears from the excellent results obtained by quenching the metallation mixtures with dimethyl disulfide, chlorotrimethylsilane, dimethylformamide and iodine. Introduction of a primary alkyl group is possible, but this reaction proceeds only smoothly in the presence of HMPT. It allows the alkylations with alkyl bromides (and iodides) to be completed in a relatively short time at temperatures below -70°C (at higher temperatures *o*-potassiofluorobenzene eliminates potassium fluoride with formation of the highly reactive benzyne).[2]



Scheme 1: Metallation and functionalization of fluorobenzene.

The metallation of fluorobenzene can be carried out in three different ways all giving the same results:[3]

a) Dropwise addition of a 50% molar excess of fluorobenzene to a strongly cooled mixture of $^{n}BuLi$ and $KO^{t}Bu$ in THF/hexane.

b) Dropwise addition of a solution of $^{n}BuLi$ in hexane to a strongly cooled mixture of fluorobenzene (≤ 50% excess), $KO^{t}Bu$ and THF.

c) Dropwise addition of a solution of $KO^{t}Bu$ in THF to a strongly cooled mixture of fluorobenzene (≤ 50% excess), $^{n}BuLi$ and hexane.

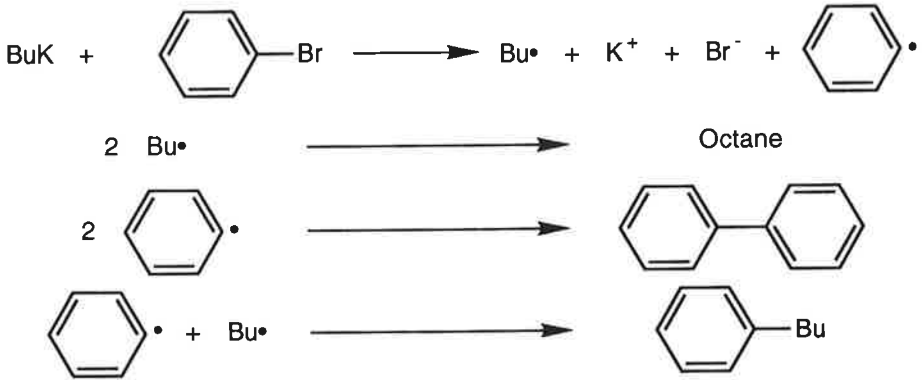
The metallation is extremely fast. Since, in view of the low stability of the arynoïd, temperature control is important, methods b and c are preferred over a. Method c is most convenient for experimental reasons, as the solution of $^{n}BuLi$ needs not be transferred into the dropping funnel.

The reaction of other halobenzenes with superbases.

The other halobenzenes showed a totally different behaviour towards the superbase mixtures $^{n}BuLi\cdot NaO^{t}Bu$ and $^{n}BuLi\cdot KO^{t}Bu$.

Chlorobenzene proved to be much less reactive towards superbase mixtures. When we treated chlorobenzene with $^{n}BuLi\cdot KO^{t}Bu$ in THF/hexane at -100°C and subsequently quenched the metallation mixture with dimethyl disulfide, mainly chlorobenzene was recovered. Traces of methylthiobenzene and *ortho*-(methylthio)-n-butylbenzene were found. Methylthiobenzene is presumably formed by halogen-metal exchange and subsequent reaction with dimethyl disulfide. The other product may be considered as the result of elimination of potassium chloride from *ortho*-potassio-chlorobenzene, addition of butylpotassium to the intermediate benzyne and successive reaction with dimethyl disulfide. Neither *meta*- nor *para*-functionalized chlorobenzene was found. Similar results were obtained when we used other superbase mixtures in THF/hexane, such as ^{n}BuLi·NaO^{t}Bu, ^{n}BuLi·CsO^{t}Bu, ^{n}BuLi·3KO^{t}Bu, ^{t}BuLi·KO^{t}Bu, ^{t}BuLi, LDA·KO^{t}Bu and ^{n}BuLi·KO^{t}Bu·TMEDA in hexane.[4] Obviously fluorine is a superior *ortho* director compared to chlorine. However, chlorine does have some *ortho* directing properties, which is shown in the metallation of *m*-dichlorobenzene. This compound was selectively metallated in good yield at the 2-position with ^{n}BuLi or ^{n}BuLi·KO^{t}Bu in THF/hexane at -70°C.[5] Also the fact that after treatment of chlorobenzene with superbase mixtures traces of products arising from a benzyne mechanism are found shows that (some) *ortho*-metallated chlorobenzene is formed initially.

Bromobenzene reacts with *n*-butyllithium in THF to give phenyllithium in high yield. This halogen-metal exchange reaction proceeds fast even at temperatures in the region of -80°C. After quenching with dimethyl disulfide methylthiobenzene can be obtained in almost quantitative yield. Treatment of bromobenzene with ^{n}BuLi·NaO^{t}Bu in THF/hexane at -100°C, followed by quenching with dimethyl disulfide also gave methylthiobenzene in good yield. Traces of biphenyl and octane were found. After reaction with ^{n}BuLi·KO^{t}Bu, however, under the same conditions large amounts of biphenyl and octane were obtained in addition to methylthiobenzene and traces of n-butylbenzene. No *o*-(methylthio)bromobenzene or products arising from a benzyne decomposition reaction were found. We assume that biphenyl, n-butylbenzene and octane are formed *via* a single electron transfer (SET) mechanism, as depicted in scheme 2:



Scheme 2: SET and coupling reactions involving butylpotassium and bromobenzene.

Iodobenzene reacts with *n*-butyllithium even faster than bromobenzene. Phenyllithium is formed in near quantitative yield within a few minutes in THF/hexane at -80°C. When iodobenzene was treated with $^{n}BuLi{\cdot}NaO^{t}Bu$ or $^{n}BuLi{\cdot}KO^{t}Bu$ large amounts of biphenyl and octane, besides traces of methylthiobenzene and n-butylbenzene, were obtained after quenching with dimethyl disulfide. We showed that biphenyl is not formed *via* reaction between phenylpotassium and unreacted iodobenzene. When 1 molar equivalent of iodobenzene was added to phenylpotassium in THF/hexane at -80°C no biphenyl was formed at all.[6] Instead we observed the formation of a yellow suspension in THF. An ate complex $[\phi\text{-I-}\phi]^{-}\ K^{+}$ might have been formed, similar to the complex $[\phi\text{-I-}\phi]^{-}\ Li^{+}$ found by Reich *et al.* who studied this complex during their investigations on the halogen-lithium exchange reaction.[7] After quenching the mixture with dimethyl disulfide we obtained equal amounts of iodobenzene and methylthiobenzene, both in good yield.

The different results obtained with the various halobenzenes and superbase mixtures can be explained taking into account the following:

i) the *ortho* directing properties of the halogens. These diminish in the order F > Cl > Br > I, due to the decreasing electronegativity of the halogen in this order. More electronegative substituents will polarize the *o*-carbon-hydrogen bond to a greater extend, thus activating it for deprotonation. Furthermore, after deprotonation the negatively charged carbon atom will be stabilized better by a more electronegative *o*-substituent.

ii) the strenght of the carbon-halogen bond, which decreases in the order C-F > C-Cl > C-Br > C-I.

iii) the ease of reduction of the carbon-halogen bond, decreasing in the order C-I > C-Br > C-Cl > C-F.[8] The amount of "radical products" (i.e. biphenyl, octane, n-butylbenzene) found in the reactions performed also decreases in this order.

iv) the polarity (and reactivity) of the carbon-metal bond, which decreases in the order C-K > C-Na > C-Li, due to decreasing electropositivity and atom radius of the alkali metal in this order. The amount of "radical products" obtained in the reactions with the various halobenzenes decreases in the order $^{n}BuK > {}^{n}BuNa > {}^{n}BuLi$, which corresponds well with Bordwell's rule, which states that "*the more strongly basic the carbanion the greater the likelihood that it will react by an electron-transfer pathway rather than an S_N2 pathway*".[9]

Experimental methods

All reactions were performed under an inert nitrogen atmosphere. Solvents were dried before use. *n*-Butyllithium and heavier alkali metal alkoxides were obtained commercially. All products are known compounds (see ref [2] and the catalogues of Aldrich and Janssen Chimica), the purity of the products was greater than 99%. Products were analyzed with NMR spectroscopy and by GLC. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

Metallation of fluorobenzene (method c).

A 1 L round-bottomed flask with vertical necks was equipped with a dropping funnel-gas inlet combination, mechanical strirrer and thermometer-gas outlet combination. A mixture of 28.8 g (0.30 mol) of fluorobenzene and 120 mL of THF was placed in the flask. The mixture was cooled to below -80°C, then 131 mL of a 1.6 M solution (0.21 mol) of *n*-butyllithium in hexane was added in a few minutes with efficient stirring, while maintaining the temperature below -70°C (applying *occasional* cooling with a bath of liquid nitrogen, care being taken that the solution did not solidify on the bottom of the flask). The dropping funnel was charged with a solution of 23.5 g (0.21 mol) of KO^tBu in 60 mL of THF. This solution was added over 15 minutes with efficient stirring (splashing of the metallation mixture on the upper part of the wall of the flask has to be avoided to prevent decomposition), while keeping the temperature between -95 and -105°C. After an additional 10 minutes the clear, light brown or almost colorless solution, was ready for functionalization reactions.

Functionalization reactions.

Alkylation with bromohexane.

To the metallation mixture was added over a few minutes 33.0 g (0.20 mol) of 1-bromohexane while maintaining the temperature around -100°C. Subsequently a mixture of 40 mL of purified HMPT (hexamethyl phosphoric triamide)[2] and 30 mL of THF was added over 10 minutes with efficient stirring and maintaining a temperature range of -85 to -90°C. The mixture was stirred for 1 hour at -85°C, then the cooling bath was removed and the temperature allowed to rise to -40°C. Water (200 mL) was added with vigorous stirring. After separation of the layers, the aqueous layer was extracted three times with 50 mL portions of pentane. The combined organic solutions were washed four times with water to remove the HMPT and were subsequently dried over magnesium sulfate and concentrated *in vacuo*. The remaining liquid was carefully distilled through an efficient column to give *o*-hexyl-fluorobenzene in *ca.* 90% yield, bp. 98°C (12 mm Hg).

Reaction with chlorotrimethylsilane and dimethyl disulfide.

Freshly distilled (from a small amount of N,N-diethylaniline) chloro-trimethylsilane 24.0g (0.22 mol) or 20.8 g (0.22 mol, diluted with 50 mL of diethyl ether) of dimethyl disulfide was added dropwise over 10 minutes with efficient stirring while maintaining the temperature of the reaction mixture between -90 and -100°C. After the addition the cooling bath was removed and the temperature allowed to rise to -40°C. Water (200 mL) was added, the layers separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with water and then dried over magnesium sulfate. The liquid remaining after removal of the solvent under reduced pressure was carefully distilled to give 2-trimethylsilyl-fluorobenzene, bp 60°C (15 mm Hg) and 2-methylthio-fluorobenzene, bp. 80°C (15 mm Hg) in 90% yield.

Reaction with iodine.

Pre-cooled diethyl ether (300 mL) was added to the solution containing potassiofluorobenzene, while keeping the temperature below -90°C. A solution of 61.0 g (0.24 mol) of iodine in 100 mL of THF was added portionwise to the vigorously stirred metallation mixture, while maintaining the temperature below -85°C. After an additional 5 minutes the cooling bath was removed and the reaction mixture was hydrolyzed with a warm (35°C) solution of 20 g of sodium thiosulfate in 200 mL of water. The work-up is carried out as described above. 2-Fluoroiodobenzene, bp. 75°C (12 mm Hg) was obtained in 90% yield.

Reaction with dimethylformamide.

A mixture of 18.2 g (0.25 mol) of dimethylformamide and 50 mL of diethyl ether was added over ca. 10 minutes to the metallation mixture with vigorous stirring and cooling between -80 and -100°C. After an additional 2 minutes the mixture was cautiously poured into a mechanically stirred mixture of 100 mL of 30 % aqueous hydrochloric acid and 500 mL of ice water. The layers were separated and three extractions with diethyl ether were carried out. The combined organic solutions were washed twice with brine and subsequently dried over magnesium sulfate. The isolation of the product, 2-fluorobenzaldehyde, bp. 75°C (12 mm Hg), was carried out as described for the other products (yield ~ 85%).

Reactions of other halobenzenes with the superbase mixtures.
A 250 mL necked round-bottomed flask was equipped with a dropping funnel-gas inlet combination, mechanical strirrer and thermometer-gas outlet combination. A mixture of 0.10 mol of heavier alkali metal *tert*-butoxide or *tert*-amylate and 60 mL of THF was placed in the flask. The mixture was cooled to below -80°C, then 63 mL of a 1.6 M solution (0.10 mol) of *n*-butyllithium in hexane was added over a few minutes with efficient stirring, while maintaining the temperature below -70°C. To this mixture was added within a few minutes a solution of 0.10 mol of the halobenzene in 10 mL of THF, while keeping the temperature between -95 and -105°C. After an additional 10 minutes 15 g (0.16 mol) of dimethyl disulfide was added. Work-up was carried out as described above. The crude product (obtained after concentration *in vacuo*) was analyzed with GC analysis.

The reaction between halobenzene and superbase was very exothermic in all cases in which the SET mechanism dominates.

References

1 Gilman, H.; Soddy, T. S. *J. Org. Chem.* **22** (1957) 1715.

2 Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag, Heidelberg (1987).

3 The reaction also proceeds very efficiently with the superbase mixture ^{n}BuLi·NaO^{t}Bu, but as potassium *tert*-butoxide is less costly the mixture ^{n}BuLi·KO^{t}Bu is generally preferred.

4 Recently Iwao reported the selective *ortho* metallation of chlorobenzene with ^{s}BuLi in THF at -105°C. When we treated chlorobenzene with ^{n}BuLi or ^{t}BuLi in THF/hexane at -100°C and subsequently quenched the metallation mixture with dimethyl disulfide, no *ortho*-methylthiochlorobenzene was obtained at all. Iwao, M. *J. Org. Chem.* **55** (1990) 3622.

5 Reaction with ^{n}BuLi: Kress, T. H.; Leanna, M. R. *Synthesis* (1988) 803. The lithiated compound (2-lithio-1,3-dichlorobenzene) proved to be stable in THF up to *ca.* -20°C (compare *o*-lithiochlorobenzene which decomposes in THF at -60°C). The reaction of 1,3-dichlorobenzene with ^{n}BuLi·KO^{t}Bu was performed in our laboratory.

6 Method: iodobenzene was treated with 1 equivalent of *n*-butyllithium in pentane at room temperature. The resulting white precipitate, consisting of phenyllithium, was isolated and subsequently dissolved in THF. After cooling the slightly yellow solution to -80°C 1 equivalent of potassium *tert*-alkoxide, dissolved in THF/hexane was added. A clear, slightly red solution was formed. Iodobenzene (1 equivalent) was added to the resulting mixture at -80°C. A bright yellow suspension was formed within a few minutes. After addition of dimethyl disulfide at -80°C, iodobenzene and methylthiobenzene were obtained in equal amounts, both in good yield (heating the yellow suspension to room temperature resulted in decomposition).

7 Reich, H. J.; Green, P.; Philips, N. H. *J. Am. Chem. Soc.* **111** (1989) 3444; Reich, H. J.; Green, P.; Philips, N. H. *J. Am. Chem. Soc.* **113** (1991) 1414.

8 A similar order was found by Ashby *et al.* who investigated the reaction of alkylhalides with lithium dialkylamides. These reacted simultaneously *via* carbene, carbanion and radical mechanisms. The amount of SET products decreased in the order I > Br > Cl. Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **58** (1993) 424. See also Lipschutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Little, R. D.; Baizen, M. M *J. Org. Chem.* **48** (1983) 3306; Mbarok, M.; Peters, D. G. *J. Org. Chem.* **47** (1982, 47.

9 Bordwell, F. G.; Clemens, A. H. *J. Org. Chem.* **46** (1981) 1035.

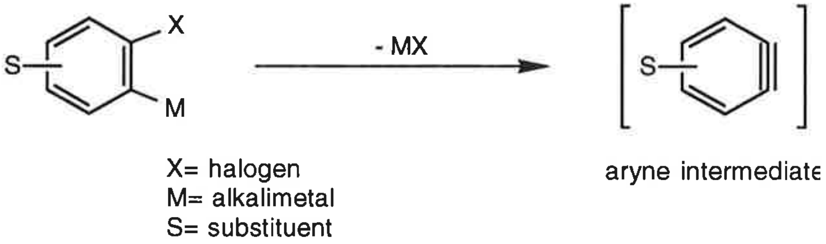
Chapter 4

The Stability of *ortho*-Metallated Halobenzenes

Introduction

Fluorobenzene can be effectively metallated at the *ortho* position with a superbase mixture consisting of equimolar amounts of *n*-butyllithium and potassium *tert*-alkoxide.[1] The temperature during this metallation reaction has to be maintained at *ca.* -90°C due to the low thermal stability of the intermediate *ortho*-potassiofluorobenzene.

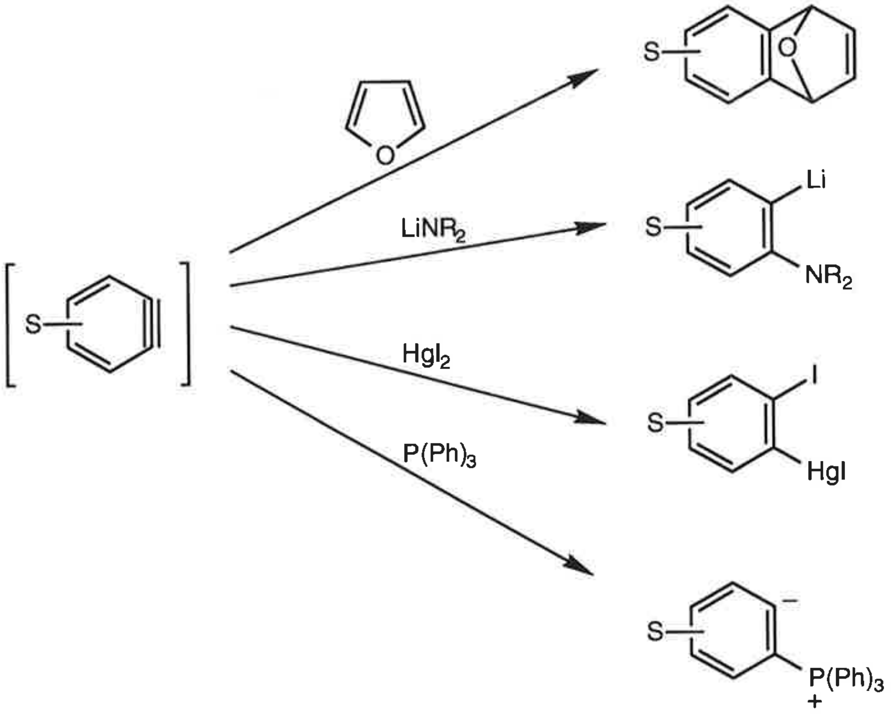
This instability is a general feature of *ortho*-metallated halobenzenes.[2] Within a narrow temperature range the metallated intermediate eliminates metal halogenide with formation of an aryne. The temperature at which this elimination occurs not only depends on the structure of the metallated halobenzene but also upon the reaction conditions.



Scheme 1: Decomposition of an *ortho*-metallated halobenzene.

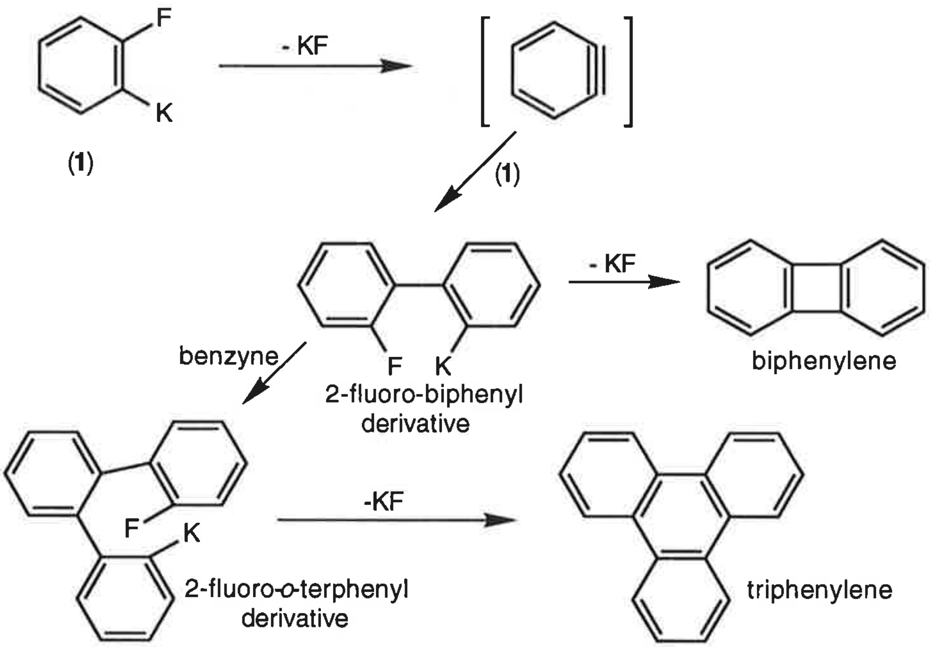
Although the highly reactive aryne intermediates have been extensively used in organic synthesis, the mechanism of formation of these extremely short-living species is not yet known in detail.[3] On basis of their behaviour in reactions biradical or charge separated structures have been suggested, but for the sake of simplicity the aryne is usually depicted as in scheme 1.[2]

The aryne intermediate is very reactive in a number of polar and cyclic additions. Some typical examples are shown in scheme 2.[2]



Scheme 2: Some typical reactions of aryne intermediates.

Although the generation of arynes *via* decomposition of *ortho*-metallated halobenzenes is very effective it suffers from some drawbacks. Firstly the aryne readily adds to organometallic compounds, such as unreacted *n*-butyllithium (used for the preparation of the metallated halobenzene) or not yet decomposed *ortho*-metallated halobenzene. It is therefore sometimes difficult to tune the product distribution in these decompositions. Generally, when an *ortho*-metallated halobenzene is allowed to decompose, a range of products is found after quenching.[4] The reactions leading to some of the products usually found are shown in scheme 3 for *ortho*-potassiofluorobenzene in THF; besides the products depicted in this scheme traces of several other coupling products are found.



Scheme 3: Decomposition of *ortho*-potassiofluorobenzene (**1**) and some of the subsequent coupling reactions.

Furthermore the decomposition is extremely exothermic due to the formation of the metal halogenide and stable polycyclic compounds. Careful working therefore is required when using *ortho*-metallated halobenzenes on a preparative scale.

These problems have led to the development of other methods for aryne generation, which are often easier to control. Compounds such as benzene-diazonium-2-carboxylate or benzothiadiazole dioxide (which decomposes to benzyne with the elimination of gasses, such as carbon dioxide) are generally thermally more stable and less reactive than metallated halogen benzenes.[5]

Nevertheless, *ortho*-metallated halobenzenes remain the most facile sources of arynes, on account of their easy access and high efficiency of their decomposition.

As mentioned earlier, some factors influence the stability of arynoïds (i.e. the precursors of arynes):

i) the nature of the halogen obviously is one of the determining factors. Generally a decreasing order of stability of F > Cl > Br > I for lithiated halobenzenes is found, following the order of strenght of the corresponding carbon-halogen bonds.[2]

ii) substituents can strongly influence the stability. For example, whereas *ortho*-lithiofluorobenzene decomposes in THF at -30°C, the sulfonyl substituted arynoïd 3-fluoro-2-lithio-1-phenylsulphonylbenzene is stable in THF up to +60°C.[6]

iii) also the solvent is of great importance. Nefedov *et al.* investigated the influence of various solvents upon the stability of *ortho*-lithiated fluoro- and bromobenzene.[7] The stability is increased by solvents with Lewis-base character. Cyclic ethers have been shown to stabilize these compounds better than do acyclic ethers, because of a better coordination to the lithium atom. The size of the ether seems to have little influence. For example, the lithiated compounds decomposed at the same temperatures in di-*n*-butyl ether and diethyl ether.

Aim of the present research

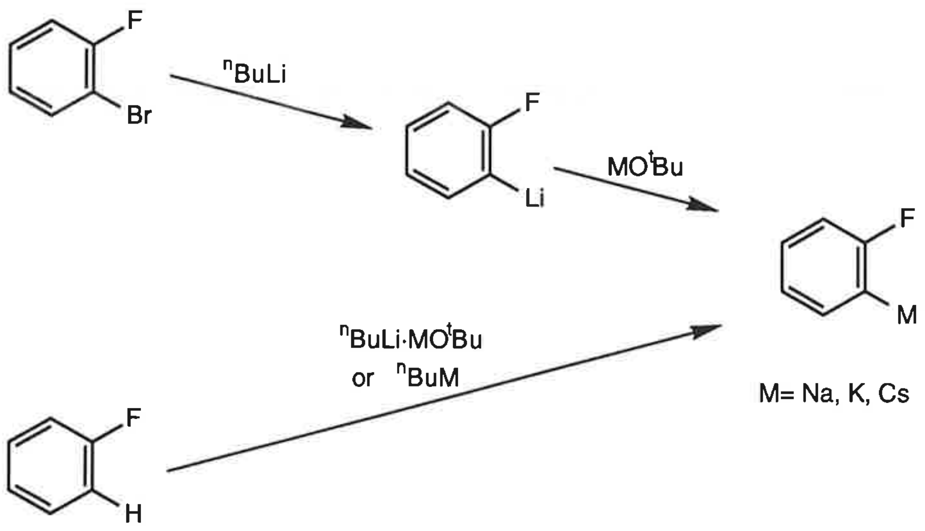
There is a vast amount of literature on reactions performed with *ortho*-metallated halobenzenes and the arynes derived from these precursors. Practically all of these precursors involve lithium species, however. The corresponding sodium, potassium and cesium compounds have been used in a few cases only.[2] These heavier alkali metal analogues are often easily accessible.

In spite of all these synthetical results, little specific information about decomposition temperatures of *ortho*-metallated halogen compounds, especially of the heavier alkali metal compounds, is known. In this chapter we present the results of our investigations on the influence of the alkali metal upon the stability of *ortho*-metallated halobenzenes. Major part of the investigations concerns fluorobenzene. This compound can be effectively *ortho*-metallated with base mixtures containing the various heavier alkali metals, while the *ortho*-metallated derivatives are relatively stable compared to the chloro, bromo and (especially) iodo analogues.

Results and discussion

Generation of *ortho*-metallated fluorobenzenes.

Ortho-lithiofluorobenzene can be obtained *via* bromine-lithium exchange between *ortho*-bromofluorobenzene and *n*-butyllithium in various organic solvents. The heavier alkali metal analogues can be prepared by addition of a heavier alkali metal alkoxide to a solution containing *ortho*-lithiofluorobenzene, which results in metal-metal exchange, or by direct deprotonation of fluorobenzene using superbase mixtures like $^{n}BuLi \cdot MO^{t}Bu$ (M= Na, K, Cs) or pure alkylalkali bases.[8] All of theses reactions are best performed in THF as the stability of the metallated intermediates is highest in this solvent compared to diethyl ether or alkanes.[7] The reactions described above are shown in scheme 4.



Scheme 4: Ways for preparing *ortho*-metallated fluorobenzene in THF.[9]

Quench experiments with dimethyl disulfide and chlorotrimethylsilane showed that all of the reactions shown in scheme 4 proceed in high yield (~ 90%) at -100°C in THF/hexane.[9]

The stability of *ortho*-metallated fluorobenzene.

In order to determine the decomposition temperature of a compound a solution in pure THF containing the *ortho*-metallated fluorobenzene (prepared at *ca.* -110°C in one of the ways described before) was allowed to warm up very slowly (rate *ca.* 0.06°/s) from -110°C. During this warming up the temperature of the solution was monitored using an electronic thermometer connected to an XY recorder. Decomposition of the compound was indicated by a sudden strong increase of the temperature, generally accompanied by a coloration of the mixture to dark brown or black. Usually with *ca.* 30 mL of a 0.4 to 0.8 M solution a temperature increase of 20 to 40 degrees within only a few seconds was observed. In the following figure a typical warming up curve is shown.

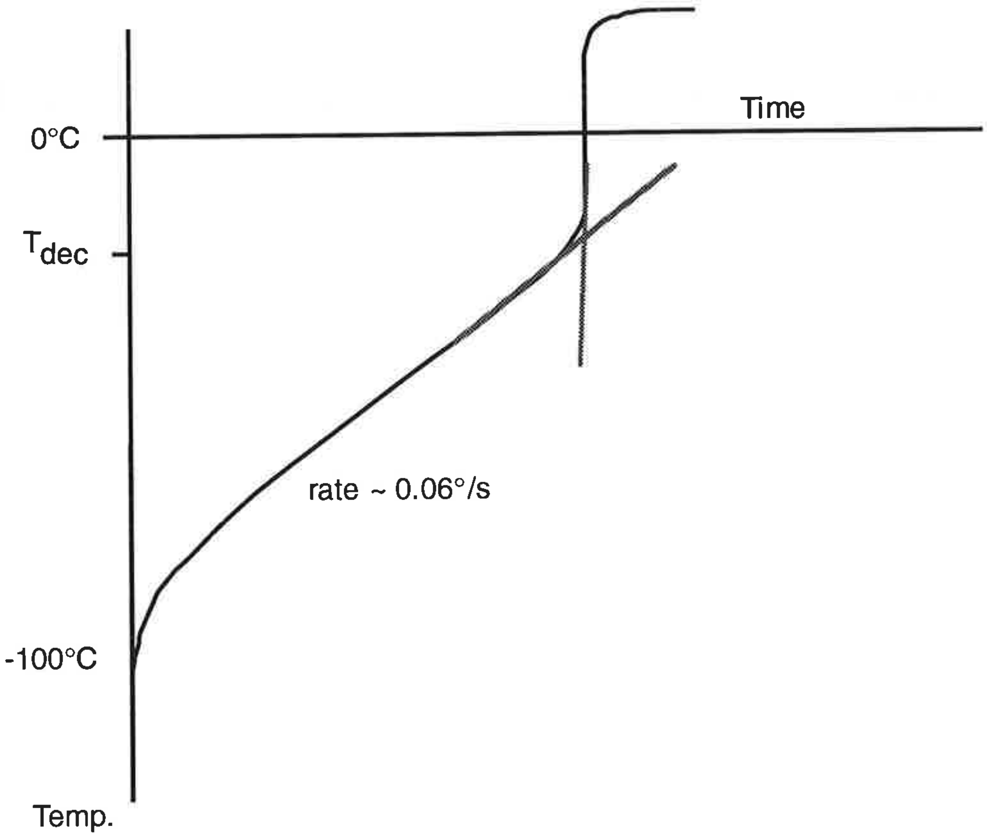


Figure 1: Typical warming up curve of a metallated fluorobenzene (Temp= temperature, T_{dec}= decomposition temperature).

Solutions of *ortho*-metallated fluorobenzene, containing the various alkali metals, were prepared in pure THF at *ca.* -110°C. Generally these mixtures were initially colorless or slightly yellow. Table 1 shows the decomposition temperatures determined as described.

Table 1: Determination of decomposition temperature of *ortho*-metallated fluorobenzene (determined over a concentration range of 0.2 to 0.8 M).

ortho-M-fluorobenzene M=	decomposition temperature (°C)[a]	color after decomposition
Li	-30	clear pink
Na	-45	black
K	-30	black
Cs	-12	black

[a] Determined as the average value of 4 to 5 measurements, maximum deviation between the various measurements *ca.* 2 degrees.

In order to check the reliability of these values, synthetical experiments were performed. Mixtures containing the various *ortho*-metallated fluorobenzenes were prepared on a preparative scale in THF at -110°C, stirred for 15 minutes at a certain temperature (mentioned in tables 2 and 3), and subsequently quenched with chlorotrimethylsilane at -90°C. By efficient cooling the dissolved *ortho*-metallated fluorobenzene was prevented to decompose in an uncontrolled way during the reaction time. Yields obtained in these experiments are shown in tables 2 and 3.

Table 2: Yields of *ortho*-trimethylsilylfluorobenzene obtained after stirring a solution of *ortho*-potassiofluorobenzene (initial concentration 0.6 M) in THF for 15 minutes at various temperatures.

temperature (°C)	yield (%)[a]	color of the mixture
-90	90	yellow
-70	87	pink
-60	75	reddish brown
-50[b]	67	reddish brown
-40	50	dark brown
-30	43	dark brown
-20[c]	14	black

[a] Determined as the average value of 2 experiments. [b] When the metallation mixture was stirred for 45 minutes at this temperature the yield obtained was 47%. [c] The experiment could not be performed at a temperature higher than -20°C as the heating effect became too large, as a consequence of which temperature control was impossible. The yield in these cases presumably was close to 0%.

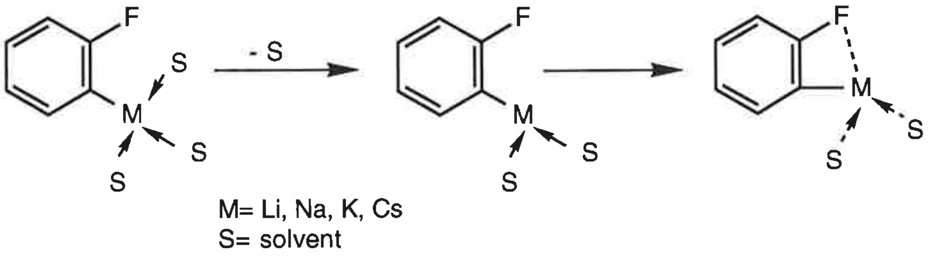
Table 3: Yields of *ortho*-trimethylsilylfluorobenzene obtained after stirring a solution of *ortho*-metallated fluorobenzene (initial concentration 0.6 M) in THF/hexane for 15 minutes at various temperatures.

alkali metal	temperature (°C)	yield (%)	color of the mixture
Li	-30	45	yellow-brownish
Na	-50	62	dark brown
Na	-30	20	brown-black
Cs	-30	64	reddish brown

When the reaction was performed at a temperature sufficiently far below the decomposition temperature yields were reasonable to good in all cases. When the reaction was carried out at a temperature above the decomposition temperature yields dropped to low values. Comparison of the reactions performed at -30°C shows that the yields increase in the order Na < Li ~ K < Cs. This is also the order of stability found in our decomposition experiments. It may be concluded that the synthetic results and decomposition experiments correspond well.

The metallation mixtures used during the decomposition experiments were prepared *via* the two routes depicted in scheme 4. For a particular alkali metal both routes led to the same decomposition temperature. This implies that the presence of lithium alkoxide in the metallation mixture does not have an influence on the decomposition. When we added other compounds, such as TMEDA, PMDTA or LiBr (in the case of lithium compounds), at -110°C to the metallation mixture we also obtained the same results. This suggests that, at the moment of decomposition, no strong interaction between these compounds and the *ortho*-metallated fluorobenzene is present.[10]

We propose the following mechanism for decomposition. At a temperature below the decomposition temperature the alkali metal is surrounded by solvent molecules, therefore any metal-halogen interaction is prevented.[11] At a certain temperature some of the solvent-metal interactions are broken and a metal-halogen interaction appears. It is this interaction that probably leads to the aryne formation. On basis of our results we suggest that this interaction, which determines the decomposition temperature, is purely electrostatic, and that the halogen and alkali metal leave the aromatic compound simultaneously. The decomposition temperature is therefore determined by the combination of halogen and alkali metal.



Scheme 5: Possible mechanism leading to metal-fluorine interactions

Coulombs law states that the electrostatic interaction between two charges (in this case a negatively charged fluorine and positively charged alkali metal) is proportional to Q_1Q_2/r, where Q_1 and Q_2 are the respective charges and r is the distance between them.[12]It may first be assumed that in the case of *ortho*-metallated fluorobenzene Q_1 and Q_2 are equal in all cases (i.e. for the different alkali metals), as the polarity of the carbon-fluorine bond does not vary much and all of the carbon-alkali metal bonds are similarly ionic. As the length of the carbon-metal bond increases in the order C-Li < C-Na < C-K < C-Cs[13], also the distance r will increase in this order (this was confirmed by *ab initio* calculations[14]), as is visualized in figure 2.

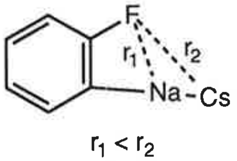


Figure 2: Schematical comparison of metallated fluorobenzenes.

This means that the electrostatic attraction between the metal and fluorine, that is the *in*stability of the *ortho*-metallated fluorobenzene, decreases in the order F-Li > F-Na > F-K > F-Cs. This is, for sodium, potassium and cesium, exactly the order of stability of corresponding *ortho*-metallated fluorobenzenes as found in our experiments. *Ab initio* calculations on metallated fluorobenzene show that (in absence of solvent molecules) the metal is indeed strongly turned towards fluorine.[14]

An increasing distance M-X, combined with a smaller electrostatic attraction makes it more difficult for the *ortho*-metallated halobenzene to transform to a transition-state in which M and X have approached each other in such a way that separation of MX is possible. This higher activation energy results in a higher stabilty.

The stability of the *lithium* compound is higher than expected from this consideration. This is possibly the result of aggregate formation of the lithium compound, contrary to the heavier alkali metal compounds which are generally monomers in THF.[15] The distance between the lithium atom and fluorine atom can increase when aggregates are formed, as illustrated in figure 3 for a monomer and (possible) dimer. This increase results in a higher stability.[16] Furthermore, the carbon-lithium bond may be somewhat less polarized than the other carbon-alkali metal bonds, resulting in a lowering of the charge Q on the lithium atom, hence in a lower electrostatic attraction.[17]

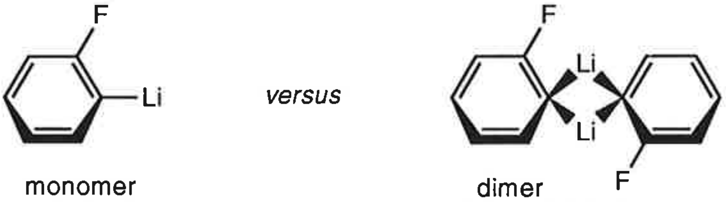


Figure 3: *ortho*-Lithiofluorobenzene monomer and (possible) dimer.

The stability of other *ortho*-metallated halobenzenes.

Ortho-lithiochlorobenzene can be effectively prepared by halogen-lithium exchange from *ortho*-bromochlorobenzene and *n*-butyllithium in THF at -100°C. This intermediate decomposed at ~ -60°C. It appeared to be impossible to directly deprotonate chlorobenzene with superbase mixtures like ^{n}BuLi·KO^{t}Bu.[18] The heavier alkali metal analogues were therefore prepared *via* metal-metal exchange by addition of a heavier alkali metal alkoxide to *ortho*-lithiochlorobenzene in THF. A solution of sodium, potassium or cesium *tert*-alkoxide in THF was cautiously added to a solution of *ortho*-lithiochlorobenzene in THF at -110°C. An immediate decomposition took place, which was observable by a strong increase in temperature and blackening of the solution. It appeared to be impossible to obtain the heavier alkali metal analogues of *ortho*-lithiochlorobenzene.

Similar results were obtained with *ortho*-metallated bromobenzene. Solutions of *ortho*-lithiobromobenzene in THF decomposed at ~ -80°C. We were unable to obtain solutions of the heavier alkali metal analogues due to their extremely low stability.

These results can be explained with the differences in strength between the carbon-halogen bonds. The carbon-chlorine and carbon-bromine bonds are much weaker compared to the carbon-fluorine bond. The mechanism with electrostatic attraction, as described for *ortho*-metallated fluorobenzene, is probably operative also in these cases. The larger halogen atoms, however, cannot be considered as a simple negative charge induced by differences in electronegativity as is presumably the case for the fluoro compounds. Due to the diffuse orbitals around the larger halogens and smaller differences in electronegativity between carbon and the larger halogens the charge on the halogen will mainly be a polarization induced charge. The origin of the higher stability of the lithio compounds compared to the heavier alkali metal analogues is presumably the same as described for the fluoro compounds.

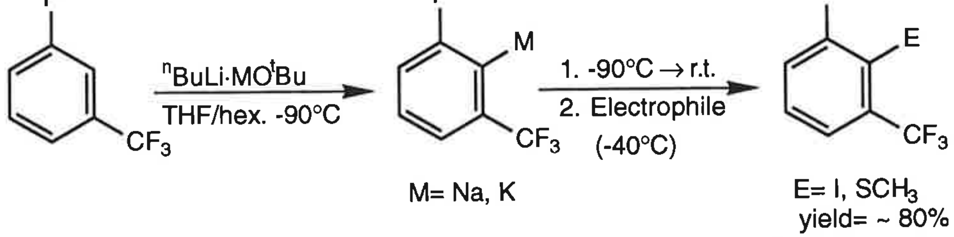
The stability of other reactive metallated halobenzenes.

Several metallated halobenzenes exploded during attempts to isolate them as solids in absence of coordinating ligands. We experienced this when we tried to isolate a very small amount of *ortho*-lithiofluorobenzene. During this operation a violent explosion occurred. We therefore decided to investigate the stability of some of these unstable compounds in solution in THF.

o-Lithiobromobenzene shows a similar low stability. The *meta* and *para* isomers can be isolated as white powders, but they have to be handled with care as they are shock sensitive. The ease of decomposition and the violence of the explosion of the isolated compound increases with decreasing distance between bromine and lithium. It is not known whether this decomposition occurs intra- or intermolecularly. Solutions of the *meta* and *para* isomers in THF appeared to be stable up to room temperature, as was shown with decomposition as well as with quench experiments.

We found a similar difference in stability between solid[19] and dissolved (in THF) *ortho*-lithio- and potassio-α,α,α-trifluorotoluene.

3-Fluoro-α,α,α-trifluorotoluene was metallated selectively at the 2-position in THF at -90°C with ^{n}BuLi·KO^{t}Bu and ^{n}BuLi·NaO^{t}Bu in THF/hexane and the solutions subsequently warmed up to *room temperature* (r.t.). Functionalization gave the expected derivatives (see scheme 6). The high yield (~ 80%) of these products are a reflection of the relatively high stability of the intermediary potassium and sodium compounds. An α,α,α-trifluoro group has a strong stabilizing effect on *ortho*-metallated fluorobenzenes.



Scheme 6: Metallation and functionalization of 3-fluoro-α,α,α-trifluorotoluene.

We next tried to stabilize *ortho*-metallated fluorobenzene by replacing the alkali metal by copper (I), as it is known that coppercarbenoïds, other reactive metallated halogen compounds, are much more stable than their alkali metal analogues.[20] A solution of CuBr·LiBr in THF was added at -90°C to a metallation mixture containing *ortho*-lithiofluorobenzene in THF, after which the temperature was allowed to rise to room temperature. Subsequently an electrophile was added. After addition of iodine to the copper compound we were able to isolate 2-fluoro-iodobenzene in 66% yield. Dimethyl disulfide and iodobenzene reacted very slowly, giving 2-methylthio-fluorobenzene and 2-fluorobiphenyl respectively as the only products. After stirring the copper compound for 4 hours at room temperature with dimethyl disulfide we obtained 2-methylthio-fluorobenzene in 35% yield (the unreacted copper compound probably has reacted with water, added during work-up, to fluorobenzene. No decomposition products were found.). It appeared to be even possible to stabilize *ortho*-lithiochlorobenzene in a similar way. A solution of CuBr·LiBr in THF was added at -90°C to a metallation mixture containing *ortho*-lithiochlorobenzene in THF, after which the temperature was allowed to rise to room temperature. Subsequently iodine was added, and after work-up 2-chloro-iodobenzene was isolated in 80% yield.

Experimental methods

General conditions.

All reactions were carried out under a nitrogen atmosphere. All solvents were dried before use. *n*-Butyllithium (1.6 Molar solution in hexane) and heavier alkali metal alkoxides were obtained commercially. Metallation mixtures were cooled with a liquid nitrogen bath. All products were isolated by distillation and analyzed by NMR spectroscopy and GLC. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

The apparatus for the determination of decomposition temperatures was designed on basis of equipment described in the literature.[21] It consisted of an evacuable Schlenk tube, in which the measuring probe, also a Schlenk tube, can be fitted *via* a ground glass joint. The measuring probe was fitted with a Pt-100 resistor mounted in a stainless steel tube. Temperature measurements were performed on a Systemteknik S2541 thermolyzer connected to an X-Y plottter. During measurements the probe was filled with 20 to 30 mL of the sample to be measured. This sample was stirred with a PTFE-coated magnetic stirring bar. See figure 4.

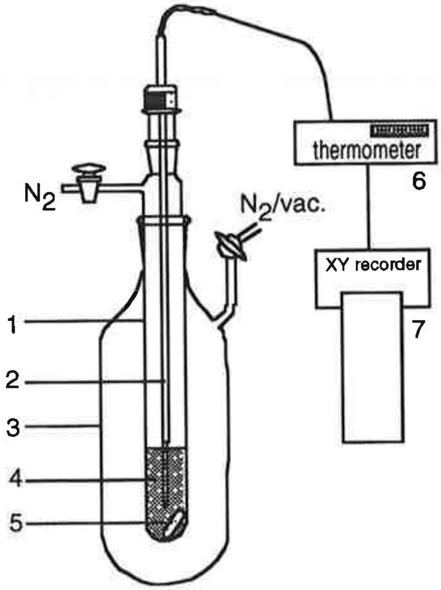


Figure 4: Apparatus used for decomposition experiments. 1: measuring probe, 2: Pt-100 resistor, 3: evacuable insulating jacket, 4: metallation mixture, 5: magnetic stirring bar, 6: electronic thermometer (Systemteknik S2541 thermolyzer), 7: X-Y recorder.

General remarks concerning the determination of decomposition temperatures.

i) the optimum concentration of our metallation mixtures was found to lie between 0.4 and 0.8 M. At concentrations below 0.4 M the heating effect of the decomposition was too small for an accurate determination of the decomposition temperature. At concentrations higher than 0.8M the decreasing solubilities at lower temperatures, especially in the case of the sodium, potassium and cesium compounds, gave rise to unreliable results. The decomposition temperature appeared to be independent on the concentration. The heating effect, however, increased with the concentration.

ii) the heating effect increased in the order Cs < K ~ Li < Na, which is the inverse of the order of stability. Most decomposition experiments were performed with metallation mixtures of 0.6 M. In the cases of cesium compounds a concentration of 0.8M was used, in order to determine the decomposition temperature more accurately.

iii) decomposition experiments were performed in neat THF, in order to have maximum solubilities even at low temperatures and at high concentrations. The presence of hexane (from the *n*-butyllithium solution for instance) could decrease the solubilities. We later found that decomposition temperatures of the metallated fluorobenzenes were the same in undiluted THF and in THF/hexane (~ 1/1) mixtures.

Decomposition experiments.

Decomposition of ortho-lithiofluorobenzene prepared by bromine-lithium exchange.

In the measuring probe, equipped with a magnetic stirring bar, was placed 10 mL of a 1.6 M (16 mmol) solution of *n*-butyllithium in hexane. All hexane was removed in an oil-pump vacuum. The probe was then equipped with the thermometer. The stirred yellow concentrated *n*-butyllithium was cooled to *ca.* -100°C with a liquid nitrogen bath, care being taken that it did not solidify. Subsequently 20 mL of precooled (~ -60°C) THF was added slowly with a syringe, while maintaining the temperature below -80°C (occasional cooling was applied when necessary). The mixture was cooled to -110°C and a pre-cooled (~ -60°C) solution of 2.8 g (16 mmol) of *ortho*-bromofluorobenzene in 7 mL of THF was added *via* a syringe while carefully maintaining the temperature at -110°C to -120°C. The metallation mixture was stirred for

5 minutes at -110°C, after which the measuring probe was rinsed with alcohol, dried and placed in the insulating jacket, which had previously been evacuated and flushed with nitrogen (this prevents precipitation of ice on the inside and allows the solution to be watched during the measurement). The cooling bath was removed and the insulating jacket evacuated (in this way the heat exchange with the surroundings is minimized). The well stirred metallation mixture was subsequently allowed to warm up, while its temperature was monitored and recorded. Generally the increase in temperature was about 0.06°/s. The temperature was monitored with the electronic thermometer and recorded with the XY recorder. At ~ -30°C, a sudden strong increase was observed, during which the mixture turned pink. The increase of the temperature within a few seconds amounted to *ca.* 30 degrees Celsius (see figure 1).

Decomposition of ortho-potassiofluorobenzene prepared by metal-metal exchange.

A solution of *ortho*-lithiofluorobenzene in 17 mL of THF was prepared as described above. The well stirred solution was cooled to -110°C and a solution of 1.8 g (16 mmol) of potassium *tert*-butoxide in 10 mL of THF was added *via* a syringe while carefully maintaining the temperature at between -107 and -113°C. After a few minutes the metallation mixture was prepared for the decomposition experiment as described above. At -30°C the temperature suddenly started to rise very fast, a temperature increase of *ca.* 30 degrees Celsius within a few seconds was observed. During this decomposition the mixture turned black.

Decomposition of ortho-potassiofluorobenzene prepared by deprotonation with a superbase mixture.

A solution of 16 mmol of *n*-butyllithium in 10 mL of THF was prepared as described above. To the well stirred solution was added a solution of 1.8 g (16 mmol) of potassium *tert*-butoxide in 10 mL of THF *via* a syringe while carefully maintaining the temperature between -107 and -113°C. The mixture was stirred for a few minutes at this temperature after which 1.6 g (16 mmol) of fluorobenzene in 7 mL of THF was cautiously added *via* a syringe, while keeping the temperature at *ca.* -110°C. After stirring for a few minutes the metallation mixture was prepared for the decomposition experiment. At -30°C the temperature suddenly started to rise very fast, a temperature increase of *ca.* 30 degrees Celsius within a few seconds was observed. During this decomposition the mixture turned black.

Decomposition experiments with the corresponding sodium and cesium compounds were performed similarly, using sodium *tert*-butoxide and cesium *tert*-amylate respectively. Decomposition of the sodium and cesium compounds started at respectively -45°C and -12°C, in both cases the mixtures turned black. The temperature increase amounted to *ca.* 40 degrees for the sodium compound (0.6 M) and *ca.* 30 degrees for the cesium compound (0.8 M), both within a few seconds. The results are summarized in table 1.

Decomposition of ortho-alkalifluorobenzene prepared by deprotonation with a pure alkylalkali base.

Pure *n*-butylsodium, *n*-butylpotassium and *n*-butylcesium were prepared according to modified literature procedures.[22] *n*-Butyllithium was used in a concentrated form (all hexane was removed by evaporation in an oil-pump vacuum).

The pure base (16 mmol) was transferred to the measuring probe (the concentrated *n*-butyllithium was prepared in the probe). The probe was cooled with liquid nitrogen, and 17 mL of THF was added *via* a syringe, while maintaining the temperature at *ca.* -90°C. Subsequently the solution was cooled to -110°C. To the well stirred solution of the base was added a mixture of 1.6 g (16 mmol) of fluorobenzene and 10 mL of THF, while maintaining the temperature at -110°C. After stirring for a few minutes at this temperature the metallation mixture was used for the decomposition experiment.

All of these preparations of *ortho*-metallated fluorobenzenes at low temperature gave slightly yellow to colorless solutions. In the cases of the heavier alkali metal compounds sometimes a suspension was formed at low temperatures (around -100°C), which dissolved at somewhat higher (-80°C) temperatures. The appearance of a brown or black colour already during the preparation of the *ortho*-metallated fluorobenzene was considered as the consequence of an experimental mistake. In such cases the experiment was repeated.

Experiments with ortho-metallated chlorobenzene and bromobenzene.

Solutions of *ortho*-lithiochlorobenzene or *ortho*-lithiobromobenzene were prepared at -110°C by bromine-lithium exchange as described above. The decomposition temperatures were determined at -60°C and -90°C, respectively. In the case of the heavier alkali metal analogues the solution of the alkoxide in THF was added cautiously to the lithium compound at -110°C, nevertheless immediate blackening of the mixture and a strong increase in temperature was observed. No accurate decomposition temperatures could be determined.

Typical synthetic experiment with *ortho*-metallated fluorobenzene.

Metallation of fluorobenzene with ^{n}*BuLi·KO*^{t}*Bu, subsequent stirring at -40°C and quenching with chlorotrimethylsilane.*

In a 250 mL three-necked round-bottomed flask was placed 75 mL of a 1.6 M solution (0.12 mol) of *n*-butyllithium in hexane. All hexane was removed by evaporation in an oil-pump vacuum. The flask was equipped with a dropping funnel-gas inlet combination, mechanical strirrer and thermometer-gas outlet combination. The *n*-butyllithium was cooled and 75 mL of pre-cooled (~ -60°C) THF was added while maintaining the temperature at *ca.* -90°C. To the well stirred solution was added a solution 13.4 g (0.12 mol) of potassium *tert*-butoxide in 100 mL of THF while maintaining the temperature at -90°C. After a few minutes the mixture was cooled to -110°C and a solution of 14.4 g (0.15 mol) of fluorobenzene in 25 mL of THF was added cautiously while maintaining the temperature at -110°C. The slightly yellow mixture was stirred for 5 minutes after which the cooling bath was removed. The temperature was allowed to rise to -40°C, applying occasional cooling. The dark coloured metallation mixture was efficiently stirred for 15 minutes at -40°C (occasional cooling being neccessary) after which it was quickly cooled to -90°C. Subsequently 16.4 g (0.15 mol) of freshly distilled (from a small amount of *N,N*-diethylaniline) chlorotrimethylsilane was added dropwise over 10 minutes with efficient stirring while maintaining the temperature of the reaction mixture between -90 and -100°C. After the addition the cooling bath was removed and the temperature allowed to rise to -40°C. Water (200 mL) was added, the layers separated and the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were washed once with water and then dried over magnesium sulfate. The liquid remaining after removal of the solvent under reduced pressure was carefully distilled to give 10.1 g of 2-trimethylsilyl-fluorobenzene (50% yield), bp 60°C (15 mm Hg).

When the experiment is carried out at a temperature around the decomposition temperature care has to be taken to prevent an extremely exothermic decomposition. The contents of the flask may be splashed out due to the rapid evolution of butane and glassware may break. Attention has to be paid at all times and cooling is neccessary when the temperature starts to rise.

Other experiments with metallated aromatic halides

Investigations on the stability of meta- and para-lithiobromobenzene.

Meta- and *para*-lithiobromobenzene (0.02 mol) were prepared with standard Schlenk techniques by the reaction of dibromobenzene with 1 equivalent of *n*-butyllithium in pentane at room temperature. The lithio compound was isolated by centrifugation and washed three times with hexane. After removal of all hexane by evaporation in an oil pump vacuum the white lithium compound was cautiously transferred into the Schlenk tube. Pre-cooled THF (30 mL, ~ -60°C) was added with cooling while maintaining the temperature of the metallation mixture at *ca.* -80°C. The decomposition temperature was determined as described above. In both cases no sudden increase of the temperature was observed in the region of -80°C to room temperature while the solutions remained almost colorless (the mixtures were not further heated).

It should be emphasized that the dry lithium compounds may decompose violently by shock.

Investigations on the stability of metallated benzotrifluoride and m-fluorobenzotrifluoride.

A 250 mL three-necked round-bottomed flask was equipped with a dropping funnel-gas inlet combination, mechanical strirrer and thermometer-gas outlet combination. A mixture of 0.10 mol of benzotrifluoride or *m*-fluorobenzotrifluoride and 60 mL of THF was placed in the flask. The mixture was cooled to below -80°C, then 63 mL of a 1.6 M solution (0.10 mol) of *n*-butyllithium in hexane was added over a few minutes with efficient stirring, while maintaining the temperature below -70°C. The dropping funnel was charged with a solution of 11.2 g (0.10 mol) of KO^{t}Bu in 60 mL of THF. This solution was added over 15 minutes with efficient stirring, while keeping the temperature around -80°C. Subsequently the temperature was allowed to rise to between 10 and 20°C. The metallation mixture was stirred for 30 minutes at this temperature after which it was cooled to -60°C. An electrophile (dimethyl disulfide or iodine (as a solution in THF)) was added in a slight excess. Work-up was carried out as described above for fluorobenzene. The products 2-methylthiobenzotrifluoride (bp. 100-105°C (20 mm Hg), 50%), 3-fluoro-2-methylthio-benzotrifluoride (100-110°C (20 mm Hg), 82%) and 3-fluoro-2-iodo-benzotrifluoride (70°C (1 mm Hg), 75%) were obtained.

2-methylthiobenzotrifluoride: ^{1}H-NMR: δ= 2.50 (s, 3H, SCH_3), 7.22 (bt, 1H, H4), 7.37 (bd, 1H, H3), 7.47 (bt, 1H, H5), 7.62 (bd, 1H, H6) ^{13}C-NMR: δ= 16.2 (q, *J*= 1.7 Hz, SCH_3), 124.0 (q, *J*= 271.8 Hz, CF_3), 124.7 (s, C5), 126.6 (s, C3), 127.4 (s, C4), 127.9 (q, *J*= 61.3 Hz, C1), 132.0 (q, *J*= 1.1 Hz, C6), 138.3 (q, *J*= 1.0 Hz, C2)

3-fluoro-2-methylthiobenzotrifluoride: ^{1}H-NMR δ= 2.43 (s, 3H, SCH_3), 7.26 (dd, *J*= 8, **8** Hz, 1H, H4), 7.37 (ddd, *J*= 8, 8, **5** Hz, 1H, H5), 7.47 (d, *J*= 8 Hz, 1H, H6) All signals are broad due to couplings with fluorine, coupling constants depicted in boldface are fluorine couplings. ^{13}C-NMR: δ= 18.5 (d, *J*= 6.3 Hz, SCH_3), 119.4 (d, *J*= 24.5 Hz, C4), 122.2 (td, *J*= 5.3, 3.2 Hz, C2), 123.1 (qd, *J*= 272.4 , 3.0 Hz, CF_3), 129.4 (s, C5 or C6), 129.5 (s, C5 or C6), 134.4 (qd, *J*= 29.1, 2.3 Hz, C1), 163.9 (d, *J*= 245.9 Hz, C3)

3-fluoro-2-iodo-benzotrifluoride: ^{1}H-NMR δ= 7.22 (ddd, *J*= 8, **8**, 2.4 Hz, 1H, H4), 7.42 (ddd, *J*= 8, 8, **5** Hz, 1H, H5), 7.46 (dd, *J*= 8, 2.3 Hz, 1H, H6) All signals are broad due to couplings with fluorine, coupling constants depicted in boldface are fluorine couplings. ^{13}C-NMR: δ= 118.6 (d, *J*= 25.5 Hz, C4), 122.3 (qd, *J*= 274.8, 3.3 Hz, CF_3), 123.3 (td, *J*= 5.3 , 3.2 Hz, C2), 130.0 (s, C5 or C6), 130.1 (s, C5 or C6), 135.7 (qd, *J*= 29.9, 2.2 Hz, C1), 162.4 (d, *J*= 245.0 Hz, C3)

Preparation of ortho-copperfluorobenzene and subsequent functionalization.

In a 250 mL three necked round-bottomed flask, equipped with a dropping funnel-gas inlet combination, mechanical strirrer and thermometer-gas outlet combination, were placed 8.75 g (0.05 mol) of o-bromofluorobenzene and 40 mL of THF. The mixture was cooled to -80°C and 32 mL of a 1.6M solution of (0.05 mol) *n*-butyllithium was added while maintaining the temperature at -80°C. After stirring for a few minutes a solution of 5.2 g (0.06 mol) of lithium bromide and 8.6 g (0.06 mol) of copper (I) bromide in 40 mL of THF was added portionwise over a few minutes at -80°C. The mixture was stirred for a few minutes at this temperature after which the temperature of the red-brown colored mixture was allowed to rise to room temperature. Subsequently a slight excess of electrophile was added. The mixture was stirred at room temperature. The quench reaction was monitored by GC analysis (in all cases traces of 2,2'-difluorobiphenyl were found, as the result of some homo coupling).

When a solution of iodine in THF was added a very fast reaction occurred, which ran to completion within a few minutes. After work-up (a solution of sodium cyanide was added in all cases during work-up in order to solubize copper salts) 2-fluoroiodobenzene (bp 55-60°C (1 mm Hg)) was isolated in 66% yield.

With dimethyl disulfide, a slow reaction took place. The mixture slowly turned green. After stirring for 4 hours, work-up was performed and 2-methylthiofluorobenzene (bp. 60-65°C (1 mm Hg)) was isolated in 35% yield. No high boiling products were obtained.

After addition of iodobenzene to the metallation mixture 2-fluorobiphenyl was formed in a slow reaction. After stirring the black mixture for one day the amount of 2-fluorobiphenyl still increased (slowly). GC analysis showed that no by-products were formed.

When the same procedure was followed for *o*-bromochlorobenzene, 2-chloroiodobenzene was isolated in 86% yield after quenching with iodine.

References

1 Fossatelli, M; Verkruijsse, H. D.; Brandsma, L. *Synth. Commun.* **20** (1990) 1701; see also previous chapter.

2 Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes* Academic Press, New York (1967); Huisgen, R. Sauer, J. *Angew. Chem.* **72** (1960) 91, Heaney, H. *Chem. Rev.* **62** (1962) 81.

3 Investigations on the benzyne structure continue, however: Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.* **113** (1991) 7414; Linnert, H. V.; Riveros, J. M. *J. Chem. Soc., Chem. Commun.* (1993) 48. Also theoretical calculations have been performed on the benzyne intermediate: Radom, L.; Nobes, R. H.; Underwood, D. J.; Li, W.-K. *Pure & Appl. Chem.* **58** (1986) 75;

4 Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **78** (1956) 2217; our own investigations, see also ref. [2].

5 Del Mazza, D.; Reinecke, M. G. *J. Org. Chem.* **53** (1988) 5799; Wickam, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Hardee Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **56** (1991) 2045.

6 Bosold, F.; Zulauf, P.; Marsch, M.; Harms, K.; Lohrenz, J.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **30** (1991) 1455.

7 Nefedov, O. M.; Dyachenko, A. I. *Angew. Chem.* **84** (1972) 527; D'yachenko, A. I.; Ioffe, A. I.; Nefedov, O. M. *Bull. Acad. Sci. USSR* **2** (1979) 339.

8 Wakefield, B. *The Chemistry of Organolithium Compounds* Pergamon Press, Oxford (1974); Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag, Heidelberg (1987).

9 *Ortho*-lithiofluorobenzene can also be obtained by direct deprotonation of fluorobenzene with *n*-butyllithium at -50°C in pure THF, but this reaction proceeds very slowly. Gilman, H.; Soddy, T. S. *J. Org. Chem.* **22** (1957) 1715, see also previous chapter

10 This, however, does not exclude solvent-metal interactions just before decomposition, as in all cases an excess of THF was present.

11 Substituents on the ring can have the same function as solvent molecules, by pulling the metal away from the halogen any halogen-metal interaction is prevented and therefore the stability is increased.

12 Coulomb's law states that the the energy between two charges Q_1 and Q_2 separated at a distance r is $E = (1/(4\pi\varepsilon_0))* Q_1Q_2/r$ ($\varepsilon_0= 8.854*10^{-12}$ F/m, in vacuum).

13 Some data concerning the alkali metal-carbon bonds are given in table 5, taken from: Schade, C.; von Ragué Schleyer, P. *Advances in Organometallic Chemistry* **27** (1987) 169.

Table 5: Fysical data of carbon-alkali metal bonds.

bond	bond lenght C-M (Å)[a]	ionic radius M (Å)[b]	electronegativity M[c]
C-Li	2.28	0.60	0.97
C-Na	2.62	0.95	1.01
C-K	3.22	1.33	0.91
C-Cs	3.53	1.69	0.86

[a] Average value from X-ray structures of alkylalkali compounds. [b] According to Pauling: Pauling, L. *The Nature of the Chemical Bond* Cornell Univ. Press, Ithaca, New York (1960). [c] According to Allred-Rochow: Rochow, E. J.; Allred, A. L. *J. Inorg. Nucl. Chem.* **5** (1958) 264. Electronegativity of carbon : 2.50.

14 Calculations were carried out using the program Gamess with a basis set SV 6-31G*: Dupuis, M; Spangler, D.; Wendoloski, J. J. *Gamess* NRCC Program QG01 (1980) Vol 1; Guest, M. F.; Harrison, R. J.; van Lenthe, J. H.; van Corler, L. C. H. *Theor. Chim. Acta.* **71** (1987) 117; van Lenthe, J. H. *Supercomputers* **5** (1985) 33. See also van Eikema Hommes, N. J. R.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **31** (1992) 755.

[15] Solov'yanov, A. A.; Beletskaya, I. P. *Russ. Chem. Rev.* **47** (1978) 425; Schade, C.; Bauer, W.; von Ragué Schleyer, P. *J. Organomet. Chem.* **295** (1985) C25; Pi, R.; Bauer, W.; Brix, B; Schade, C.; von Ragué Schleyer, P. *J. Organomet. Chem.* **306** (1986) C1. see also ref [14].

[16] Possibly decomposition occurs within monomers in the case of the lithium compound, but the preference for formation of dimers will delay the formation of these monomers, and therefore delays the formation of lithium-fluorine contacts.

[17] Discussion on the extent of ionicity of the various carbon-alkalimetal bonds is still going on. It is generally assumed, however, that the C-Na, C-K and C-Cs bond are virtually equally polarized, the C-Li bond may be somewhat less polar, although not all chemists agree on this topic. See thesis Sjoerd Harder, University of Utrecht (1990); Sygula, A.; Rabideau, P. W. *J. Am. Chem. Soc.* **114** (1992) 821.

[18] See previous chapter.

[19] It is described that phenyl Grignard reagents containing a trifluoromethyl group in the *ortho*, *meta* or *para* position can suddenly explode during their preparation. When *p*-trifluoromethylphenylmagnesium chloride was prepared on a large scale this even resulted in the destruction of a chemical plant and the loss of life. Ashby, E. C.; Al-Fekri, D. M. *J. Organomet. Chem.* **390** (1990) 275.

[20] Whereas $LiCF_3$ is extermely unstable in THF (decomposition occurs at ~ -149°C in a Trapp-mixture (i.e. THF: diethyl ether: hexane= ~ 1:1:1), the copper analogue $CuCF_3$ is stable even at room temperature. Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **108** (1986) 832. Pentafluorophenylcopper has been prepared before, it is more stable compared to monofluorophenylcopper: Cairncross, A.; Sheppard, W. A. *J. Am. Chem. Soc.* **90** (1968) 2186. Similar derivatizations as described for *ortho*-lithiofluorobenzene have been reported for the trifluoromethyl substituted organometallic compound 2,4,6-tris(trifluoromethyl)-phenyllithium: Carr, G. E.; Chambers, R. D.; Holmes, T. F. *J. Organomet. Chem.* **325** (1987) 13.

[21] Bauer, W.; Seebach, D. *Helv. Chim. Acta* **67** (1984) 1972; Harder,S. ref. [17].

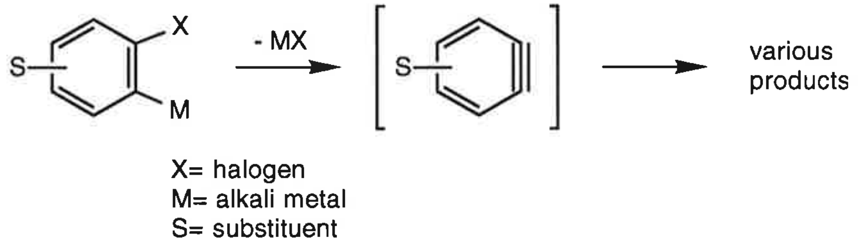
[22] See von Ragué Schleyer, ref [14]. See also Chapter 9.

Appendix

The Crystal Structure of 3-Bromo-2-lithio-thiophene·TMEDA

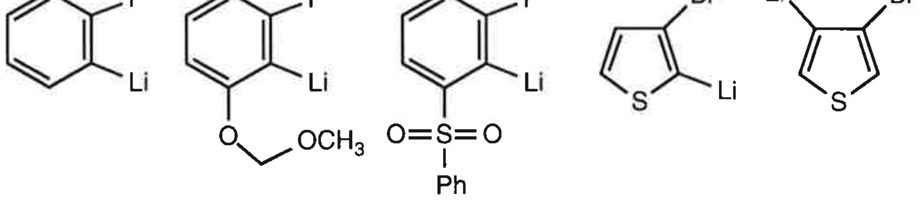
Introduction

Aromatic compounds containing an alkali metal and a halogen atom at two adjacent carbon atoms are often called arynoïds.[1] Many representatives are very unstable and eliminate metal halogenide with formation of arynes (see scheme 1). This decomposition is generally accompanied by a strong heating effect and results in the formation of a variety of compounds. In a few cases isolation of one product in good yield is possible.[1,2]



Scheme 1: Decomposition of an arynoïd.

Attempts to isolate the arynoïd *ortho*-lithiofluorobenzene (**1**) may lead to vigorous explosions.[3] The stability of arynoïds can be increased by introducing coordinating ligands around the alkali metal. Solvatation can contribute to a greater stability. THF, for example, stabilizes o-lithiofluorobenzene more than does diethyl ether, due to its better coordinating properties.[4] Coordinating groups present in the aromatic compound, as in compounds **2** and **3** in figure 1, can have an even greater positive influence on the stability. By pulling the metal away from the halogen the substituent prevents formation of the benzyne intermediate in compounds **2** and **3**. *Ortho*-lithiofluorobenzene (**1**) decomposes in THF at *ca.* -30°C. The presence of an ether function in the phenyl compound (**2**) increases the decomposition 'point' in THF to -15°C.[3] The sulfonyl compound **3** can be heated to up to +60°C before decomposition occurs.[5] It even appeared to be possible to obtain crystals of the complex from **3** and PMDTA (*N*,*N*,*N'*,*N"*,*N"*-pentamethylethylenediamine), which showed no Li-F interactions.[5]



1 **2** **3** **4** **5**

Figure 1: Some arynoïds (**1**, **2** and **3**) and heteroarynoïds (**4** and **5**).

Heteroaromatic compounds containing an alkali metal and halogen at neighbouring carbon atoms are generally much more stable than their aromatic analogues. Whereas there is a vast amount of literature on benzyne type reactions, there is only a limited number of these decomposition reactions known for pyridine and furan compounds. So far no decomposition *via* an aryne mechanism has been observed for thiophene compounds.[1,6] The reason for this higher stability is not yet known, but stabilization by the heteroatom of the negative charge on the carbon atom bearing the metal and structural aspects probably play an important role.

In view of this higher stability of heteroarynoïds and our experience with thienyllithium compounds we decided to try to isolate and characterize a thiophene arynoïd. A structure determination of such a compound could provide valuable information for a number of reasons:

i) although a lot of research has been done on thienyllithium compounds, only one crystal structure, *viz.* 2-benzothienyllithium, is known in this class of compounds.[7]

ii) such a crystal structure can possibly provide information on the mechanism of decomposition of arynoïds.[8] Boche *et al.* succeeded in determining the crystal structure of three arynoïds, *viz.* **3**·PMDTA, 3-bromo-2-lithio-benzofuran·O(^{i}Pr)$_2$ and 3-iodo-2-lithio-1-methylindole·2THF.[5,9] These compounds showed no halogen-lithium interactions due to the strong coordinating properties towards lithium of the sulfonyl group (for **3**) and internal oxygen (for the benzofuran compound) and solvent molecules. The sulfur-lithium coordination is much weaker than the oxygen-lithium coordination, therefore a thiophene arynoïd be an interesting model for investigating interactions in arynoïds.

Results and Discussion

In our investigations on the polymetallation of bromothiophenes we succeeded in isolating 3-bromo-2-lithio-thiophene (**4**) and 3-bromo-4-lithio-thiophene (**5**) in absence of coordinating ligands. These compounds have been used in syntheses but have never been isolated.[10] Both **4** and **5** are white solids, reacting violently with air and both are shock-sensitive (explosion !). Addition of TMEDA to a suspension of **4** in hexane resulted in dissolution the lithium compound and crystals were obtained after cooling. Crystals of **4**·TMEDA are stable at room temperature and far less sensitive to air and shocks. The crystal structure is shown in figure 2.

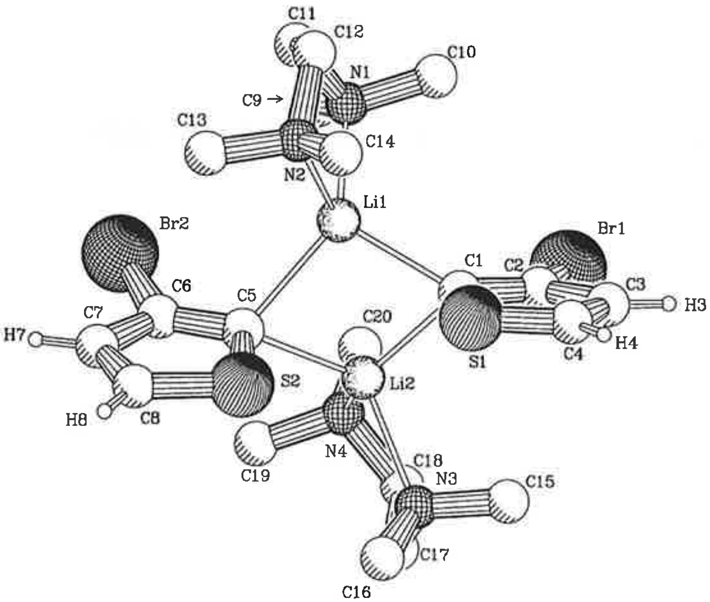


Figure 2: Molecular structure of [**4**·TMEDA]$_2$. Selected distances (Å) and angles (°): Li2-S2 3.080(10), Li2-S1 3.322(9), Li1-S2 3.299(8), Li1-S1 3.106(10), S2-C5 1.767(5), C5-C6 1.324(9), C6-Br2 1.931(6), C5-Li1 2.237(10), C5-Li2 2.218(12), S2-C8 1.581(10), C6-C7 1.432(10), C7-C8 1.405(11); C2-Br1 1.922(6), Li1-N1 2.123(9), Li1-N2 2.186(11), Li1-Br2 3.895(7), Li2-Br2 4.360(8), Li1-Br1 4.380(8), Li2-Br1 3.958(6); C8-S2-C5 98.1(3), S2-C5-C6 101.8(4), C5-C6-C7 121.1(6), C5-C6-Br2 121.7(4), Li1-C5-C6 123.4(5), S2-C5-Li1 110.4(3); S2-C5-Li2 100.6(4), Li1-C5-Li2 73.8(4), C2-C1-Li1 143.0(5); C2-C1-Li2 122.3(5); Li1-C1-Li2 72.1(4), Li1-C5-C6-Br2 52.2(7), Li2-C5-C6-Br2 -56.8(9), S2-C5-C6-Br2 176.6(3), Li1-C1-C2-Br1 -50.6(10), Li2-C1-C2-Br1 52.9(7).

The structure of **4**·TMEDA consists as a *cis* dimer, in which the anionic carbon atoms are bridged through lithium. Further coordination to lithium is provided by the TMEDA molecules. No intramolecular S-Li bridging is present, the S-Li distances vary from 3.08 to 3.32 Å (compare to the internal O-Li distance of 1.95 Å in 3-bromo-2-lithio-benzofuran·O(^{i}Pr)$_2$).[5] These structural features were also present in the previously investigated lithiated thiophenes.[7,11] Stabilization of the negative charge on the carbon atoms in **4**·TMEDA might occur by negative hyperconjugation and polarization effects of sulfur. In the similar 3-bromo-2-lithio-benzofuran·O(^{i}Pr)$_2$ the strong internal Li-O contacts provides strong stabilization.[5]

In figure 3 views along the Li1-Li2 axis and along the planes of the rings are shown.

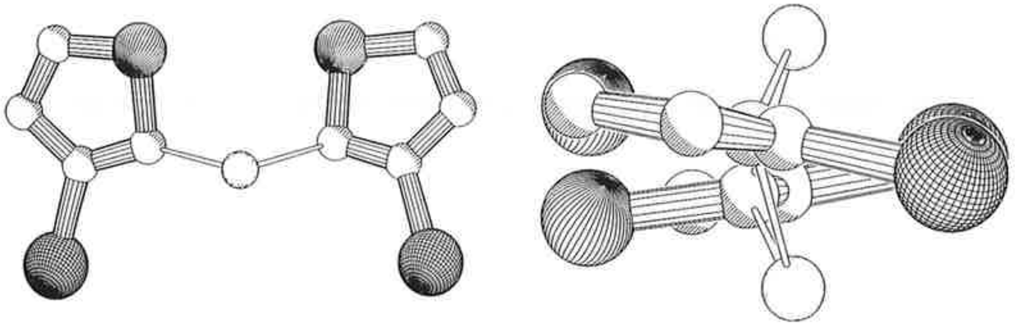


Figure 3: View of **4** along the Li1-Li2 axis and along the planes of the rings. TMEDA molecules and hydrogen atoms have been omitted for clarity.

In order to reduce steric hindrance of the bromine atoms which are both placed on the same side of the dimer the rings are tilted towards each other and somewhat twisted.

The stability of **4**·TMEDA towards β-elimination of lithium bromide can be explained by the relatively large Li-Br distances, varying from 3.90 to 4.38 Å (in 3-bromo-2-lithio-benzofuran·$O(^{i}Pr)_2$ the same distance varies from 3.87 to 5.33 Å). There is no Li-Br approach, which is visualized by the C6C5Li1 (123.4°) and C2C1Li2 (122.3°) angles, which are normal for five-membered rings. In a compound activated towards elimination one would also expect an elongated C-Br bond, the C6Br2 (1.931 Å) and C2Br1 (1.922 Å) distances are normal, however (compare the same distance in 3-bromo-2-lithio-benzofuran·$O(^{i}Pr)_2$: 1.893 Å). The origin of these long Li-Br distances are probably the geometry of the five membered ring, dimer formation (in a monomer the Li-Br distance would be shorter) and strong solvatation by the solvent.

From the results mentioned above it seems a general feature that in lithiated halogen containing five-membered heteroaromatics no lithium-halogen contacts exist in the presence of solvents such as TMEDA or (cyclic) ethers. The presence of strong coordinating groups further diminishes the possibilities of the appearance of such contacts. Models for arynoïds are therefore best sought in the group of lithiated halobenzenes (preferrably in the presence of not or only weakly coordinating groups). Their low stability could turn out to be a severe obstacle, however.

Upon addition of TMEDA to a suspension of **5** in hexane only part of the solid passed into solution. Cooling of the mother liquid gave crystals which appeared to consist solely of **4**·TMEDA, which is probably formed *via* an exchange reaction catalysed by 3-bromo-thiophene. Such-like isomerisations are known to occur with the various metallated halo-thiophenes.[7]

Experimental methods

2,3-Dibromothiophene and 3,4-dibromothiophene were prepared according to literature procedures.[12]

All reactions and manipulations were carried out under an inert nitrogen atmosphere using standard Schlenk techniques. All solvents were dried before use.

To a stirred solution of 2.42 g (10 mmol) of 2,3-dibromothiophene in 50 ml of hexane was added 6.25ml of a 1.6 M solution of ^{n}BuLi (10 mmol) in hexane at room temperature. Immediately a white precipitate (**4**) was formed. The precipitate was washed twice with hexane and subsequently dried under oil-pump vacuum. The remaining white powder was extremely reactive with air and shock-sensitive (*explosion !*). To a suspension of **4** in 50 ml of hexane was added 1.00 g (9 mmol) TMEDA upon which most of the precipitate dissolved. By cooling the mother liquid slowly to -30°C crystals of **4**·TMEDA, suitable for X-ray anaysis, precipitated.

^{1}H- and ^{13}C-NMR spectra of the crystals were recorded on a Bruker AC 300 at room temperature in benzene-d_6:

^{1}H NMR: δ= 1.77 (s, 4H TMEDA); 1.95 (s, 6H TMEDA); 7.35 (d, H4, *J*= 4.2 Hz, 1H); 7.61 (d, H5, *J*= 4.2 Hz, 1H)

^{13}C NMR: δ= 46.0 (CH_3 TMEDA); 57.2 (CH_2 TMEDA); 121.4 (C6); 130.8 (C7); 133.3 (C8); 167.4 (m, C5)

Crystal structure determination.

Crystals are transparent colourless. A specimen suitable for data collection was cut to an appropriate size [0.20*0.25*0.25 mm] in an inert protective oil. X-ray data were collected on an ENRAF-NONIUS CAD4T/rotating anode system at 100 K. Numerical details have been collected in table 1. Cell parameters were derived from the setting angles of 25SET4 reflections in the range $10 < \theta < 14°$. The reflection data were corrected for Lp, a linear decay and absorption (DIFABS[13], correction range 0.80: 1.38). The structure was solved with DIRDIF[14] and refined by full matrix least-squares on F with SHELLX76[15]. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were taken into account at calculated positions (C-H= 0.98Å) with two common isotropic displacement parameters, riding on their carrier atoms. One reflection was omitted from the final weighted refinement. Scattering factors were taken from Cromer and Mann[16], corrected for anomalous dispersion[17]. geometrical calculations were done with PLATON[18].

Similar treatment of **5** also gave a white powder after isolation. Quench experiments with dimethyl disulfide showed this to consist solely of **5**. Addition of excess TMEDA to a suspension of **5** in hexane resulted in only partial dissolution. After centrifugation the clear liquid was decanted into a Schlenk vessel. The crystals which were formed upon cooling proved to be pure **4**·TMEDA (determined by ^{1}H- and ^{13}C-NMR and X-Ray structure determination).

Table 1: Crystal data and details of structure determination of **4**·TMEDA.

Crystal data	
empirical formula	C20 H36 Br2 Li2 N4 S2
formula weight	570.35
crystal system	triclinic
space group	P-1 (n^{o} 2)
a, b, c [Angstrom]	10.199(1) 10.936(1) 13.737(1)
alpha, beta, gamma [deg]	91.73(1) 103.32(1) 112.34(1)
V [Ang^3]	1367.2(2)
Z	2
D(calc) [g/cm^3]	1.385
F(000) [electrons]	584
Mu(MoKa) [/cm]	30.9
crystal size [mm]	0.20*0.25*0.25
Data collection	
temperature (K)	100
radiation [Angstrom]	MoKa(Mon) 0.71073
theta min-max [deg]	1.53, 27.5
scan type	omega/ 2 theta
scan, [deg]	0.70 + 0.35 tan(theta)
hor. and vert. aperture [mm]	3.02 4.00
reference reflection(s)	30% linear decay
dataset	-13: 12; -14: 14; -16: 17
tot. uniq. data, R(av)	11931, 6285. 0.092
observed data [I > 2.5 sigma(I)]	3566
Refinement	
Nref, Npar	3565, 297
R, wR, S	0.059, 0.060, 1.54
weighting scheme	w-1= sigma^2(F) + 0.0004 F^2
max. and av. shift/error	0.18, 0.027
min. and max. resd. dens. [e/ Ang^3]	-0.67, 1.27

References

1 Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes* Verlag Chemie Weinheim/Academic Press New York (1967).

2 Fossatelli, M.; Brandsma, L. *Synthesis* (1992) 756.

3 Harder, S., unpublished results.

4 Nefedov, O.M.; Dyachenko A.I. *Angew. Chem.* **84** (1972) 527.

5 Bosold, F.; Zulauf, P.; Marsch, M.; Harms, K.; Lohrenz, J.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **30** (1991) 1455.

6 Reinecke, M.G. *Tetrahedron* **38** (1982) 427; Radom, L.; Nobes, R.H.; Underwood, D.J.; Li, W.K. *Pure Appl. Chem.* **58** (1986) 75.

[7] Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J.A.; Bauer, W.; Pi, R.; Von Ragué Schleyer , P.; Schöllhorn, H.; Thewalt, U. *Organometallics* **8** (1989) 1688; Thesis Sjoerd Harder, University of Utrecht, 1990.

[8] Some crystal structures are known in which halogen-lithium interactions appear, none of these compounds involve arynoïds however. The crystal structure of 2,4,6-tris(trifluoromethyl)phenyllithium·Et_2O showes internal Li-F interactions, stabilizing this compound. Stalke, D.; Whitmire, K. H. *J. Chem. Soc., Chem. Commun.* (1990) 833. The crystal structure of lithium-N-(fluorosilyl)pentafluoroaniline also showes (N)Li-F interactions. Stalke, D.; Klingebiel, U.; Sheldrick, G. M. *Chem. Ber.* **121** (1988) 1457.

[9] Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **126** (1993) 1887.

[10] Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **B 30** (1976) 505; Tserng, K.Y.; Bauer, L. *J. Org. Chem.* **40** (1975) 172.

[11] Besides the published structure determination of 2-lithiobenzothiophene Harder *et al.* described the solid state structure of 2-lithiothiophene. These results were not published however. See ref [7].

[12] 3,4-dibromo-thiophene: Reinecke, M.G.; Adickes, H.W.; Pyun, C.J. *J. Org. Chem.* **36** (1971) 2690.
2,3-dibromo-thiophene: Gronowitz, S.; Dahlgren, K. *Ark. Kemi* **21** (1963) 201.
see also: Keegstra, M. A.; Brandsma, L. *Synthesis* (1988) 890.

[13] Walker, N.; Stuart, D. *Acta Crystallogr., Sect. A* **39** (1983) 158.

[14] Beurskens, P. T.; Admiraal, G.; Beurskens G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O. *The DIRDIF Program System* Technical Report of the Crystallographic Labaratory; University of Nijmegen, The Netherlands (1992).

[15] Sheldrick, G. M. *SHELX76. Crystal structure and analysis package.* University of Cambridge, Cambridge, England (1976).

[16] Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A* **24** (1968) 321.

[17] Cromer, D. T.; Liberman, D. *J. Chem. Phys.* **53** (1970) 1891.

[18] Spek, A. L. *Acta Crystallogr., Sect. A* **46** (1990) C34.

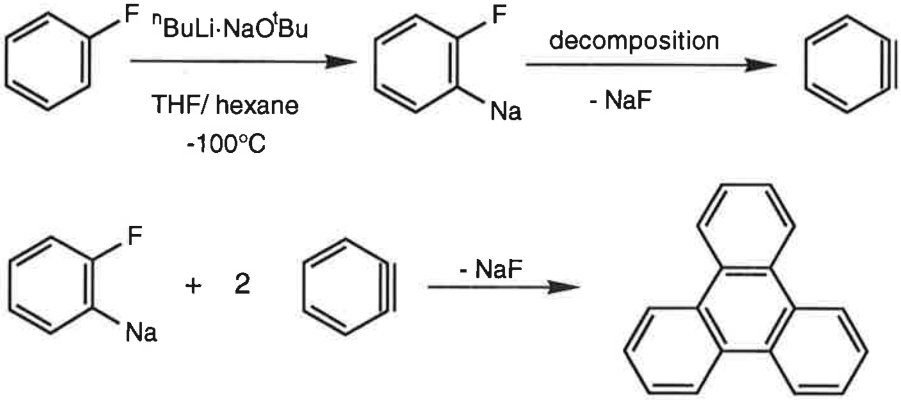
Chapter 5

An Efficient Synthesis of Triphenylene

Results

Triphenylene (**1**) can be obtained by ring-closure or dehydrogenation of polycyclic compounds. Though yields are often high, a serious draw-back of these syntheses is that the precursors are not simply available.[1] Another synthetic principle involves the decomposition of (*in situ* prepared) *ortho*-metallated halobenzenes.[2] A 30% yield of (**1**) has been reported for the decomposition of *o*-lithio-iodobenzene prepared from *o*-diiodobenzene and lithium in diethyl ether.[3] Wittig *et al.*[4] obtained **1** in 20% yield from the reaction of *o*-bromofluorobenzene with magesium in tetrahydrofuran. Heaney *et al.*[5] reported a yield as high as 85% for the same conversion, but our results were comparable with those of Wittig *et al.*.

Previously we reported on the facile *ortho*-metallation of fluorobenzene with equimolar mixtures of *n*-butyllithium and potassium *tert*-butoxide in tetrahydrofuran.[6] The analogous reactions with sodium and cesium *tert*-butoxide also proceed satisfactorily. During a study on the decomposition of *o*-lithio-fluorobenzene and analogues with a heavier alkali metal we noticed that sodiated fluorobenzene decomposed more easily than the other alkali metal derivatives. Analysis of the mixture obtained after decomposition of *ortho*-sodiofluorobenzene in THF revealed that appreciable amounts of **1** were present in the product mixture, whereas in the other cases only minor amounts had been formed.



1 66%

Scheme 1: Decomposition of *ortho*-sodiofluorobenzene and subsequent formation of triphenylene.

The isolated yield of **1** appeared to depend strongly upon the rate at which the temperature was allowed to rise after, in the region above -40°C, the decomposition had become clearly observable by the heating effect. Moderate yields (15 to 30%) were obtained when by efficient cooling the temperature was allowed to rise to 0°C over periods of 15 to 30 minutes. Over 60% yield could be obtained by quickly immersing the reaction flask completely in a bath with liquid nitrogen as soon as (at *ca.* -30°C) the temperature had begun to rise very fast; nevertheless the temperature rose within a few seconds to *ca.* 20°C. The fast decomposition of the metallated fluorobenzene may give rise to a temporarily high concentration of benzyne and hence to a high yield of (**1**).

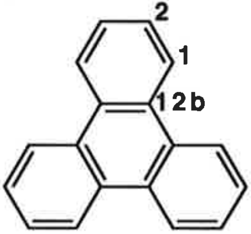
The high yield of triphenylene in the case of decomposition of *ortho*-sodiumfluorobenzene might be explained by an effective approach of the sodium ion and fluorine atom in the 2-fluoro-2"-sodium-terphenyl precursor of triphenylene (see figure 1), resulting in facile elimination of sodium fluoride and formation of triphenylene. In the other alkali metal terphenyl derivatives this approach may not be attained.

Figure 1: Precursor of triphenylene, 2-fluoro-2"-sodium-terphenyl.

Experimental methods

Reactions were carried out under an atmosphere of nitrogen. All solvents were dried before use. *n*-Butyllithium (1.6 Molar solution in hexane) and heavier alkali metal alkoxides were obtained commercially. Metallation mixtures were cooled with a liquid nitrogen bath. Products were isolated by distillation and analyzed by NMR spectroscopy and GLC analysis. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) using CS_2 as solvent and C_6D_6 as internal standard (CS_2/C_6D_6: 90/10 v/v%). GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

In a 500 mL three-necked round-bottomed flask, equipped with a mechanical stirrer, thermometer and dropping-funnel (in combination with gas-inlet and -outlet, respectively) was placed 63 mL of a 1.6 M (0.10 mol) solution of *n*-butyllithium in hexane, which was cooled to below -50°C. Fluorobenzene (11.5 g, 0.12 mol) was added and the mixture was further cooled with liquid nitrogen to -100°C. Then a solution of 9.6 g (0.10 mol) of sodium *tert*-butoxide in 100 mL of tetrahydrofuran was added over a few minutes with efficient stirring while maintaining the temperature between -90°C and -100°C. The temperature of the light-yellow, clear mixture was allowed rise to -30°C over 10 minutes (occasional cooling may be neccessary). At this point, when a strongly exothermic reaction was observed, the flask was promptly immersed completely in a bath with liquid nitogen (when no cooling is applied, the temperature may rise to over 60°C and part of the reaction mixture may be splashed out of the flask due to the rapid evolution of butane). The temperature rose over a few seconds to 20°C. The black slurry was then treated with 100 mL of ice water and, after separation of the layers, three extractions with 50 mL portions of diethyl ether were carried out. The combined organic fractions were dried over magnesium sulfate and subsequently concentrated *in vacuo*. Crystallization of the remaining solid from tetrachloromethane gave triphenylene as white needles: 5.0 g (66%); mp 189-191°C, lit. 189-191°C.[4,5] NMR-data (CS_2/C_6D_6 (90/10 v/v%)), for numbering see below: ^{1}H-NMR: δ= 7.45 (dd, H2, *J*= 9.6, 3.3 Hz, 6H), 8.41 (dd, H1, *J*= 9.5, 3.4 Hz, 6H); ^{13}C-NMR: δ= 123.7 (C1), 127.5 (C2), 130.1(C12b). NMR data are in accordance with literature.[7]



When the same procedure was applied with potassium or cesium *tert*-alkoxide in stead of sodium *tert*-butoxide only traces of triphenylene were obtained. Main products were 2-fluorobiphenyl and 2-fluoro-*o*-terphenyl (i.e. 2-fluoro-1,1':2',1"-terphenyl). Decomposition of *o*-lithiofluorobenzene in THF, prepared by bromine lithium exchange between *o*-bromofluorobenzene and *n*-butyllithium in THF at -90°C, also gave only traces of triphenylene.

References

1 Nenitzescu, C. D.; Curcaneanu, D. *Ber. Dtsch. Chem. Ges.* **70** (1937) 346; Sato, T.; Goto, Y.; Hata, K. *Bull. Chem. Soc. Jpn.* **40** (1967) 1994; Hansch, C.; Geiger, C. F. *J. Org. Chem.* **23** (1958) 477; Hausigk, D. *Chem. Ber.* **101** (1968) 473.
2 Heaney, H. *Chem. Rev.* **62** (1962) 81, and references cited therein.
3 Heaney, H.; Mann, F. G.; Millar, I. T. *J. Chem. Soc.* (1956) 1.
4 Wittig, G.; Knauss, E. *Chem. Ber.* **9** (1958) 895.
5 Bartle, K. D.; Heaney, H.; Jones, D. W.; Lees, P. *Tetrahedron* **21** (1965) 3289.
6 Fossatelli, M; Verkruijsse, H. D.; Brandsma, L. *Synth. Commun.* **20** (1990) 1701; see Chapters 3 and 4.
7 Kalinowski, H. A.; Berger, S.; Braun, S. *^{13}C-NMR-Spektroskopie* Thieme, Stuttgart (1984); Jonathan, N.; Gordon, S.; Dailey, B. P. *J. Chem. Phys.* **36** (1962) 2443.

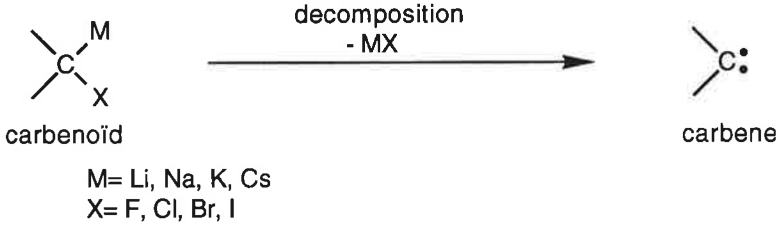
Chapter 6

The Influence of the Alkali Metal on the Stability of Carbenoïds
A Preliminary Investigation

Introduction

Since the publication of a series of articles by Closs and Closs on the metallation of dichloromethane in the late fifties[1] the field of carbenoïd chemistry has been investigated extensively. The applications in organic synthesis not only comprise the use of carbenoïds as precursor of carbenes but also their functionalization.

Decomposition of carbenoïds generally occurs by 1,1-elimination of alkali metal halogenide:



Scheme 1: Decomposition of a carbenoïd.

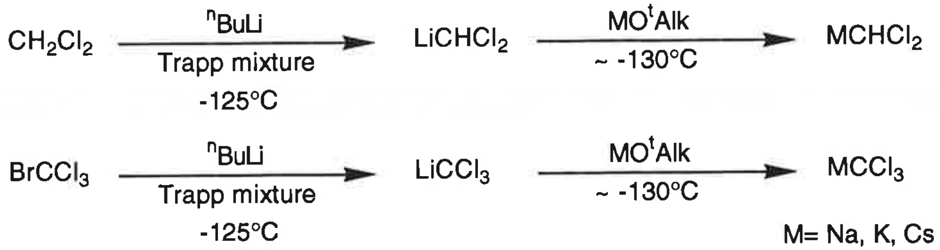
Some carbenes are very reactive in additions to unsaturated systems, especially C-C and C-O double bonds. The products are cyclopropanes and epoxides respectively.[2] Another important reaction of carbenes is their insertion into various bonds, e.g. C-H and C-Li bonds.[3] The various applications of carbenoïds in organic synthesis have been reviewed.[4]

Carbenoïds are generally prepared in solvents with Lewis-base character, as they are better stabilized by these solvents[5,6] Little is known about the influence of the *alkali metal ion* on the stability of carbenoïds.[7] The present chapter deals with some preliminary investigations on this subject which is a continuation of our studies on the stability of *ortho*-metallated fluorobenzene (described in the preceeding chapter).

Methods and results

Generation of carbenoïds.

The investigations described below have been done on the following carbenoïds $MCHCl_2$, $MCCl_3$, $MCBr_3$ and $MCBr_2Ph$ (M= Li, Na, K, Cs). The species were generated by known methods, examplified in the equations below:



Scheme 2: Preparation of carbenoïds by deprotonation and bromine-lithium exchange, followed by transmetallation.

The apparatus in which the carbenoïds were generated is similar to the one used for the generation of *ortho*-metallated fluorobenzene and its decomposition. A double-walled flask was used instead of a double Schlenk-vessel.

The reaction was performed in a mixture consisting of pentane, diethyl ether and THF, similar to the one used by Trapp *et al.* [6] This so-called Trapp-mixture has a relatively low viscosity, even at temperatures in the region of -130°C.

The lithium carbenoïds were generated at ~ -125°C. Heavier metal carbenoïds were prepared by subsequently adding a heavier alkali metal *tert*-alkoxide (MO^tBu for M= Na and K and CsO^tAm).

A major problem was to control whether the metallations at these low temperatures were complete. Under these conditions almost all electrophiles react slowly. With dimethyl disulfide products were formed that react with water during the (aqueous) work-up.

Functionalization of $LiCHCl_2$ with pivaldehyde gave the expected carbinol $(CH_3)_3$-C(OH)-$CHCl_2$ in a 85% yield. When prior to the reaction with pivaldehyde a solution of sodium *tert*-butoxide in the Trapp-mixture was added at -120°C, the same carbinol was obtained in 73% yield.

The stability of carbenoïd species.

In order to determine the decomposition temperature of the carbenoids their solutions were allowed to warm-up slowly in the reaction vessel (described in the experimental methods) while the temperature was recorded. Decomposition was indicated by a sudden increase of the temperature by 30 to 60° within a few seconds, when working with 27 mL of a 0.6 M solution (in the case of $KCCl_3$ even 80° within 5 seconds). At the same time the mixtures became dark-colored.

In the first series of experiments the stability of $LiCCl_3$ in different solvent mixtures was investigated. As is shown in table 1 the stability of $LiCCl_3$ seems to decrease with decreasing polarity of the solvent mixture for $LiCCl_3$ in different solvent mixtures.[8]

Table 1: Decomposition temperatures T_d (°C) of $LiCCl_3$ in different solvent mixtures.[9]

Carbenoid	amount	mL THF	mL ether	mL alkanes[a]	T_d (°C)
$LiCCl_3$	15 mmol	6 [b]	6 [b]	15 [b]	-50
$LiCCl_3$	15 mmol	0	12	15	-124
$LiCCl_3$	15 mmol	0	0	27	<-125

[a] Hexane from butyllithium solution (9 ml), and pentane. [b] This is a modified Trapp mixture.

Next the decomposition temperatures of the various $MCHCl_2$, $MCCl_3$, $MCBr_3$ and $MCBr_2Ph$ (M= Li, Na, K, Cs) in the Trapp-mixture were measured.

Table 2: Decomposition temperatures (°C) for carbenoïds of initially 0.5 M in a modified Trapp-mixture.[a]

M	$MCHCl_2$	$MCCl_3$	$MCBr_3$	$MCBr_2Ph$
Li	-45[b]	-50[c]	-62[d]	-41[c]
Na	-97	-98	-103	-99
K	-118	-122	-113	-118
Cs	-119	-126	-119	-119

[a] THF/diethyl ether/alkanes= ~ 6/6/15. [b] Prepared by deprotonation. [c] Prepared by bromine-lithium exchange. [d] Generally $LiCBr_3$ is prepared from $HCBr_3$ and LDA. In order to have the same reaction conditions for all carbenoïds we choose to prepare it from CBr_4 and $^{n}BuLi$, so no HDA (a strong Lewis-base) is present in solution.

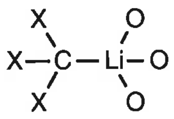
The dissociations of MCX_3 (X= Cl, Br) and $MCHCl_2$ were attended with a strong colouration to brown or black and formation of a black suspension, in the case of $MCBr_2Ph$ the mixture turned red.

Preliminary experiments showed that MCF_3 was extremely unstable: with all alkali metals decomposition occurred below -130°C. Similar results were found for MCI_3, with the exception of $LiCI_3$, which decomposed at ~ -118°C.

The trend shown in all decompositions is clear: stability *de*creases in the order M= Li >> Na > K > Cs and X= Cl ≈ Br >> I ≈ F.

Discussion.

NMR-studies by Seebach *et al.* suggested that in the presence of THF $LiCX_3$ (X= Cl, Br) exists in a monomeric or dimeric form.[10] The measured carbon-lithium coupling constants suggest a monomer conformation as they do not vary very much with the various halogens; in a dimer conformation halogen bridging would exert a larger influence. Therefore it is probable that $LiCX_3$ exists at low temperature in a monomer form with little or no metal-halogen interactions, most likely tetrahedral, see figure 1. Generally sodium, potassium and cesium compounds are monomers in THF.[11]



X= Cl, Br
O= oxygen atom from THF

Figure 1: Monomeric carbenoïd species.

Decomposition of the carbenoïd involves separation of MX. It is assumed that the metal and halogen leave the carbenoïd simultaneously, this requires a preliminary interaction of metal and halogen. Two possible mechanisms for this to occur are:

1) dissociation of MX induced by coulombic interaction of both the negatively charged halogen and the positively charged alkali metal, resulting in dissociation of the molecule. Approach of M and X is driven purely by coulombic interactions, at a certain moment a critical distance M-X is reached and metal halogenide eliminates. One stipulation for this model is a rather ionic metal-carbon bond and highly polar halogen-carbon bond. Such an electrostatic interaction was also found for the dissociation of another class of unstable metallated halocompounds, the arynoïds (see previous chapter).

2) a mechanism which is based on the possibility for the molecule to transform, at a certain temperature, into a stable conformation of higher energy which opens a favourable pathway to dissociation. In this case the energy-gap between two conformations is of importance in the first place, not Coulombic interaction (of course Coulombic interactions are present in the molecule, but they ar not decisive for the stability). In several *ab initio* calculational studies on carbenoids various stable, though sometimes exotic, non-tetrahedral structures have been calculated.[12]

Figure 2 shows schematical graphical energy diagrams for both hypotheses. Following the first hypothesis, non of the successive conformations leading to decomposition is stable, the highest energy conformation is a transition state. In the second hypothesis at least one of the successive conformations is stable.

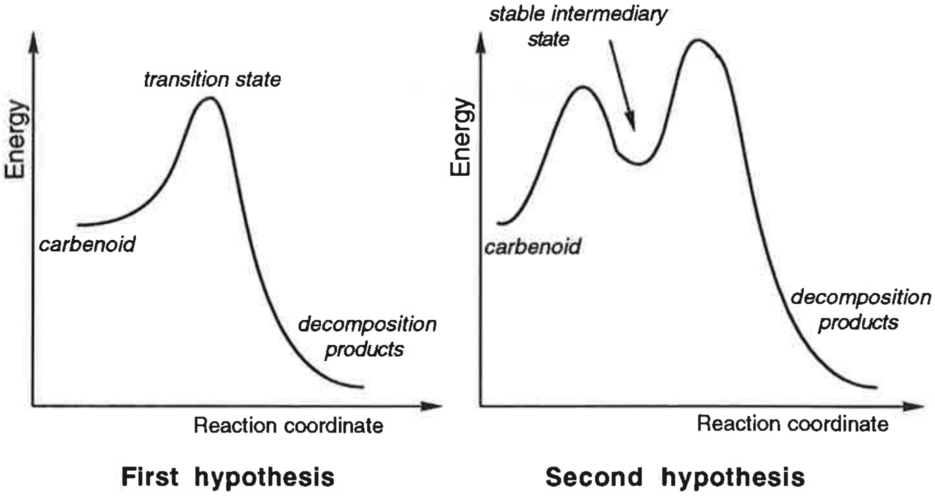
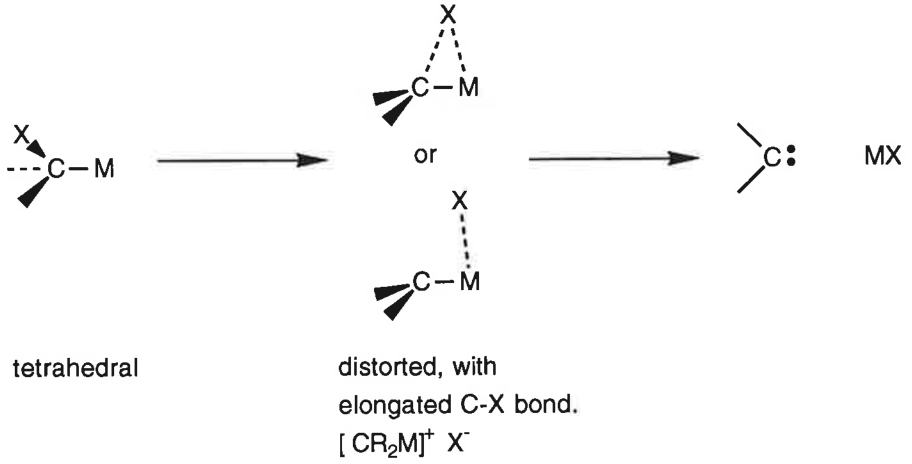


Figure 2 : Schematic energy diagrams for decomposition according to hypotheses 1 and 2.

Our experimental results do not agree with the first hypothesis. As coulombic attraction will decrease with larger atoms, due to smaller electric charge per area, polarisation effects and larger distances, a stability order Cs > K > Na > Li would be expected (this is indeed the order of stability found for arynoïds, for which dissociation of MX is determined by electrostatics[13]). The stability order found by us for carbenoïds is opposite.

The overall stability order of Li >> Na > K > Cs and Cl ≈ Br >> I > F found in our experiments agrees fairly with the second hypothesis. The more strongly a substituent is bound to the central carbon atom, the more difficult it will be to conform to another structure, i.e. the more stable the carbenoïd will be. The strenght of the carbon-metal bond increases in the order C-Cs < C-K < C-Na < C-Li and the strenght of the carbon-halogen bond increases in the order C-I < C-Br < C-Cl < C-F. These correspond with the orders of stabilities found for the carbenoïds (except for fluorine, which will be discussed later). Experimental observations also subscribe to the second hypothesis. The number of halogens and the presence of subsituents does not have a *large* influence on the stability of the carbenoids. This relatively small influence of the halogen suggests a structure of the carbenoïd immediately before decomposition like $[R_2CM]^{\delta+} X^{\delta-}$. On basis of these results we propose the following mechanism for the decomposition of carbenoïds.



Scheme 5: Probable mechanism of decomposition of a carbenoïd.

Similar intermediary structures were found in various quantumchemical calculations, which predict the presence of stable conformations in which lithium-halogen interactions occur.[14] A dihalogenocarbene-metal halide complex with a structure $X^{-}\cdots M^{+}\cdots CCl_2$ has even been shown to exist by infrared examination by Andrews *et al.* of a matrix isolated complex.[15] Further evidence of the existence of $[R_2CM]^{\delta+} X^{\delta-}$ species, was given by Walborsky *et al.* in synthetic experiments with analogous vinylic carbenoids.[16] The crystal structure of such a vinylic carbenoïd, 1-chloro-2,2-bis(4-chlorophenyl)-1-lithiumethene·TMEDA·2THF, indeed showed an elongated carbon-chlorine bond, whereas the carbon-lithium bond was of normal lenght.[17] The crystal structure showed that no chlorine-lithium interactions were present.[18] Recently Boche *et al.* showed with theoretical calculations and crystal structures that in α-oxygen-substituted organolithium compounds, species similar to carbenoïds, the carbon-oxygen bond is elongated.[19]

For compounds $[R_2CM]^{\delta+} X^{\delta-}$ the determining step for decomposition will be the breaking of the carbon-metal bond. As the strength of this bond increases in the order Cs < K< Na< Li, the stability should also decrease in this order. This is indeed the case.

The second hypothesis also implies a larger role for steric effects: the larger the metal and halogen atoms, the easier it will be to effectuate a distorted (non)tetrahedral conformation which opens a pathway to dissociation, hence a stability order of Cs < K < Na < Li and I < Br < Cl < F (the relatively low stability of fluorine compounds will be discussed later).

The relatively high stability of the lithium compounds compared to the other alkali metal compounds can be explained by (stabilizing) bridging effects, *i.e.* an interaction of the HOMO of the carbanion and a low-lying p-orbital on the metal, see figure 3.[20] Bridging decreases in the order Li > Na > K > Cs, which clearly resembles the stability order of the carbenoids.

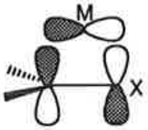


Figure 3 : Bridging of the metal atom and the anion.

The anomalous behaviour of the trifluoro and triiodo compounds can be explained as they presumably have unusual structures. The lithiumtrifluoro compound probably has extremely polarized Li-C and C-F bonds, which may result in the formation of some exotic structure. The steric crowding around the carbon atom in triiodomethyllithium can result in facile lithium-iodine contacts and hence a ready decomposition.

Experimental methods

General conditions.

Decomposition measurements were performed in a Dewar-type 150 mL three necked round-bottomed flask equipped with a dropping funnel, mechanical stirrer and a thermometer. Functionalization experiments were performed in a 250 mL three necked round-bottomed flask equipped with a dropping funnel, mechanical stirrer and a thermometer. A Systemteknik S2541 Thermolyzer fitted with a Pt-100 resistor mounted in a stainless tube and connected to a X-Y plotter was used as thermometer. All reactions were performed under an inert atmosphere of nitrogen. Solvents were dried before use. Liquid nitrogen was used for cooling. During all experiments splashing of the metallation mixture on the wall of the flask was prevented, in order to avoid decomposition. The temperature of upper parts of the flask is often higher and decomposition of the carbenoid can easily occur.

Decomposition Experiments.

Synthesis and decomposition of trichloromethyllithium (Method I).

In the flask were placed 6.0 mL of THF, 6.0 mL of diethyl ether, 6.0 mL of pentane and 3.0 g (15.0 mmol) bromotrichloromethane. The well stirred mixture was cooled to -125°C. To the resulting white suspension was added in ca. 60 minutes 9.5 mL of a 1.6M solution (15.0 mmol) of *n*-butyllithium in hexane while maintaining the temperature between -115 and -125°C (The time needed for addition was long due to the low cooling capacity of the flask and the fact that the reaction is very exothermic). The slightly grey suspension was stirred for 10 minutes at -120°C. The cooling bath was removed and the temperature of the slightly grey mixture was allowed to rise slowly (cotton wool was placed around the flask, the temperature increased with ca. 0.02°/s). Decomposition at ~ -50°C was indicated by a very fast rising of the temperature and formation of black lumps in a brown liquid.

Determination of the influence of solvent mixture on the stability of trichloromethylithium.

Trichloromethyllithium (15.0 mmol) was prepared at -130°C as described above in solvent mixtures as described in table 1. Subsequently decomposition temperatures were determined.

Synthesis and decomposition of trichloromethylsodium (Method II).

A suspension of 15.0 mmol of trichloromethyllithium in 6 mL of THF, 6 mL of diethyl ether and 6 mL of pentane was prepared according to method I. To this mixture was added over 20 to 30 minutes a mixture of 1.4 g (15.0 mmol) sodium tertbutoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane while maintaining the temperature at ca. -130°C. (If the sodium tertbutoxide is added at a too fast rate a darkening of the mixture occured due to partial decomposition). After stirring the suspension for 10 minutes at this temperature the cooling bath was removed, cotton wool was placed around the flask and the temperature was allowed to rise slowly. Decomposition at ~ -98°C was indicated by a very fast rising of the temperature and formation of black lumps in a brown liquid.

Synthesis and decomposition of trichloromethylpotassium.

The decomposition-experiment was performed according to method II. A mixture of 1.7 g (15 mmol) potassium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the trichloromethyllithium suspension at ca. -135°C. A slighty grey suspension was formed. During decomposition at ~ -122°C the mixture turned black.

Synthesis and decomposition of trichloromethylcesium.

The decomposition-experiment was performed according to method II. A mixture of 3.1 g (15 mmol) cesium tert-amylate, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the trichloromethyllithium suspension at ca. -140°C. A grey suspension was formed. During decomposition at ~ -126°C the mixture turned black.

Synthesis and decomposition of tribromomethyllithium.

According to method I a yellow suspension of 15.0 mmol tribromomethyllithium was prepared, starting from 5.0 g (15 mmol) tetrabromomethane. During decomposition at ~ -62°C the mixture turned black.

Synthesis and decomposition of tribromomethylsodium.

The decomposition-experiment was performed according to method II. A mixture of 1.4 g (15 mmol) sodium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the yellow tribromomethyllithium suspension at ca. -130°C. During this addition no change in colour was observed. The mixture turned black during decomposition at ~ -103°C.

Synthesis and decomposition of tribromomethylpotassium.

The decomposition-experiment was performed according to method II. A mixture of 1.7 g (15 mmol) potassium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the tribromomethyllithium suspension at ca. -130°C. During this addition no change in colour was observed. The mixture turned black during the decomposition at ~ -113°C.

Synthesis and decomposition of tribromomethylcesium.

The decomposition-experiment was performed according to method II. A mixture of 3.1 g (15 mmol) cesium tert-amylate, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the tribromomethyllithium suspension at ca. -130°C. During this addition no change in colour was observed. The mixture turned black during the decomposition at -119°C.

Synthesis and decomposition of dichloromethyllithium.

According to method I a white suspension of 15.0 mmol dichloromethyllithium was prepared, starting from 1.28 g (15 mmol) dichloromethane. During decomposition at ~ -45°C the mixture turned black.

Synthesis and decomposition of dichloromethylsodium.

The decomposition-experiment was performed according to method II. A mixture of 1.44 g (15 mmol) sodium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the dichloromethyllithium suspension at ca. --130°C. A white suspension was formed. During decomposition at -97°C the mixture turned black.

Synthesis and decomposition of dichloromethylpotassium.

The decomposition-experiment was performed according to method II. A mixture of 1.68 g (15 mmol) potassium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the dichloromethyllithium suspension at ca. -130°C. A white suspension was formed. During decomposition at ~ -118°C the mixture turned black.

Synthesis and decomposition of dichloromethylcesium.

The decomposition-experiment was performed according to method II. A mixture of 3.3 g (15 mmol) cesium tert-amylate, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the dichloromethyllithium suspension at ca. -130°C. A white suspension was formed. During decomposition at ~ -119°C the mixture turned black.

Synthesis and decomposition of α,α-dibromobenzyllithium.

According to method I a white suspension of 15.0 mmol α,α-dibromobenzyllithium was prepared, starting from 4.94 g (15 mmol) α,α,α-tribromotoluene. During decomposition at ~ -41°C the mixture turned black.

Synthesis and decomposition of α,α-dibromobenzylsodium.

The decomposition-experiment was performed according to method II. A mixture of 1.44 g (15 mmol) sodium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the α,α-dibromobenzyllithium suspension at ca. -130°C. A white suspension was formed. During decomposition at -99°C the mixture turned black.

Synthesis and decomposition of α,α-dibromobenzylpotassium.

The decomposition-experiment was performed according to method II. A mixture of 1.68 g (15 mmol) potassium tert-butoxide, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the α,α-dibromobenzyllithium suspension at ca. -130°C. A white suspension was formed. During decomposition at ~ -118°C the mixture turned black.

Synthesis and decomposition of α,α-dibromobenzylcesium.

The decomposition-experiment was performed according to method II. A mixture of 3.3 g (15 mmol) cesium tert-amylate, 1.5 mL of THF, 2.0 mL of diethyl ether and 1.5 mL of pentane was added to the α,α-dibromobenzyllithium suspension at ca. -130°C. A white suspension was formed. During decomposition at ~ -119°C the mixture turned black.

Caution! Care has to be taken in all cases when the temperature is allowed to rise in order to detect decomposition as the decomposition reaction is extremely exothermic. The rise in temperature amounted even to about 80°C in 5 seconds (observed in case of the decomposition of trichloromethylpotassium). In most cases a rise of 30 to 60°C in a few seconds was observed.

Functionalization Experiments.

Functionalization of dichloromethyllithium with pivaldehyde.

In the flask was placed a mixture of 4.25 g (0.05 mol) of dichloromethane, 20 mL of THF, 20 mL of diethyl ether and 20 mL of pentane. After cooling to -120°C 34.0 mL of a 1.6 M solution of (0.05 mol) *n*-butyllithium in hexane was added dropwise over 30 minutes while maintaining the temperature at -120°C. The white suspension was stirred for an additional 30 minutes at this temperature. A solution of 8.6 g (0.10 mol) pivaldehyde in a mixture of 5 mL of THF, 5 mL of diethyl ether and 5 mL of pentane was added dropwise over 30 minutes while maintaining the temperature at -120°C. The white suspension was stirred for an additional 30 minutes at this temperature. The cooling bath was removed and the temperature was allowed to rise. At -50°C 100 mL of water was added. The water layer was acidified with a 5 M HCl solution after which the layers were separated. The water layer was extracted three times with 50 mL diethyl ether. The combined organic layers were dried on magnesium sulfate and concentrated at reduced pressure. The carbinol $(CH_3)_3C(OH)\text{-}CHCl_2$ was obtained after distillation over a short Vigreux column, 7.1 g (83%). bp. 85-90°C (20 mm Hg). ^{1}H-NMR ($CDCl_3$): δ= 1.14 (s, $(CH_3)_3C$, 9H), 3.62 (d, $CH(OH)CHCl_2$, 1H, *J*= 1.6 Hz), 5.97 (d, $CH(OH)CHCl_2$, 1H, *J*= 1.6 Hz).

When the temperature of the metallation mixture was allowed to rise to -60°C the yield was ~ 75%.

Functionalization of dichloromethylsodium, obtained by metal-metal exchange.

A solution of 0.05 mol of dichloromethyllithium was prepared as described above. At -120°C a mixture of 5.60 g (0.05 mol) of sodium *tert*-butoxide, 5 mL of THF, 5 mL of diethyl ether and 5 mL of pentane was added over 30 minutes with good stirring. The white suspension was stirred for an additional 30 minutes at -120°C. Subsequently a mixture of 8.6 g (0.10 mol) of pivaldehyde, 5 mL of THF, 5 mL of diethyl ether and 5 mL of pentane was added dropwise over 30 minutes while maintaining the temperature at -120°C. The white suspension was stirred for an additional 30 minutes at this temperature. Work-up was further done as described above. The carbinol was obtained in 73% yield (6.3 g).

No product was obtained when, before quenching, the temperature of the metallation mixture was allowed to rise to -60°C.

References

1 Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **81** (1959) 4996; Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **82** (1960) 5723.

2 Huang, R. L.; Goh, S. H.; Ong, S. H. *The Chemistry of Free Radicals* Edward Arnold Publishers Ltd., London (1974); Kirmse, W. *Carbene Chemistry* Academic Press, New York (1971); Gilman, H.; Jones, R. H. *J. Organomet. Chem.* **18** (1969) 348; Burger, U.; Huisgen, R. *Tetrahedron Lett.* **35** (1970) 3053; Burger, U.; Huisgen, R. *Tetrahedron Lett.* **35** (1970) 3057; Skell, P. S.; Cholod, M. S. *J. Am. Chem. Soc.* **91** (1969) 7131; Bessard, Y.; Schlosser, M. *Tetrahedron* **47** (1991) 7323.

3 Houben-Weyl *Methoden der Organischen Chemie E19B-2* Georg Thieme Verlag, Stuttgart (1989); March, J. *Advanced Organic Chemistry* *3rd ed.* John Wiley & Sons, New York (1985).

4 Köbrich, G. *Angew. Chem.* **79** (1967) 15; Köbrich, G. *Angew. Chem.* **12** (1972) 563; Nefedov, O. M; D'yachenko, A. I.; Prokof'ev, A. K. *Russ. Chem. Rev.* **46** (1977) 941; Siegel, H. *Topics in Current Chemistry* **106** (1982) 55.

5 Haszeldine. R. N. *J. Chem. Soc.* (1954) 1273; Castro, B. *Bull. Soc. Chim. Fr.* 1540 (1967).

6 Köbrich, G.; Merkle, H. R.; Trapp, H. *Tetrahedron Lett.* **15** (1965) 969

7 Fischer, R. H.; Köbrich, G. *Chem. Ber.* **101** (1968) 3230; Köbrich, G.; Flory, K.; Fischer, R. H.*Chem. Ber.* **99** (1966) 1793; Martel, B.; Hiriart, J. M. *Tetrahedron Lett.* **29** (1971) 2737.

8 The same effect was found by Nefedov *et al.*: Nefedov, O. M.; Dyachenko, A. I. *Angew. Chem.* **84** (1972) 527; D'yachenko, A. I.; Ioffe, A. I.; Nefedov, O. M. *Bull. Acad. Sci. USSR* **2** (1979) 339.

9 All decomposition temperatures have been determined at least in duplo and results were reproducible. Estimated error is ±2°C.

10 Seebach, D.; Siegel, H.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta.* **63** (1980) 2046.

11 Solov'yanov, A. A.; Beletskaya, I. P. *Russ. Chem. Rev.* **47** (1978) 425; Schade, C.; Bauer, W.; von Ragué Schleyer, P. *J. Organomet. Chem.* **295** (1985) C25; Pi, R.; Bauer, W.; Brix, B; Schade, C.; von Ragué Schleyer, P. *J. Organomet. Chem.* **306** (1986) C1.

12 Clark, T.; von Ragué Schleyer, P. *J. Chem. Soc., Commun.* (1979) 883; Clark, T.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **101** (1979) 7747; Clark, T.; von Ragué Schleyer, P. *Tetrahedron Lett.* **51** (1979) 4963; Rohde, C.; Clark, T.; Kaufmann, E.; von Ragué Schleyer, P. *J. Chem. Soc., Chem. Commun.* (1982) 882; Luke, B. T.; Pople, J. A.; von Ragué Schleyer, P.; Clark, T. *Chem. Phys. Lett.* **102** (1983) 148; Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. *Ab Initio Molecular Orbital Theory* John Wiley & Sons, New York (1986).

13 See chapter 4.

14 *Ab initio* calculations on CH_2LiF isomers : Vincent, M. A.; Schaefer III, H. F. *J. Chem. Phys.* **77** (1982) 6103. See also ref[12].

15 Hatzenbühler, D. A.; Andrews, L.; Carey, F. A. *J. Am. Chem. Soc.* **97** (1975) 187.

[16] Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **106** (1984) 5035; Walborsky, H.M.; Duraisamy, M. *Tetrahedron Lett.* **26** (1985) 2743; Topolski, M.; Duraisamy, M.; Rachon, J.; Gawronski, J.; Gawronska, K.; Goedken, V.; Walborsky, H. M. *J. Org. Chem.* **58** (1993) 546.

[17] Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **32** (1993) 1032.

[18] The crystal structure was determined at -90°C.

[19] Boche, G.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W.; Thümmler, C.; Koch, W. *Chem. Ber.* **125** (1992) 2265.

[20] von Ragué Schleyer, P.; Clark, T.; Kos, A. J.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **106** (1984) 6467.

Chapter 7

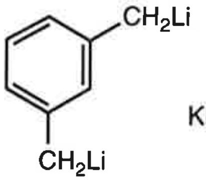
On the Halogen-lithium Exchange Reaction of Some Polybromothiophenes and -benzenes and Corresponding Iodium Compounds

Introduction

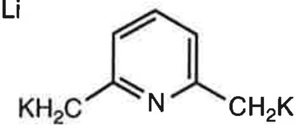
Generation and isolation of di- or polymetallated organic compounds continues to be a challenge to chemists working in the field of polar organometallics.[1,2]

There are two major ways for preparing polymetallated compounds:

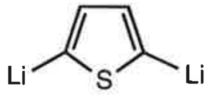
i) Deprotonation with strongly basic systems like ^{n}BuLi·KO^{t}Bu in THF or pentane or with ^{n}BuLi·TMEDA in hexane. Some examples of dianions prepared in this way are shown below.[2,3]



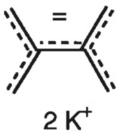
(^{n}BuLi·TMEDA in hexane)



(^{n}BuLi·KO^{t}Bu·TMEDA in pentane)

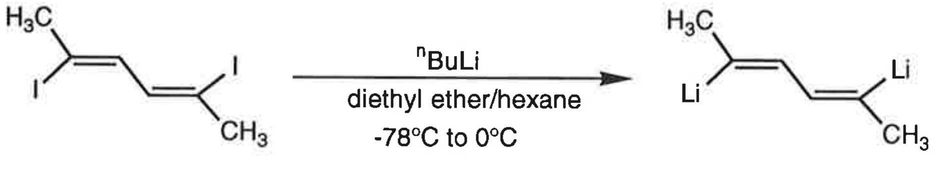


(^{n}BuLi·TMEDA in hexane)



(^{n}BuLi·KO^{t}Bu in pentane)

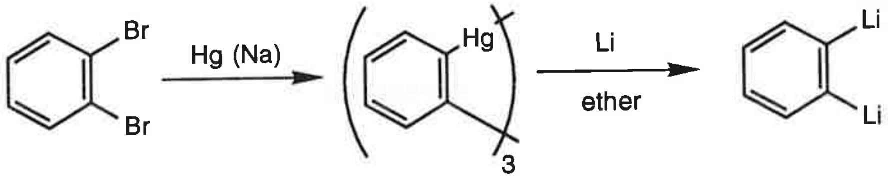
ii) Halogen-lithium exchange using *n*-butyllithium. Generally iodides or bromides are used as substrates. As a rule the substitution of chlorine by lithium proceeds difficultly, while fluorine cannot be replaced at all.[1,4] The successful preparation of 1,4-dilithiumbenzene and 2,5-dilithiumthiophene from the corresponding dibromo compounds and ^{n}BuLi in THF or diethyl ether has been reported.[5,6] Another example is the generation of 2,5-dilithiumhexadiene from the 2,5-diiodo derivative:[7]



Scheme 1: Dimetallation of 2,5-diiodo-2,4-hexadiene.

Some other, less current, methods have been used also. Although generally effective they suffer from disadvantages such as the need for special apparatus and less ready accessibility of the required substrates. Some examples are shown below.

iii) Transmetallation. In this group tin-lithium[8] and mercury-lithium exchanges are the most frequently used. In this way the otherwise unaccessible *o*-dilithiumbenzene has been prepared:[9]

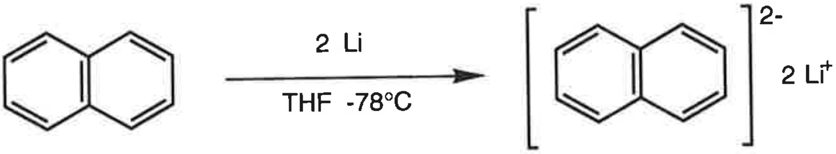


Scheme 2: Synthesis of *o*-dilithiumbenzene.

Recently some convenient selenium-lithium and tellurium-lithium exchanges have been performed, giving otherwise difficultly accessible dilithium compounds.[10]

iv) Reactions with alkali metals. These reactions can be subdivided into two categories.

a-reductions of unsaturated systems. Several anions have been prepared in this way. Even a tetraanion of a polyphenyl compound has been reported.[11] A typical example is given below:[12]



Scheme 3: Double reduction of naphthalene.

b-reactions of polyhalogen compounds with alkali metals. Lagow developed a method in which polychloro compounds were reacted with lithium vapour at high temperature (700 to 1000°C). Polylithium species such as tetralithiummethane were obtained in this way.[13]

v) Pyrolysis of organolithium compounds. This is one of the oldest methods for preparing polylithium compounds, developed by Ziegler. He discovered in 1955 that heating of methyllithium at 225°C gave dilithiummethane and methane. Many other polylithium compounds, such as CLi_4, C_2Li_2, C_3Li_4 etc., have been prepared in this way.[14]

Aim of the present research

Generally the presence of di- or polylithium species is shown with quench reactions, using chlorotrimethylsilane or an alkylating reagent. From the obtention of the products in satisfactory yields it is concluded that the generation of the intermediary species has proceeded with corresponding efficiency.[5,6,15,16,17,18] From the large practical experience in our laboratory the importance of reaction conditions (e.g. order of addition) upon the results of quench experiments is known. We therefore decided to reinvestigate some claims concerning di- and polymetallations in the heteroaromatic and aromatic areas. Dimethyl disulfide was used as quench reagent, because experience had shown that when this electrophile is used the product compositions obtained correctly reflects the composition of the metallation mixtures.

Results

The reactions of polybromo- and polyiodothiophenes with *n*-butyllithium have been described on several occasions.[6,15,16,17,18] Results vary strongly though reaction conditions generally are comparable (^{n}BuLi in diethyl ether at *ca.* -60°C for half an hour).

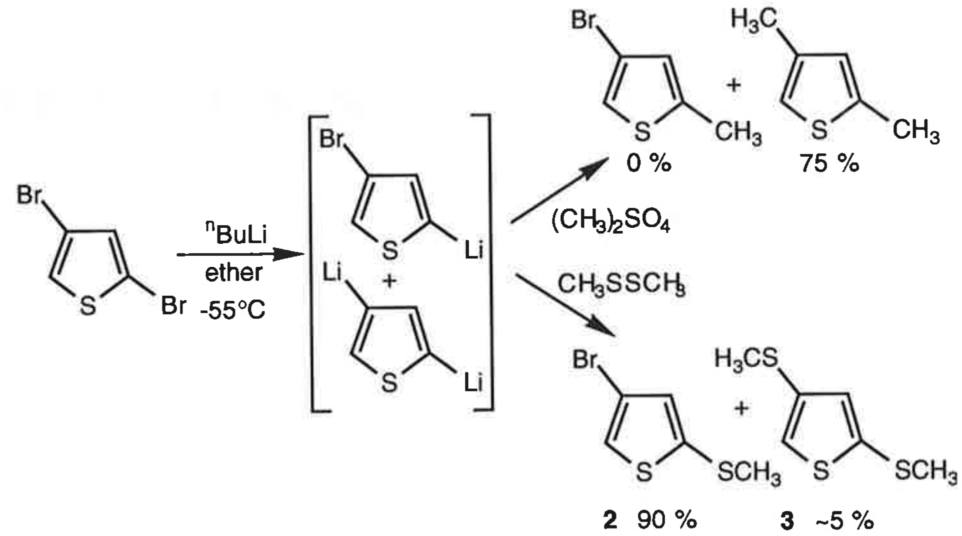
Formation of 2,5-dilithiumthiophene.

Addition at -55°C of 2,5-dibromothiophene to a solution of three equivalents of *n*-butyllithium in diethyl ether resulted in the formation of a white suspension. Dropwise addition of the corresponding amount of dimethyl disulfide afforded 2,5-bis(methylthio)thiophene in an excellent yield. The same result was obtained when the suspension was added portionwise to a cooled mixture of a large (200 mol%) excess of dimethyl disulfide and diethyl ether. The analogous reaction was reported by van Pham *et al.*[6] who described that treatment of 2,5-dibromothiophene with two equivalents of *n*-butyllithium in THF/hexane at -55°C and subsequent addition of an electrophile ($(CH_3)_3SiCl$, $(CH_3)_3SnCl$, CO_2) gave the 2,5-bis(functionalized)thiophenes in high yield.

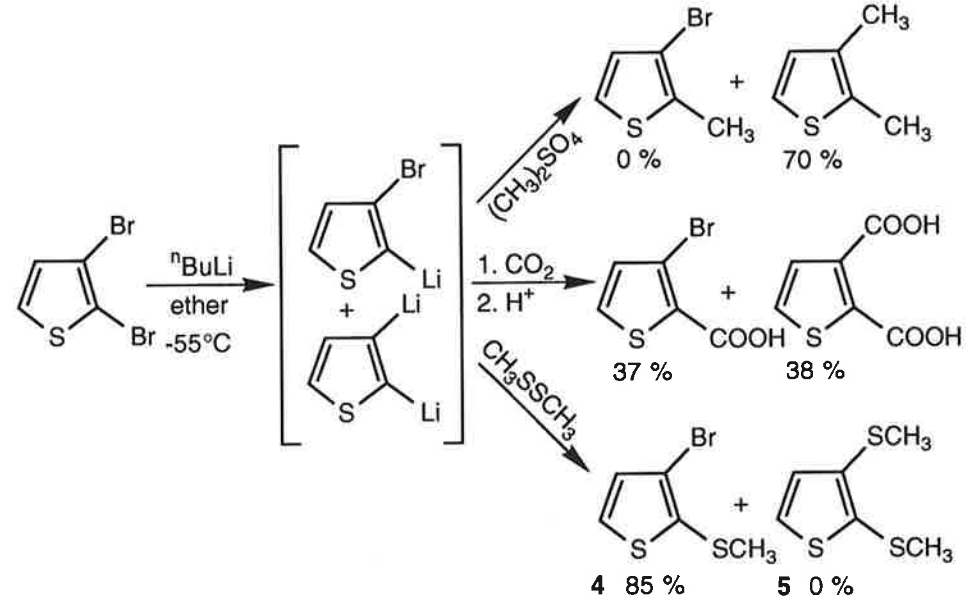
On basis of these results it may be assumed that 2,5-dilithiumthiophene is generated from the 2,5-dibromocompound with high efficiency. The same dilithium compound is obtained from thiophene and two equivalents of ^{n}BuLi·TMEDA.[3]

Reaction of 2,4-, 2,3- and 3,4-dibromothiophene with *n*-butyllithium and subsequent functionalization.

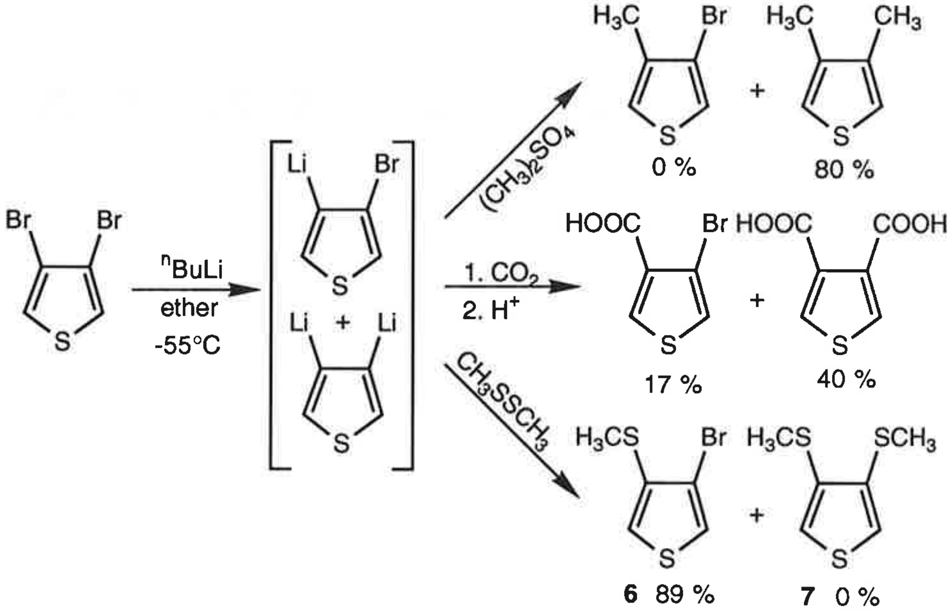
Janda *et al.* obtained the pure dimethyl derivatives by adding the 2,4-, 2,3- and 3,4-dibromo thiophenes to a solution of a slight excess of *n*-butyllithium in diethyl ether at -70°C and subsequently introducing dimethyl sulfate (see schemes 4, 5 and 6).[15] We repeated these reactions with 2,4- and 2,3-dibromothiophene under the same conditions and obtained similar results. Tserng *et al.* performed the same reactions but functionalized the mixtures with carbon dioxide by pouring the metallation mixture (in diethyl ether) on to dry ice.[16] Starting from 2,3-dibromothiophene and 3,4-dibromothiophene they obtained mixtures of comparable amounts of mono- and dicarboxylic acids (see schemes 5 and 6). By dropwise addition of (excess) dimethyl disulfide to the metallation mixture, prepared as described by Janda and Tserng, we obtained exclusively *mono*methylthio derivatives in high yields. Portionwise addition of the metallation mixture to a large (200 mol%) excess of dimethyl disulfide in diethyl ether gave the same results. Only in the case of 2,4-dibromothiophene we obtained (in addition to the monomethylthio derivative) a very small amount of the corresponding bis(methylthio)-thiophene. Results are shown in schemes 4, 5 and 6.



Scheme 4: Metallation and functionalization of 2,4-dibromothiophene.



Scheme 5: Metallation and functionalization of 2,3-dibromothiophene[19].



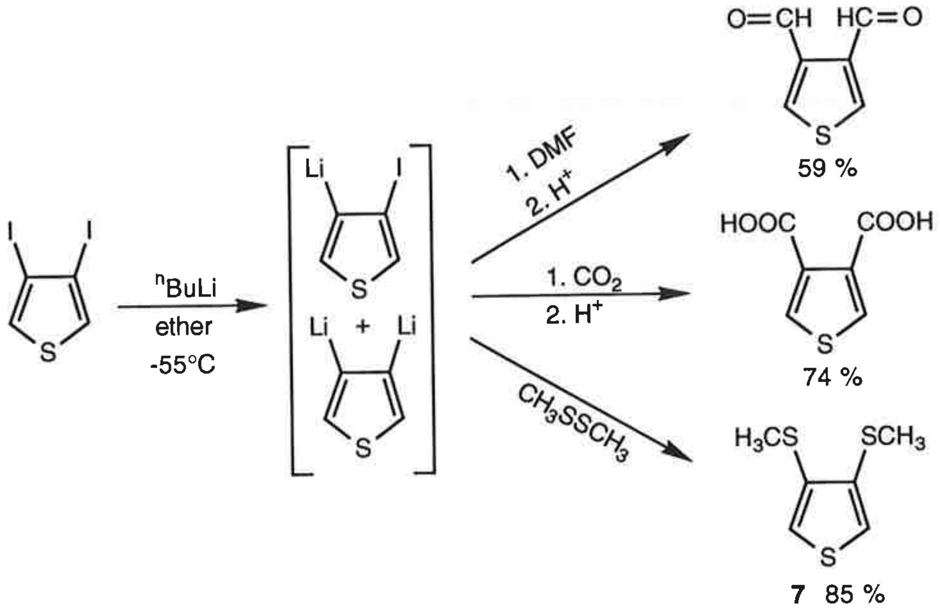
Scheme 6: Metallation and functionalization of 3,4-dibromothiophene.[19]

Dimetallation of 3,4-diiodothiophene.

It is known that in lithium-halogen exchange reactions iodine compounds react faster than do bromo derivatives. It therefore seemed interesting to investigate the reaction of a diiodothiophene having both iodine atoms at the β-carbons with respect to sulfur and which for this reason is expected to be less reactive in exchange reactions than the other isomers.[1,4]

Robba *et al.* obtained 3,4-diformylthiophene in good yield after addition of 3,4-diiodothiophene to three equivalents of *n*-butyllithium in diethyl ether at -60°C and subsequent dropwise addition of a slight excess of dimethylformamide (DMF).[17] Sicé performed the same reaction and obtained the 3,4-dicarboxylic acid derivative in good yield after quenching with solid carbon dioxide.[18]

After addition of 3,4-diiodothiophene to three equivalents of *n*-butyllithium in diethyl ether at -60°C a clear yellow solution was formed. Subsequent dropwise addition of a slight excess of dimethyl disulfide gave 3,4-bis(methylthio)thiophene in high yield. No mono(methylthio) derivative was found. Portionwise addition of the metallation mixture to a large (300 mol%) excess of dimethyl disulfide in diethyl ether gave an identical result.



Scheme 7: Metallation and functionalization of 3,4-diiodothiophene.

Whereas in the case of 3,4-dibromothiophene no 3,4-bis(methylthio)thiophene (**7**) is formed, for the diiodo compound this is the major product.

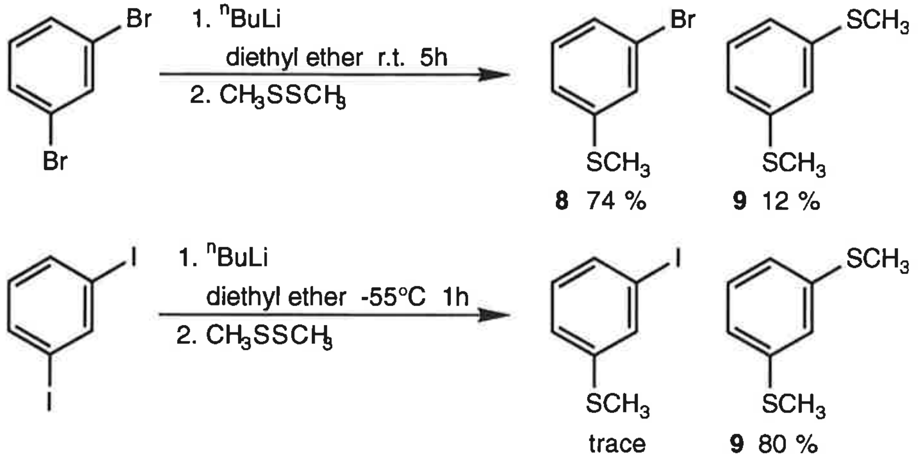
The lithiation of tri- and tetrahalogenthiophenes.

Janda *et al.* obtained 2,3,4-trimethylthiophene in 92% yield after addition of 2,3,4-tribromothiophene to a solution of *n*-butyllithium (21 equivalents) in diethyl ether at -70°C and subsequent dropwise addition of dimethyl sulfate. Under the same conditions 2,3,5-trimethylthiophene was obtained in 75% yield from the corresponding tribromo compound. Tetramethylthiophene was isolated in 75% yield after addition of tetrabromothiophene to a solution of *n*-butyllithium (30 equivalents) in diethyl ether at -70°C and subsequent dropwise quenching with dimethyl sulfate.[15] From these results they suggested the intermediate occurence of the corresponding trilithium- and tetralithiumthiophenes.

On the basis of the results of our quench experiments performed with the metallation mixtures from 2,3-, 2,4- and 3,4-dibromothiophenes it seems to us highly unlikely that generation of trilithium and tetralithium thiophenes from the corresponding bromo compounds is possible. Our attempts to polymetallate triiodo- and tetraiodothiophenes with *n*-butyllithium in THF-hexane mixtures at low temperature did not give clear results because several products were found upon quenching with dimethyl disulfide. Unfortunately diethyl ether appeared to be not a suitable solvent because solubilities were not sufficient.

Reaction of 1,3-dibromo- and 1,3-diiodobenzene with *n*-butyllithium.

It has appeared to be impossible to generate 1,2-dilithiumbenzene *via* halogen-lithium exchange. Immediate decomposition, *via* a benzyne mechanism, of *o*-lithiumiodobenzene occurs even at very low temperatures. From *o*-dibromobenzene only *o*-lithiumbromobenzene can be obtained at temperatures between -110 and -120°C. At higher temperatures lithium bromide is eliminated.[9] The dimetallation of *meta*-dibromobenzene with *n*-butyllithium in pentane has been reported.[5] It is also described that interaction between *p*-dibromobenzene and *n*-butyllithium in THF, diethyl ether or pentane readily leads to the formation of *p*-dilithiumbenzene.[5] We decided to investigate the reaction of *meta*-dibromobenzene with *n*-butyllithium in diethyl ether. We obtained only very low yields of the dimethylthio derivative (**9**) after addition of 1,3-dibromobenzene to three equivalents of *n*-butyllithium in diethyl ether, stirring for 5 hours at room temperature (r.t.) and subsequent introduction of dimethyl disulfide. Our quench experiments showed that in diethyl ether mainly monometallation occurred. With 1,3-diiodobenzene a practically complete replacement of both iodine atoms was attained within one hour at -55°C. The same results were obtained by pouring the metallation mixtures portionwise into a cooled solution of excess (100 mol%) of dimethyl disulfide in diethyl ether.



Scheme 8: Metallation and functionalization of *m*-dibromo- and *m*-diiodobenzene.

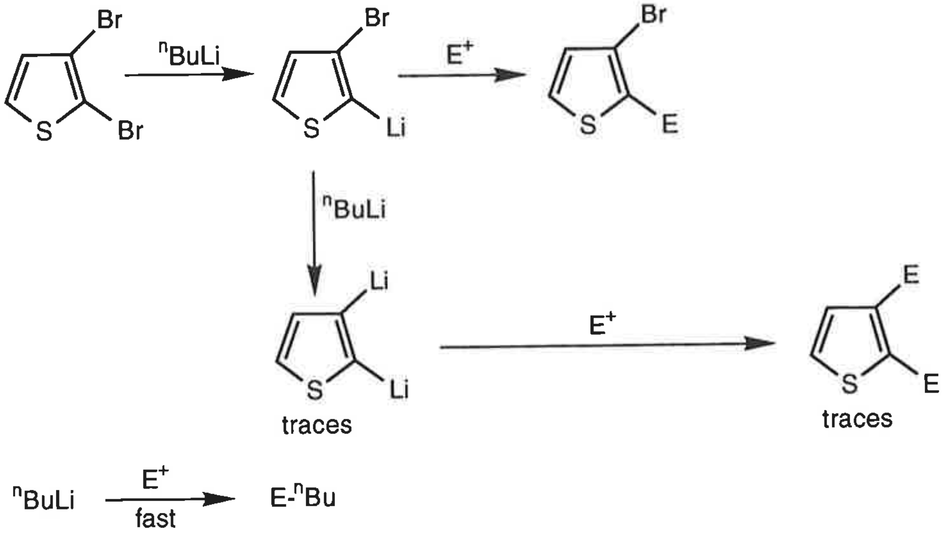
Discussion

Our metallation-functionalization experiments with the various dibromothiophenes have shown that, except 2,5-dibromothiophene, none of the dibromo compounds undergoes dimetallation to an extent greater than 5%. From the distance of the (formal) negative charges in the various dilithium compounds and the effect of sulfur it may be expected that the ease of dimetallation decreases in the order 2,5 >> 2,4 > 2,3 ; 3,4. The amount of difunctionalized product obtained in our experiments indeed decreases in this order.

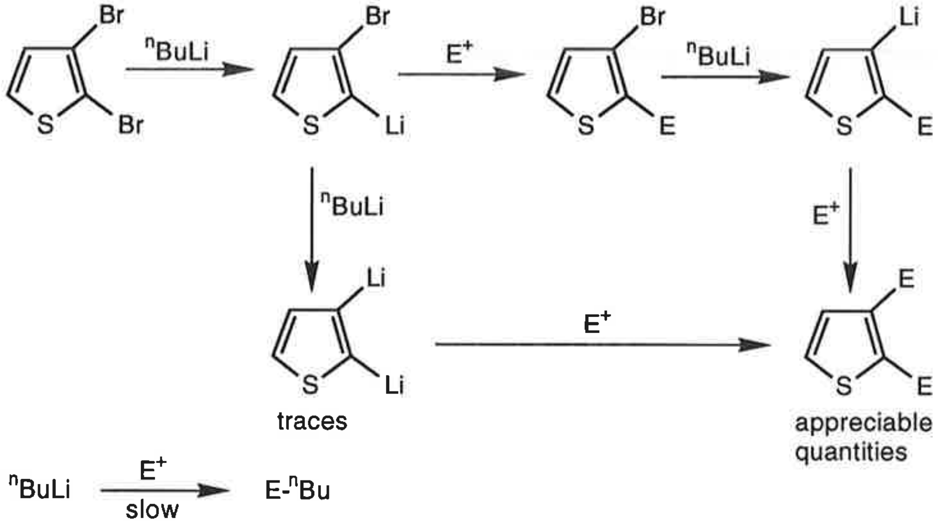
The weaker carbon-iodine bond in iodine compounds makes exchange of two iodine atoms for lithium atoms easier.

Perhaps the most striking feature is the dependency of product composition on the nature of the electrophile. We presume that prior to addition of the functionalization reagent, the ratio of the mono- and dilithiated compounds obtained from a given dibromo compound is always the same. However, the composition of the quench products varies from exclusively monofunctionalized derivatives (in the case of dimethyl disulfide) to exclusively difunctionalized derivatives (in the case of dimethyl sulfate). The order of reactivities of the electrophiles as expected by us is $CH_3SSCH_3 > CO_2 > (CH_3)_2SO_4$. Dimethyl disulfide reacts extremely fast in THF as well as in diethyl ether. The product distribution obtained is supposed to reasonably reflect the composition of the metallation mixture (mono- and dimetallated products). Although carbon dioxide is also a reactive electrophile, in the usual procedures it is handicaped by its solid state. Dimethyl sulfate reacts relatively slowly, especially in the weakly polar diethyl ether. In fact Janda *et al.* stirred the reaction mixture containing dimethyl sulfate for ~ 45 minutes in order to realize complete conversion, whereas the complete reaction with dimethyl disulfide requires not more than a few seconds under preparative conditions.

Concerning these data two reaction paths may be proposed, one for fast reacting electrophiles (scheme 9), the other for slowly reacting ones (scheme 10) as shown for 2,3-dibromothiophene.



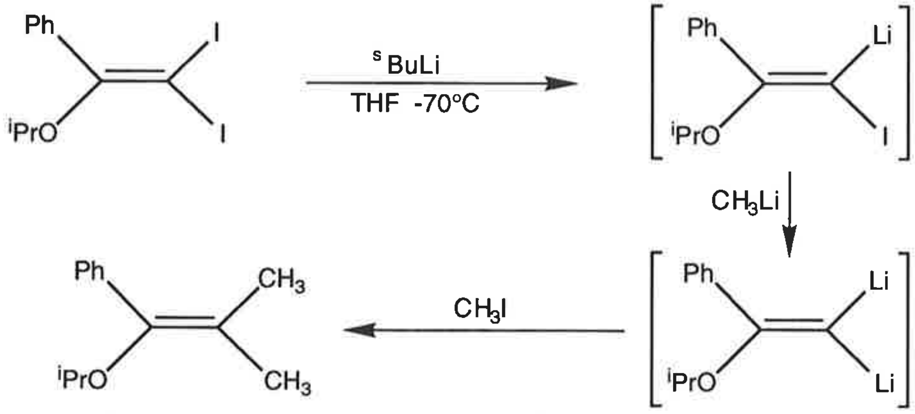
Scheme 9: Metallation of 2,3-dibromothiophene and quench reaction with a fast reacting electrophile (E, e.g. CH_3SSCH_3).



Scheme 10: metallation of 2,3-dibromothiophene and quench reaction with a slowly reacting electrophile (E, e.g. $(CH_3)_2SO_4$).

In both cases only small amounts of dilithiated product are formed. The formation of difunctionalized product must result from a metallation-functionalization-metallation-functionalization sequence involving two monoanions rather than a dianionic species. Any conclusion with respect to the degree of dimetallation therefore has to be made with great care.

Some claims concerning the generation of di- or polyanions have been reported, which later, in fact, proved to be "misinterprepations". In 1988 Barluenga *et al.* reported the synthesis of a difficultly obtainable geminal dilithium compound:[20]



Scheme 11: Geminal dimetallation reported by Barluenga *et al.*.[20]

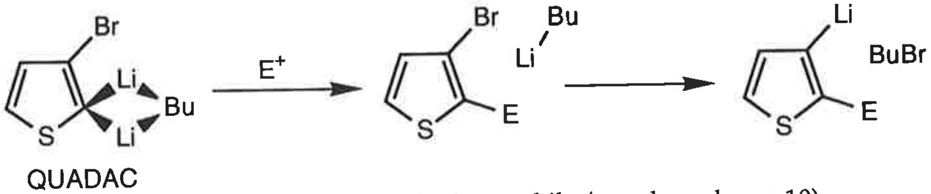
Maercker *et al.* later showed that also in this case a metallation-functionalization-metallation-fuctionalization sequence occurs and no dilithium compound is formed.[21]

The compatability of strong bases (^{n}BuLi in most cases) and certain electrophiles in solution has been convincinly demonstrated by Dimmel *et al.*.[22] Chlorotrimethylsilane, one of the most frequently used electrophiles in organolithium chemistry, proved to co-exist to some extend with *n*-butyllithium in THF/hexane instead of showing a fast reaction with all organolithium species in solution. Dichloromethane upon treatment with *n*-butyllithium in THF at -90°C gives a large number of products after quenching with chlorotrimethylsilane, all of which must be formed *via* metallation-functionalization-metallation-functionalization sequences: $((CH_3)_3Si)_2CCl_2$, $((CH_3)_3Si)_2CHCl$, $((CH_3)_3Si)_3CCl$, $((CH_3)_3Si)_3CH$, $((CH_3)_3Si)_4C$.[22] Di-, tri- or tetraanions are presumably not formed. We observed the same effect when we quenched $LiCBr_3$ (obtained by treatment of tetrabromomethane with one equivalent of *n*-butyllithium in a mixture of THF, diethyl ether and pentane at -110°C) with a large excess of ethanol at -110°C: considerable amounts of CH_2Br_2 were formed besides the desired product $CHBr_3$. The formation of a CBr_2Li_2 intermediate is unlikely.[23]

The compatability of *n*-butyllithium and dimethyl sulfate has been shown in metallation experiments with polybromo arenes.[24] Although in the reaction of polybromobenzenes with *n*-butyllithium in toluene at -78°C only dianions were formed, Hart *et al.* obtained large amounts of trimethyl derivatives after quenching with dimethyl sulfate.

Brenner *et al.* demonstrated that the reaction between methyllithium and alkylating reagents (e.g. methyliodide) is too slow to prevent remetallation of the monofunctionalized product (nitriles) by remaining methyllithium in THF/diethyl ether.[25]

In all cases formation of a complex between monolithiated substrate and excess base seems to account for the results.[26] These complexes are called QUADAC's (quasi dianion complexes).[27] The QUADAC involving 2,3-dibromothiophene and its reaction with an electrophile is shown below (compare schemes 9 and 10):



QUADAC

Scheme 12: reaction of QUADAC with electrophile (sse also scheme 10).

The first claims on QUADAC's were made in reports concerning the (di)metallation of compounds $PhCH_2Y$ with Y= CN, $PO(OEt)_2$, NO_2, SO_2Ph *etc.*.[26] A number of reported dianions of this type were reinvestigated by Crowley *et al.* who showed with NMR measurements that in the metallation mixtures no dianions were present but rather monoanions complexed with a second molecule of base. Even spectroscopic evidence on the existence of dianionic species (besides synthetic results) can be misleading as was shown in the metallation of $PhCH_2CN$ with ^nBuLi in THF.[28] On basis of infrared analysis of the metallation mixtures and (after quenching) the obtainment of $PhC(E)_2CN$ Kaiser *et al.* concluded the intermediary presence of a dilithiated species. Actually no $PhCLi_2CN$ was formed upon reaction with ^nBuLi but rather a QUADAC.[26] The most convincing evidence on the existence of QUADAC's of this kind was provided by Boche *et al.* who succeeded in isolating the QUADAC $PhCHLiCN{\cdot}LiN(i\text{-}Pr)_2$. Its crystal structure showed an arrangement similar to the one shown above.[29]

Conclusions.

With the exception of 2,5-dibromothiophene, none of the dibromothiophenes is dimetallated for more than 5% yield with *n*-butyllithium in diethyl ether at -55°C. Contrary to its bromo analogue, 3,4-diiodothiophene is completely dimetallated in one hour under the same conditions. Earlier investigators have been misled by quench results. The choice of the electrophile and the order of addition of the reagents (normal, or in a reversed sense) are of great importance upon results and can lead to wrong interpretations on the degree of metallation. The use of very fast reacting electrophiles, such as dimethyl disulfide, is recommended. Addition of the metallation mixture to a large excess of dimethyl disulfide gives the most reliable results. The presence of QUADAC's in metallation reactions may be more widespread than generally assumed, therefore many claims on dimetallations should be reinvestigated in order to check their validity.[5,30]

Experimental methods

General Conditions.

All reactions were carried out under an inert atmosphere. All solvents were dried before use. *n*-Butyllithium (1.6 Molar solution in hexane) was obtained commercially. Mixtures were cooled with liquid nitrogen baths. All products were isolated by distillation and analyzed by NMR spectroscopy and GLC. ^1H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^1H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

Preparation of starting materials.

The dibromothiophenes were prepared according to literature procedures, which are briefly described below.

Treatment of thiophene with 2 equivalents HBr/H_2O_2 gives 2,5-dibromothiophene. Reaction of this compound with 1 equivalent of lithium-di-*iso*propylamide in THF (-60°C) leads to 2,4-dibromothiophene. Treatment of thiophene with HBr/H_2O_2 (1 equivalent) gives 2-bromothiophene which, upon treatment with sodiumamide in liquid ammonia followed by hydrolysis, gives 3-bromothiophene. Subsequent bromination with Br_2 in diethyl ether affords 2,3-dibromothiophene.

Treatment of 2-bromothiophene with $NaNH_2 \cdot KO^tBu$ in liquid ammonia affords 3,4-dibromothiophene. All compounds are obtained in good to high overall yields.[31]

3,4-Diiodothiophene was prepared by the action of 2 equivalents *n*-butyllithium on tetraiodothiophene in diethyl ether/hexane at -70°C and subsequent quenching with water.[32] Tetraiodothiophene was prepared by treatment of thiophene with iodine and iodic acid in a mixture of acetic acid, water, tetrachloromethane and sulfuric acid.[33]

m-Diiodobenzene was prepared by iodination of *m*-diaminobenzene as described by Vogel.[34]

General remarks.

Thiophenes are known to show various side reactions during metallations, so control of the various reaction conditions is important:

i) temperature. Reaction of the (hetero)aryllithium compound with the butyl halide formed in the exchange reaction can be prevented by choosing the appropriate temperature. The reactivity order is as follows: BuI > BuBr in the various solvents THF >> diethyl ether > pentane/hexane. Butyl iodide, for example, reacts with lithiumthiophenes in THF smoothly at -70°C. This reaction does not occur in pentane, not even at elevated temperatures. Furthermore, at temperatures of about -30°C and higher α-deprotonation of bromothiophenes in diethyl ether is competitive with halogen-metal exchange. In this way 2,3-dilithiumthiophene has been prepared (in low yield however) from 3-bromothiophene and excess ^nBuLi in diethyl ether at -30°C.[35]

ii) solvent. Metal-halogen exchange rections proceed faster in THF (-70°C) than in diethyl ether (-55°C) but side reactions (especially alkylations) become predominant in THF. Reactions are therefore best carried out in diethyl ether. Apolar solvents as pentane or hexane are suitable when the isolation of the lithium compound is aimed. The lithium compounds are generally insoluble in alkanes. Reactions are slower in pentane and hexane compared to diethyl ether and THF, but practically no side reactions occur. Of course precipitation of the monolithium compound in pentane or hexane makes it less available for a second metallation.

iii) order of addition of reactants. Addition of *n*-butyllithium to a solution of dibromothiophene in diethyl ether gave rise to the formation of numerous side products, whereas the inverse order of addition gave pure products (see schemes 4, 5 and 6). The formation of side-products can be explained by assuming reaction between lithiated thiophenes and starting material, *via* the so called base-induced halogen dance.[36] The occurrence of the halogen dance can be explained by the great difference in reactivity towards metallation between the α- and β-position in thiophene. The α-position is *ca.* 500 times more reactive towards metallation than the β-position due to activating effects of the neighboring sulfur atom.[37] This relative high acidity of the α-position gives rise to side reactions. For example, 3-bromo-4-lithiumthiophene in hexane can be easily converted in 3-bromo-2-lithiumthiophene upon addition of TMEDA or THF. Also the way in which the electrophile during quenching is added can influence the results. Pouring the reaction mixture out into a large excess of electrophile (inverse quenching) results in immediate reaction of all organometallic species. Addition of the electrophile over a longer period to the reaction mixture (normal way of quenching) results in slower conversion of organometallic species and can hence result in side reactions (e.g. reaction of base with already functionalized species).

Metallation procedure.

In a 250 mL three-necked round-bottomed flask equipped with stoppers and a gas-outlet was placed 94 ml of a 1.6 M solution of (0.15 mol) *n*-butyllithium in hexane. The hexane was evaporated in an oil pump vacuum. To the concentrated butyllithium was added 100 ml of diethyl ether while cooling with an ice bath. The flask was equipped with a mechanical stirrer, thermometer and dropping funnel. The solution was cooled to -55°C and a mixture of 12.1 g (0.050 mol) dibromothiophene and 10 ml of diethyl ether was added over 5 minutes while stirring and maintaining the temperature at -55°C. The clear yellow reaction mixture was stirred for 30 minutes at this temperature. Dimethyl disulfide (15.0 g (0.160 mol)) was added in one portion with vigorous stirring. A white suspension was formed and a fast increase of the temperature was observed. After 5 minutes 50 ml of water were added at -20°C. The layers were separated and the water layer was extracted three times with diethyl ether (30 ml), after which the combined organic layers were dried over magnesium sulfate. The organic solution was concentrated under reduced pressure. Distillation of the remaining liquid through a short Vigreux column at reduced pressure gave the product. Yields and boiling points are given below.

For 3,4-diiodothiophene (16.8 g, 0.050 mol); *m*-dibromobenzene (11.8 g, 0.050 mol) (reaction time 5 hours at room temperature) and *m*-diiodobenzene (16.5 g, 0.050 mol) the procedure was identical to the one described above.

Metallation followed by inverse quenching.

The metallation was carried out as described above. The metallation mixture was poured in portions of about 30 mL over *ca.* one minute into a vigorously stirred precooled (-60°C) solution of 28 g (0.30 mol) dimethyl disulfide in 50 mL diethyl ether. After stirring the mixture for some minutes 200 mL of water was added. Work-up was done as described above.

Metallation of 2,5-dibromothiophene.

2,5-bis(methylthio)thiophene (1).

Compound **1** was obtained in a yield of 9.70 g (93%), as a slightly yellow liquid, bp. 120°C (1 mm Hg).

^{13}C-NMR: δ= 21.9 (SCH_3), 131.0 (C3, C4), 139.2 (C2, C5).

^{1}H-NMR: δ= 2.45 (SCH_3, 6H), 6.88 (s, H3, H4, 2H).

Metallation of 2,4-dibromothiophene.

4-bromo-2-methylthiothiophene (2).

Compound **2** was obtained in a yield of 9.41 g (90%), as a slightly yellow liquid, bp. 100-105°C (1 mm Hg).

^{13}C-NMR: δ= 21.5 (α-SCH_3), 109.2 (C4), 124.4 (C5), 130.9 (C2), 132.1 (C3).

^{1}H-NMR: δ= 2.48 (s, α-SCH_3, 3H), 6.95 (d, H3, J= 1.5 Hz, 1H), 7.16 (d, H5, J= 1.5 Hz, 1H).

2,4-bis(methylthio)thiophene (3).

Compound **3** was obtained in a maximum yield of 0.44 g (5%), it was also prepared seperately by subsequent treatment of **2** with *n*-butyllithium (1 equivalent) and dimethyl disulfide in diethyl ether at -60°C for GLC and NMR comparison, obtained as a reddish liquid, bp. 105°C (1 mm Hg).

^{13}C-NMR: δ= 17.3 (β-SCH_3), 21.5 (α-SCH_3), 121.1 (C5), 130.7 (C3), 130.9 (C4), 138.2 (C2).

^{1}H-NMR: δ= 2.43 (s, β-SCH_3, 3H), 2.47 (s, α-SCH_3, 3H), 6.89 (d, H3, J= 1.5 Hz, 1H), 6.93 (d, H5, J= 1.5 Hz, 1H).

Metallation of 2,3-dibromothiophene.

3-bromo-2-methylthiothiophene (4).

Compound **4** was obtained in a yield of 8.87 g (85%), as a slightly yellow liquid, bp. 90-100°C (1 mm Hg).

^{13}C-NMR: δ= 20.5 (α-SCH_3), 115.8 (C3), 127.8 (C5), 130.9 (C4), 132.9 (C2).

^{1}H-NMR: δ= 2.44 (s, α-SCH_3, 3H), 6.95 (d, H4, J= 5.5 Hz, 1H), 7.24 (d, H5, J= 5.6 Hz, 1H).

2,3-bis(methylthio)thiophene (5).

Compound **5** was obtained in a yield of 0% after metallation of 2,3-dibromothiophene. Compound **5** was prepared for GLC and NMR comparison by treatment of **4** with *n*-butyllithium (1 equivalent) and dimethyl disulfide in diethyl ether at -60°C. **5** was obtained as a reddish liquid, bp. 115°C (1 mm Hg).

^{13}C-NMR: δ= 17.7 (β-SCH_3), 20.5 (α-SCH_3), 127.1 (C5), 128.5 (C4), 131.0 (C3), 137.1 (C2).

^{1}H-NMR: δ= 2.38 (s, SCH_3, 3H), 2.40 (s, SCH_3, 3H), 6.89 (d, H4, J= 5.5 Hz, 1H), 7.22 (d, H5, J= 5.5 Hz, 1H).

Metallation of 3,4-dibromothiophene.

3-bromo-4-methylthiothiophene (6).

Compound **6** was obtained in a yield of 9.31 g (89%), as a slightly yellow liquid, bp. 100 - 105°C (1 mm Hg).

^{13}C-NMR: δ= 17.0 (β-SCH_3), 111.9 (C3), 119.3 (C5), 123.7 (C2), 135.2 (C4).

^{1}H-NMR: δ= 2.44 (s, β-SCH_3, 3H), 6.89 (d, H5, J= 3.4 Hz, 1H), 7.31 (d, H2, J= 3.4 Hz, 1H).

3,4-bis(methylthio)thiophene (7).

Compound **7** was obtained in 0% yield after metallation of 3,4-dibromothiophene. Compound **7** was prepared for GLC and NMR comparison by reaction of **6** with *n*-butyllithium (1 equivalent) at -60°C and quenching with dimethyl disulfide. It was obtained as a reddish liquid, bp. 120°C (1 mm Hg).

^{13}C-NMR: δ= 17.3 (β-SCH_3), 120.8 (C2, C5), 134.3 (C3, C4).

^{1}H-NMR: δ= 2.43 (s, β-SCH_3, 6H), 6.99 (s, H2, H5, 2H).

Metallation of m-dibromobenzene and m-diiodobenzene.

3-bromo-thioanisol (8).

Compound **8** was obtained in a yield of 7.50 g (74%) in the metallation of dibromobenzene and only in trace amounts in the metallation of diiodobenzene. It was obtained as a slightly yellow liquid, bp. 140-150° (1 mm Hg).

^{13}C-NMR: δ= 15.3 (SCH_3), 122.7 (C3). 124.5, 128.3, 128.8, 129.8 (C5), 140.8 (C1).

^{1}H-NMR: δ= 2.46 (SCH_3, 3H), 7.12 (dd, H5, J= 7.8 Hz, 1H), 7.16 (dt, H6, J= 8.1, 1.8 Hz, 1H), 7.26 (dt, H4, J= 7.5, 1.8 Hz, 1H), 7.38 (dd, H2, J= 1.7 Hz).

1,3-bis(methylthio)benzene (9).

Compound **9** was obtained in a yield of 1.03 g (12%) in the metallation of dibromobenzene and 6.82 g (80%) in the metallation of diiodobenzene, as a yellow liquid, bp. 140-150°C (1 mm Hg).

^{13}C-NMR: δ= 15.7 (SCH_3), 123.2 (C4/C6), 124.2 (C2), 129.1 (C5), 139.4 (C1/C3).

^{1}H-NMR: δ= 2.47 (s, SCH_3, 6H), 7.03 (tdd, H5, J= 7.7, 1.8, 0.7 Hz, 1H), 7.16 (d, H2, J= 1.7 Hz, 1H), 7.20 (dd, H4, H6, J= 8.3, 1.0 Hz, 2H).

References

1 Maercker, A.; Theis, M. *Top. Cur. Chem.* **138** (1987) 1; Schlosser, M. *Struktur und Reaktivität Polarer Organometalle* Springer-Verlag, Berlin (1973); Wakefield, B. *The Chemistry of Organolithium Compounds* Pergamon Press, Oxford (1974).

2 Barry III, C. E.; Bates, R. B.; Beavers, W. A.; Camou, F. A.; Gordon III, G.; Hsu, H. F.-J.; Mills, N. S.; Ogle, G. A.; Siahaan, T. J.; Suvannachut, K.; Taylor, S. R.; White, J. J.; Yager, K. M. *Synlett* (1991) 207.

3 Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol. I* Springer-Verlag, Heidelberg (1987); Brandsma,L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol. II* Springer-Verlag, Heidelberg (1990).

4 Jones, R. G.; Gilman, H. *Org. React.* **6** (1951) 339.

5 The dimetallation of *p*- and *m*-dibromobenzene with *n*-butyllithium in pentane at room temperature has been reported: Fraenkel, G.; Dayagi, S.; Kobayashi, S. *J. Phys. Chem.* **72** (1968) 953; Gilman, H.; Langham, W.; Moore F. W. *J. Am. Chem. Soc.* **62** (1940) 2327. Also *p*-dilithiobenzene was prepared in diethyl ether from *p*-dibromobenzene and *n*-butyllithium at room temperature : Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **72** (1950) 2953. *p*-Dilithiobenzene was prepared from *p*-dibromobenzene and *n*-butyllithium in diethyl ether at reflux temperature and in THF at -70°C: Baldwin, R. A.; Cheng, M. T. *J. Org. Chem.* **32** (1967) 1572. **Warning:** when we tried to dimetallate *p*- and *m*-dibromobenzene with *n*-butyllithium in

pentane or diehtyl ether at room temperature violent explosions occurred without demonstrable cause. Possibly *p*-lithiobromobenzene and *m*-lithio-bromobenzene precipitated on the wall of the flask at the surface of the liquid. From experience we know that these lithio compounds are highly unstable in the solid dry state.

Recently we found a remarkable influence of the way of quenching on the results of the metallation of *p*-dibromobenzene with an excess (3 equivalents) of *n*-butyllithium in THF at -60°C. When an excess of dimethyl disulfide was added portionwise to the mixture consisting of *p*-dibromobenzene and *n*-butyllithium in THF at -60°C large amounts of *p*-bis(methylthio)-benzene were found besides *p*-bromo-methylthiobenzene. When, however, the metallation mixture was poured into a large excess of pre-cooled dimethyl disulfide (inverse quenching) in THF *no p*-bis(methylthio)-benzene was found at all. Only product in this case was *p*-bromo-methylthiobenzene. The formation of *p*-bis(methylthio)benzene can be explained by the occurrence of a metallation-functionalization-metallation-functionalization sequence. No *p*-dilithio-benzene was present in the metallation mixture in THF, only monometallated species were formed. The reaction between *p*diiodobenzene and n-butyllithium (3 equivalents) in diethyl ether at -55°C and subsequent reaction with dimethyl disulfide, however, gave *p*-bis(methylthio)benzene in good yield independent of the way of quenching. Contrary to the case of *p*-dibromobenzene, in this case it may be assumed that *p*-dilithiobenzene was present in the metallation mixture.

[6] Pham, C. van; Macomber, R. S.; Mark Jr., H. B.; Zimmer, H. *J. Org. Chem.* **49** (1984) 5250.

[7] Ashe III, A. J.; Lohr, L. L.; Al-Taweel, S. *Organometallics* **10** (1991) 2424.

[8] Märckl, G.; Hofmeister, P. *Tetrahedron Lett.* (1976) 3419; Ashe III, A. J.; Lohr, L. L.; Al-Taweel, M. *Organometallics* **10** (1991) 2424; Ashe III, A. J.; Mahmoud, S. *Organometallics* **7** (1988) 1878.

[9] Wittig, G.; Bickelhaupt, F. *Chem. Ber.* **91** (1958) 883; Winkler, H. J. S.; Wittig, G. *J. Org. Chem.* **28** (1963) 1733.

[10] Maercker, A.; Bodenstedt, H.; Brandsma, L. *Angew. Chem., Int. Ed. Engl.* **31** (1991) 1339; Schoufs, H. J. M.; Maercker, A.; Brandsma, L. *J. Organomet. Chem.* **441** (1992) 1.

[11] Benken, R.; Andres, W.; Günther, H. *Angew. Chem. Int. Ed. Engl.* **27** (1988) 1182.

[12] Benken, R.; Günther, H. *Helv. Chim. Acta* **71** (1988) 694.

[13] Chung, C.; Lagow, R. J. *Chem. Commun.* (1972) 1078; Sneddon, L. G.; Lagow, R. J. *Chem. Commun.* (1975) 302; Morrison, J. J.; Chung, C.; Lagow, R. J. *J. Am. Chem. Soc.* **97** (1975) 5015.

[14] Ziegler, K; Nagel, K.; Patheiger, M. Z. *Anorg. Allg. Chem.* **282** (1955) 345, Kawa, H.; Manley, B. C.; Lagow, R. *J. Am. Chem. Soc.* **107** (1985) 5313.

[15] Janda, M.; Stibor, J. S. I.; Nemec, M.; Vopatrná, P. *Synthesis* (1972) 545. These results were reproducible.

[16] Tserng, K.-Y.; Bauer, L. *J. Org. Chem.* **40** (1975) 172.

[17] Robba, M.; Roques, B.; Bonhomme, M. *Bull. Soc. Chim. Fr.* (1967) 2495.

[18] Sicé, J. *J. Org. Chem* **19** (1954) 70.

[19] Robba *et al.* (see ref 17) treated 2,3-dibromothiophene with ^{n}BuLi in ether at reflux temperature and obtained, after quenching with dimethylformamide, a mixture of 2,5-diformyl-3-bromothiophene (35%), 3-bromo-2-formyl-thiophene and 2,3- diformyl-thiophene (yields for these last two compounds not given). Treatment of 3,4-dibromothiophene with excess ^{n}BuLi in diethyl ether at -40°C and quenching with dimethylformamide afforded 4-bromo-2,3-diformyl-thiophene in 20% yield. In these cases α-metallation is competitive with metal-halogen exchange due to the higher temperature applied.

[20] Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Am. Chem. Soc.* **110** (1988) 5567.

[21] Maercker, A.; Bös, B. *Main Group Metal Chem.* **14** (1991) 67.

[22] Dimmel, D. D.; Wilkie, C. A.; Ramon, F. *J. Org. Chem.* **37** (1972) 2662.

23 Fischer, R. H.; Köbrich, G. *Chem. Ber.* **101** (1968) 3230.

24 Nwokogu, G. C.; Hart, H. *Tetrahedron Lett.* **24** (1983) 5725.

25 Brenner, S.; Bovete, M. *Tetrahedron* **31** (1975) 153.

26 In some cases in di- or polymetallations a very large excess of base is used (for example, see ref.[15]). In these cases during quenching not only base complexed in QUADAC's but also part of the not complexed base, which has not yet reacted with the quench reagens, may lead to the occurrence of metallation-functionalization-metallation-functionalization sequences.

27 Crowley, P. J.; Leach, M. R.; Meth-Cohn, O.; Wakefield, B. J. *Tetrahedron Lett.* **27** (1986) 2909.

28 Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **93** (1971) 4237.

29 Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem.* **101** (1989) 1424.

30 Recently Lagow *et al.* reported the synthesis of hexalithiobenzene in 53% yield from the reaction of hexachlorobenzene with a large excess of ^{t}BuLi (4 equivalents per chlorine atom) in dioxane/pentane/hexane for 24 hours at -120°C. The yield was determined by queching with D_2O at -120°C. Under the same conditions after 5 hours we found no penta-, tetra-, tri-, di- or monochlorobenzene upon quenching with water (the starting material was recovered). When quenching the reaction mixture with water at -120°C and subsequently slowly raising the temperature, as reported by Lagow, many products were formed; the higher the temperature, the more products were formed. Also in this case a metallation-protonation-metallation-protonation sequence could account for the reported result. Baran Jr., J. R.; Hendrickson, C.; Laude Jr., D. A.; Lagow, R. J. *J. Org. Chem.* **57** (1992) 3759.

31 Bromination of thiophene: Keegstra, M. A.; Brandsma, L. *Synthesis* (1988) 890. Isomerization of α-bromothiophenes: Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **20** (1983) 2035; Reinecke, M. G.; Adickes, H. W.; Pyun, C. *J. Org. Chem.* **36** (1971) 2690. Preparation of 3,4-dibromothiophene: Brandsma, L.; Verkruijsse, H. *Synth. Commun.* **20** (1990) 2119.

32 Guilard, R.; Fournari, P.; Person, M. *Bull. Soc. Chim. Fr.* (1967) 4121.

33 De Luca, G.; Martelli, G.; Spagnolo, P.; Tiecco, M. *J. Chem. Soc. (C)* (1970) 2504.

34 Vogel, A. *Textbook of Practical Organic Chemistry* Longman Scientific & Technical, Harlow (England) 5th ed. (1989) 931.

35 Östman, B. *Ark. Kemi* **22** (1964) 551.

36 Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **B30** (1976) 505; Moses, P.; Gronowitz, S. *Arkiv Kemi* **18** (1962) 119; Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **20** (1983) 2035. See also Kano *et al.* ref[30].

37 Mallan, J. M.; Bebb, R. L. *Chem. Rev.* **69** (1969) 693.

Chapter 8

Dimetallation of Benzene

Results and discussion

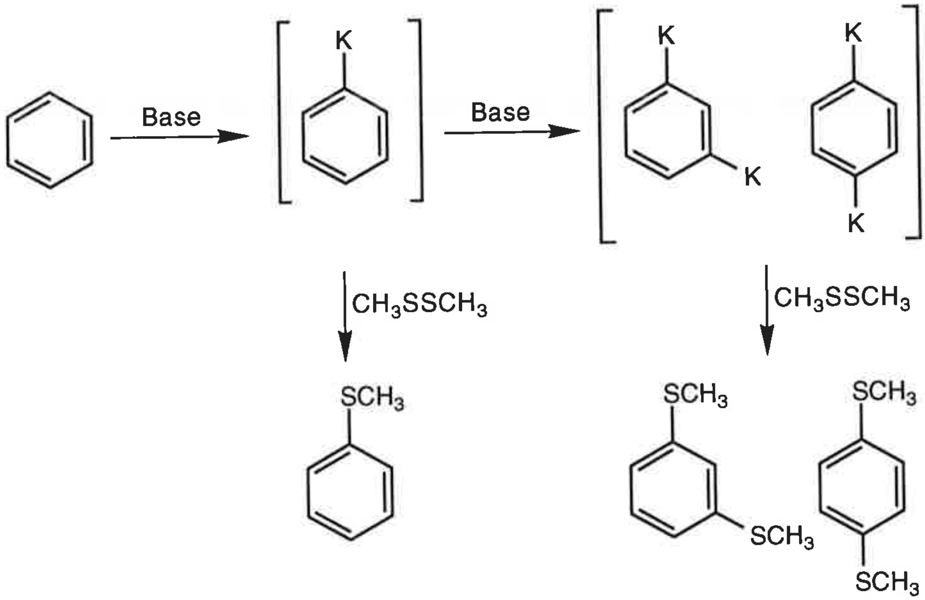
The dimetallation of benzene has been reported on various occasions. In most cases yields were low.[1] Usually reactions of benzene with alkylsodium or -potassium bases, prepared from the corresponding alkylchlorides or from alkylmercury compounds and alkali metal, were performed. The preparation of these reagents is troublesome and reproducibility is often poor.

We obtained 32% methylthiobenzene and, surprisingly, 8% of bis-(methylthio)benzene isomers (**1**) by treatment of benzene with one equivalent of ^{n}BuLi·KO^{t}Bu at room temperature in hexane followed by reaction with dimethyl disulfide. When the same reaction was performed in diethyl ether or THF only monofunctionalized product was found.

Recently Schlosser *et al.* reported on the dimetallation of benzene in hexane.[2] Interaction at room temperature between benzene and three equivalents of ^{n}BuLi·KO^{t}Bu during one hour, followed by quenching with chlorotrimethylsilane gave the isomeric disilylbenzenes (*meta*:*para*= ~1:1) in 55% yield. Following Schlosser's procedure we obtained, after quenching with dimethyl disulfide, a mixture of *meta*- and *para*-bis-(methylthio)benzene (**1**) in 25 to 30% yields only.

A number of unsuccessful attempts were made to attain improved results with the super base mixture ^{n}BuLi·KO^{t}Bu. We then decided to use more branched alkoxides ($KOCMe_2Et$, $KOCMeEt_2$ and $KOCEt_3$ with Me= methyl and Et = ethyl), which are soluble in hexane unlike KO^{t}Bu. With these alkoxides the dimetallation proceeded indeed more complete.

In all cases the metallation mixtures were quenched with the highly reactive electrophile dimethyl disulfide and products were isolated by distillation. The reactions are shown in scheme 1, the results in table 1.



(*meta*)-**1** (*para*)-**1**

Scheme 1: Mono- and dimetallation and functionalization of benzene.

Table 1: Metallation of benzene with 2 equivalents of base mixture using various potassium alkoxides (Me= methyl, Et= ethyl).

Base	equivalents (^{n}BuLi/alk.)	Temp. (°C)	time (h)	$PhSCH_3$ (%)	**1** (%)[a]
^{n}BuLi·KO^{t}Bu[b]	2/2	RT	2	46	30
^{n}BuLi·KO^{t}CMe$_2$Et	2/2	RT	2	45	48
^{n}BuLi·KO^{t}CMeEt$_2$	2/2	RT	2	33	48
^{n}BuLi·KO^{t}CEt$_3$	2/2	RT	2	25	46

[a] *Meta/para* ratio= ~ 1:1. [b] Schlosser reported a yield of 50% of difunctionalized product after treatment of benzene with two equivalents of ^{n}BuLi·KO^{t}Bu in hexane for 1 hour followed by quenching with carbon dioxide.

On going from KO^{t}Bu to the more branched alkoxides an improvement is made from 30 to about 48%. The differences between the results attained with the more branched alkoxides are minimal. Mixing one of these more branched alkoxides with *n*-butyllithium in hexane gave rise to the formation of a finer suspension compared to the suspension formed after mixing potassium *tert*-butoxide and *n*-butyllithium. It seemed to us that the *size* of the particles of the unsoluble base has an influence upon the results. Therefore experiments were carried out to decrease the particle size. None of the attempts mentioned below resulted in improved results.

i) addition of an excess of TMEDA to the mixture of *n*-butyllithium and potassium alkoxide.

ii) the use of a high-speed vibrator-mixer instead of the usual mechanical stirrer.

iii) changing the order of addition of reactants. Addition of a hexane solution of potassium alkoxide to the solution of butyllithium in hexane containing benzene is most practical. This method is not suitable in the case of KO^{t}Bu, because of its insolubilty in hexane.

iv) longer reaction times. Yields of difunctionalized products reached their optimum values usually after 2 to 3 hours.

v) use of $CsOCMe_2Et$ instead of a potassium alkoxide.

A significant improvement was attained, however, by using large excesses of the base consisting of *n*-butyllithium and (in hexane soluble) potassium *tert*-alkoxides: bis(methylthio)benzene was obtained even in a yield as high as 81% by treating benzene with eight equivalents of $^nBuLi{\cdot}KOC(Me)_2Et$ and subsequently adding dimethyl disulfide.

Peculiarly, some difunctionalized product was isolated even when using *benzene* in excess. In all cases also traces of trifunctionalized product were found (~1%). The products probably do not result from a deprotonation-functionalization-deprotonation-functionalization sequence, since similar results weer obtained if the metallation mixture was added portionwise to a large (~ 300%) excess of dimethyl disulfide.[3] In table 2 the results are summarized.

Table 2: Metallation of benzene using various base/substrate ratios.[4]

Base	equivalents (^{n}BuLi/alk.)	Temp. (°C)	time (h)	$PhSCH_3$ (%)	**1** (%)
$^nBuLi{\cdot}KOCMe_2Et$	0.25/0.25	RT	2	74	2
$^nBuLi{\cdot}KOCMe_2Et$	1/1	RT	2	60	9
$^nBuLi{\cdot}KOCMe_2Et$	3/3	RT	2	34	50
$^nBuLi{\cdot}KOCMe_2Et$	4/4	RT	2	39	54
$^nBuLi{\cdot}KOCMe_2Et$	6/6	RT	2	26	64
$^nBuLi{\cdot}KOCMe_2Et$	8/8	RT	2	15	81
$^nBuLi{\cdot}KOCMe_2Et$	2/6	RT	2	56	35
$^nBuLi{\cdot}KOCMeEt_2$	4/4	RT	2	32	57

In all cases comparable amounts of *meta*- and *para*-methylthiobenzene were obtained, the *ortho* isomer being almost absent. This result was expected since the negatively charged carbon atom in the monometallated product strongly deactivates the *ortho* position for a second metallation and to a lesser extent the *meta* position.[5]

Aggregate formation probably plays an important role in the dimetallation. The monometallated, insoluble, potassio-benzene may be incorporated into some kind of aggregate, consisting of phenylpotassium, butylpotassium and -possibly- alkoxide. The second metallation may proceed within an aggregate containing mono-potassiobenzene, having the *meta* and *para* protons in the vicinity of a butlylpotassium moiety or between different aggregates in the mixure. In the homogeneous base mixtures in diethyl ether and THF no dimetallated product was found, probably because in these solvents the base attacks the solvent before the base can react with phenylpotassium.

Experimental methods

General Conditions.

All reactions were carried out under an atmosphere of nitrogen in a three-necked, round-bottomed flask, equipped with a thermometer-gas inlet combination, mechanical stirrer and dropping funnel-gas outlet combination. Solvents were dried before use. *n*-Butyllithium (1.6 Molar solution in hexane) and potassium *tert*-alkoxides were obtained commercially.[6] All products were isolated by distillation and analyzed by NMR spectroscopy and GLC. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

Typical metallation procedure.

A mixture of 7.9 g (0.10 mol) of benzene and a 1.6 M solution of *n*-butyllithium in hexane was placed in the flask. The mixture was stirred and cooled to -15 to -20°C. A solution of the potassium *tert*-alkoxide (concentration 1 mol/l) in heptane was introduced over 2 minutes by means of a syringe while keeping the temperature between -10 and 10°C. The brown suspension was stirred at room temperature for an additional period (usually *ca.* 2 hours), then it was cooled to -40°C. Subsequently 100 mL of diethyl ether was added, followed by a 100% excess (with regard to base) of dimethyl disulfide within 3 seconds with vigorous stirring. When the temperature of the mixture had reached 10°C, 300 mL of water was added with vigorous stirring. After separation of the layers the water layer was extracted twice with pentane. The combined organic solutions were washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The remaining liquid was carefully distilled through a Vigreux column. After a small volatile fraction, methylthiobenzene passed over between 65 and 100°C (15 mm Hg) and a mixture of *m*- and *p*-bis(methylthio)benzene (1) between 100 and 125°C (15 mm Hg). The presence of the *para* isomer gave rise to partial solidification of the difunctionalized product.

methylthiobenzene:
^{13}C-NMR: δ= 15.5 (CH_3), 124.7 (C_p), 126.3 (C_o), 128.6 (C_m), 138.3 (C_i).
^{1}H-NMR: δ= 2.54 (s, CH_3, 3H), 7.18- 7.45 (m, phenyl, 5H).

1,4-bis(methylthio)benzene (1):
^{13}C-NMR: δ= 16.1 (CH_3), 127.4 (C2, C3, C5, C6), 135.0 (C1, C4).
^{1}H-NMR: δ= 2.46 (s, CH_3, 6H), 7.20 (s, phenyl, 4H).
1,3-bis(methylthio)benzene (1):
^{13}C-NMR: δ= 15.3 (CH_3), 122.6 (C4, C6), 123.6 (C2), 128.7 (C5), 139.0 (C1, C3).
^{1}H-NMR: δ= 2.46 (s, CH_3, 6H), 7.00- 7.25 (m, phenyl, 4H).

GC-MS analysis (performed on a Kratos MS80 GC-MS combination) showed the presence of traces (1 to 2%) of *ortho*-bis(methylthio)benzene, while traces (~ 1%) of tris(methylthio)benzenes were found in the residue. GC-MS data (5 major peaks, m/e (% of base peak)): *ortho*-bis(methylthio)benzene: 170 (M^+, 35), 123 (22), 61 (100), 51 (10), 45 (18). 1,2,4- or 1,2,3-tris(methylthio)benzene: 216 (M^+, 50), 169 (13), 154 (12), 108 (8), 61 (100). 1,3,5-tris(methylthio)benzene: 216 (M^+, 100), 183 (40), 154 (20), 139 (10), 125 (8).

References

[1] Morton, A. A.; Hechenbleikner, I. *J. Am. Chem. Soc.* **58** (1936) 1024; Morton, A. A.; Hechenbleikner, I. *J. Am. Chem. Soc.* **58** (1936) 2599; Morton, AA; Fallwell, F. *J. Am. Chem. Soc.* **60** (1938) 1924; Morton, A. A.; Richardson, G. M.; Hallowell, A. T. *J. Am. Chem. Soc.* **63** (1941) 327; Morton, A. A.; Little, E. L.; Strong Jr., W. O. *J. Am. Chem. Soc.* **65** (1943) 1339; Gilman, H.; Kirby, R. H.; *J. Am. Chem. Soc.* **58** (1936) 2074; Bryce-Smith, D.; Turner, E. E. *J. Chem. Soc.* (1953) 861.

[2] Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **46** (1990) 5633, contains a short review on the dimetallation of benzene.

[3] In principle, bis(methylthio)benzene can be the result of a metallation-functionalization-metallation-functionalization sequence. As the order of addition did not have any influence upon the results, we presume that this sequence does not play any role. Moreover, the consequence of such a sequence would be the formation of considerable amounts of *ortho*-bis(methylthio)benzene, since the methylthio group in methylthiobenzene (formed after the first metallation-functionalization) would direct the metallation to the *ortho* position. See also previous chapter.

[4] As of the branched alkoxides only $KOCMe_2Et$ is commercially available this alkoxide was preferred over $KOCMeEt_2$ and $KOCEt_3$.

[5] Schlosser, M. *Struktur und Reaktivität polarer Organometalle* Springer-Verlag, Berlin (1973).

[6] See also Brandsma, L.; Verkruijsse, H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag (1987).

Chapter 9

Influencing the Reactivity of Super Base Mixtures by Addition of an Excess of a *tertiary*-Alkoxide

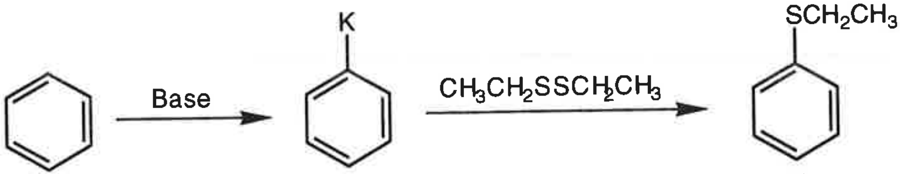
Introduction

Previous investigations have provided several useful synthetic applications of superbase mixtures composed of a lithium base and a heavier alkali metal *tert*-alkoxide, e.g. ^{n}BuLi·KO^{t}Bu.[1] The preceeding chapters of this thesis show further examples. For a number of deprotonations these superbase mixtures have shown to be indispensable or to have distinct advantages over the more conventional base systems, such as ^{n}BuLi·TMEDA or LDA. For example, when pyridine is treated with ^{n}BuLi·TMEDA extensive addition of the base to the C=N bond of pyridine occurs. Treatment with ^{n}BuLi·KO^{t}Bu in THF, however, results in metallation at the 2 and 4 positions of pyridine. The same effect is observed when vinylacetylene is treated with these mixtures. Whereas interaction between ^{n}BuLi·TMEDA and vinylacetylene gives rise to addition and subsequent oligomerization, this substrate can be selectively dimetallated in satisfactory yield with the mixture ^{n}BuLi·KO^{t}Bu in THF. When isoprene is mixed with LDA a metallation equilibrium is formed, only a small part of the isoprene is metallated. Addition of KO^{t}Bu shifts the metallation equilibrium to the right side as a result of which isoprene is metallated to a larger extent.

Lochmann recently reported that the reactivity of superbase mixtures consisting of *n*-butyllithium and a tertiairy alkoxide of a heavier alkali metal in alkylation reactions and deprotonation reactions of alkylbenzenes in heptane can be further increased by introducing additional equivalents of the heavier alkali metal alkoxide.[2] The presence of an equivalent of *lithium tert*-alkoxide, however, caused a decrease of the reactivity of benzyllithium and benzylpotassium in the metallation of 2-methylnaphtalene.[3] These initial reports led us to study the reactivity of these modified superbase mixtures. We were especially interested in the possibilities to use them as deprotonating reagents.

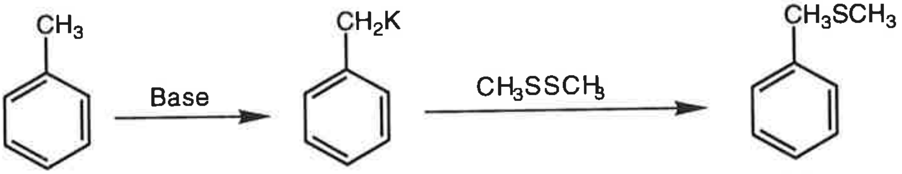
Aim of the present research

We decided to study the influence of the amount of lithium and potassium alkoxides upon deprotonation reactions, using benzene (metallation at sp^{2} center) and toluene (metallation at sp^{3} center) as model substrates. Metallation of these compounds with the 1:1 molar mixture of ^{n}BuLi and KO^{t}Bu in the solvents THF, diethyl ether and hexane does not preceed efficiently. The reasons for preferring these substrates over compounds with coordinating or activating groups is that the latter may influence the composition and reactivity of the base. For example, the methoxy group in anisole may be considered as an internal alkoxide moiety. For the functionalization of our metallation mixtures we choose diethyl disulfide and dimethyl disulfide, electrophiles that react extremely fast. Furthermore this gives products that are not too volatile, so that the losses due to evaporation during the work-up are negligible. The alkylthiolation products were isolated by distillation. The metallation-functionalization reactions are shown in schemes 1 and 2.



(1)

Scheme 1: Metallation and functionalization of benzene.



(2)

Scheme 2: Metallation and functionalization of toluene.

In addition to three mixtures of bases consisting of mixtures of *n*-butyllithium and alkali metal alkoxide pure *n*-butylpotassium was used as a base. Below a short description of the bases used in THF, diethyl ether and hexane is given.

The standard 1:1 superbase mixture was prepared by mixing equimolar amounts of *n*-butyllithium and potassium alkoxide:

$$^{n}BuLi \quad + \quad KO^{t}Bu \quad \longrightarrow \quad ^{n}BuK \quad + \quad LiO^{t}Bu$$

Scheme 3: Standard 1:1 superbase mixture, applicable in various alkanes and ethers as solvents.

On basis on the results obtained by Lochmann a mixture was prepared containing a higher ratio of potassium *tert*-alkoxide:*n*-butyllithium.[2] Lochmann found that ratios of 3:1 or 4:1 of alkoxide:*n*-butyllithium were most efficient. A higher amount of alkoxide is impractical and costly while the extra effect compared to the 3:1 and 4:1 mixtures is minimal.[4]

$$^{n}BuLi \ + \ 3\ KO^{t}Bu \quad \longrightarrow \quad ^{n}BuK \ + \ 2\ KO^{t}Bu \ + \ LiO^{t}Bu$$

Scheme 4: Superbase mixture with an excess of KO^{t}Bu.

In order to investigate the influence of the LiO^{t}Bu formed in the exchange reaction (see scheme 4) three equivalents of LiO^{t}Bu were added to the standard base mixture:

$$^{n}BuLi + KO^{t}Bu + 3\ LiO^{t}Bu \longrightarrow {}^{n}BuK + 4\ LiO^{t}Bu$$

Scheme 5: Superbase mixture with extra $LiO^{t}Bu$ added.

Pure *n*-butylpotassium was prepared according to reference[5] by mixing *n*-butyllithium and potassium *tert*-amylate in hexane at *ca.* -40°C, quickly raising the temperature to room temperature, centrifuging the mixture and washing the ^{n}BuK precipitate twice with hexane. The remaining off-white solid was transferred to the reaction vessel as a supension in hexane.

Results and discussion

Metallations in THF.

Most reactions performed with superbase mixtures were done in THF as in this solvent the solubilities of organopotassium and -lithium compounds are good. Reactions had to be carried out at *ca.* -80°C to avoid attack of THF by the base.[6] (This α-metallation of THF proceeds very smoothly at higher temperatures. The α-metallated THF decomposes to ethene and potassium ethenolate at about -30°C.) In tables 1 and 2 results of the metallations in THF are summarized.

Table 1: Metallation of benzene with various base mixtures in THF.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **1** (%)
$^{n}BuLi\cdot KO^{t}Bu$	-80	homogeneous	30	42
$^{n}BuLi\cdot 3KO^{t}Bu$	-80	homogeneous	30	59
$^{n}BuLi\cdot KO^{t}Bu\cdot 3LiO^{t}Bu$	-80	homogeneous	30	37
^{n}BuK	-80	homogeneous	30	43

[a] 0.10 mol of benzene, 0.10 mol of $^{n}BuLi$ and varying amounts of alkoxide in a mixture of 65 mL of THF and 63 mL of hexane.

Table 2: Metallation of toluene with various base mixtures in THF.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **2**[b] (%)
$^{n}BuLi\cdot KO^{t}Bu$	-80	homogeneous	30	72
$^{n}BuLi\cdot 3KO^{t}Bu$	-80	homogeneous	30	90
$^{n}BuLi\cdot KO^{t}Bu\cdot 3LiO^{t}Bu$	-80	homogeneous	30	68
^{n}BuK	-80	homogeneous	30	57

[a] 0.10 mol of toluene, 0.10 mol of $^{n}BuLi$ and varying amounts of alkoxide in a mixture of 65 mL of THF and 63 mL of hexane.[b] The product contained ~ 5% ring functionalized products, as the result of ring metallation of toluene. Presumably a mixture of *o*-, *m*- and *p*-isomers was obtained, we were unable to establish the ratio of these compounds. All three isomers have been reported as a side product in the metallation of toluene.[7]

For both substrates addition of an excess of KO^tBu resulted in an increased yield compared to the 1:1 mixture. The effect of addition of LiO^tBu is less pronounced. Yields obtained by using the pure ^nBuK base are comparable or somewhat lower, probably due to a faster competing reaction with THF. The reactivity of pure ^nBuK towards THF is reported to be higher than that of the $^nBuLi{\cdot}KO^tBu$ mixture.[8]

Metallations in diethyl ether.

Diethyl ether has never been used as a solvent for $^nBuLi{\cdot}KO^tBu$ mixtures. Metallations were carried out at *ca.* -40°C in order to avoid α-metallation of diethyl ether.[9] Results of the metallations are shown in tables 3 and 4.

Table 3: Metallation of benzene with various base mixtures in diethyl ether.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **1** (%)
$^nBuLi{\cdot}KO^tBu$	-40	homogeneous	30	52
$^nBuLi{\cdot}3KO^tBu$	-40	heterogeneous	30	49
$^nBuLi{\cdot}KO^tBu{\cdot}3LiO^tBu$	-40	homogeneous	30	28
^nBuK	-40	heterogeneous	30	0[b]

[a] 0.10 mol of benzene, 0.10 mol of ^nBuLi and varying amounts of alkoxide in a mixture of 65 mL of diethyl ether and 63 mL of hexane. [b] No reaction occurred at all.

Table 4: Metallation of toluene with various base mixtures in diethyl ether.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **2**[b] (%)
$^nBuLi{\cdot}KO^tBu$	-40	homogeneous	30	57
$^nBuLi{\cdot}3KO^tBu$	-40	heterogeneous	30	88
$^nBuLi{\cdot}KO^tBu{\cdot}3LiO^tBu$	-40	homogeneous	30	20
^nBuK	-40	heterogeneous	30	60

[a] 0.10 mol of toluene, 0.10 mol of ^nBuLi and varying amounts of alkoxide in a mixture of 65 mL of diethyl ether and 63 mL of hexane. [b] The product contained ~ 5% ring functionalized product, as the result of ring metallation of toluene. Presumably a mixture of *o*-, *m*- and *p*-isomers was obtained, we were unable to establish the ratio of these compounds. All three isomers have been reported as a side product in the metallation of toluene.[7]

Differences between the base mixtures are significant for toluene: the use of an excess of KO^tBu resulted in a strong increase in yield, whereas an excess of LiO^tBu clearly led to a decrease of the yield. For benzene the results are less clear. When the reaction was performed with pure ^nBuK no ethylthiobenzene was obtained at all and no increase in yield was observed when using the base mixture containing an excess of KO^tBu. The discrepancies between benzene and toluene may be caused by solubility differences of the $^nBuLi{\cdot}3KO^tBu$ and ^nBuK bases in the substrates benzene and toluene. Both mixtures are heterogeneous in diethyl ether but the reactive base species may be (partially) soluble in toluene and less soluble in benzene. Solvatation of the base by the substrate may result in metallation of that substrate.

Metallations in hexane.

Major advantage of hexane as a solvent is the possibility to carry out reactions at room temperature (r.t.). Reactions that require prolonged stirring can be done more easily in hexane. Disadvantage is the insolubility of most organoalkali compounds in this solvent.

Results of the metallations in hexane are shown in tables 5 and 6. During the metallations of benzene and toluene higher boiling difunctionalized products were also isolated. These difunctionalized products are probably the result of functionalization of dimetallated substrate. Inverse addition of the metallation mixture to a large (~200%) excess electrophile gave identical results, which proves that indeed dimetallated species are the origin of the difunctionalized product and not a metallation-functionalization-metallation-functionalization sequence during quenching.

Table 5: Metallation of benzene with various base mixtures in hexane.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **1** (%)	yield of dimet.[b] (%)	total % metall.[c]
^{n}BuLi·KO^{t}Bu	r.t.	heterogeneous	30	32	8	48
^{n}BuLi·3KO^{t}Bu	r.t.	heterogeneous	30	41	10	61
^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu	r.t.	heterogeneous	30	31	6	43
^{n}BuK	r.t.	heterogeneous	30	27	10	47

[a] 0.10 mol of benzene, 0.10 mol of ^{n}BuLi and varying amounts of alkoxide in 128 mL of hexane. [b] dimetallated product, after quenching isolated as a 1:1 mixture of *meta*- and *para*-bis(ethylthio)benzeen. [c] Total % metallation = % **1** + 2(% dimetallation).

Table 6: Metallation of toluene with various base mixtures in hexane.[a]

Base	Temp. (°C)	base/solvent mixture	time (min)	yield of **2**[b] (%)	yield of dimet.[c] (%)	total % metall.[d]
^{n}BuLi·KO^{t}Bu	RT	heterogeneous	30	47	11	69
^{n}BuLi·3KO^{t}Bu	RT	heterogeneous	30	51	13	77
^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu	RT	heterogeneous	30	45	10	65
^{n}BuK	RT	heterogeneous	30	42	8	60

[a] 0.10 mol of toluene, 0.10 mol of ^{n}BuLi and varying amounts of alkoxide in 128 mL of hexane. [b] The product contained ~ 5% ring functionalized product. Presumably a mixture of *o*-, *m*- and *p*-isomers was obtained, we were unable to establish the ratio of these compounds. All three isomers have been reported as a side product in the metallation of toluene.[7] [c] Dimetallated product, after quenching isolated as α,α–bis(methylthio)toluene. Also traces of α,α,α–tri(methylthio)toluene were found, probably as the result of functionalization of trimetallated toluene. [d] Total % metallation = % **2** + 2(% dimetallation).

Effects in hexane are less distinct than in diethyl ether and THF but the same trends are observed; the use of an excess KO^{t}Bu results in an increase and the use of excess LiO^{t}Bu in a decrease of the yield. It is possible, however, that the rate-determining step in hexane suspensions is the realization of contact between the soluble substrate and insoluble base. This, of course, complicates comparisons with THF and diethyl ether.

Reactions performed with potassium *tert*-amylate (KO^{t}Am,which is soluble in hexane) instead of potassium *tert*-butoxide (which is insoluble in hexane) gave yields that were ~ 5 to 10% higher. Upon mixing ^{n}BuLi and KO^{t}Am a finer precipitate was formed than in the case of using KO^{t}Bu. This will result in a better contact between base and substrate.

Dimetallated product is probably formed *via* incorporation of the initially formed, insoluble, monopotassio compound in an aggregate of the insoluble base mixture and subsequent second deprotonation. This second metallation is directed towards the *meta* and *para* positions due to the positive inductive effect of the anionic carbon atom.

Experiments towards the presence of interactions between alkylalkali compounds and alkali metal alkoxides in solution.

Superbases consisting of mixtures of *n*-butyllithium and potassium alkoxides have been extensively used in organic synthesis, but their structure in solution as well as the nature of the actual reactive species is still unknown. Structural investigations like NMR and crystallographic studies are difficult to perform due to the high reactivity of the species, and reports on their nature are often contradictory. Some experiments suggest that the reactive species is only the pure potassium compound ^{n}BuK[5,10,11] formed in the exchange reaction, while other experiments suggest the presence of mixed aggregates[6,8,12,13] (consisting of a mixture of (some of) the compounds shown in scheme 3).

On basis of the results of the metallation experiments we presume that there is a complicated interplay between alkylalkali compounds (either lithium or potassium), the alkoxide, solvent and substrate. Synthetic experiments can possibly be helpful in elucidating the actual structure of these base systems.

It is generally assumed that in hexane the exchange reaction between *n*-butyllithium and potassium alkoxides (see scheme 3) proceeds to completion. This is confirmed by the almost quantitative preparation of *n*-butylpotassium in hexane.[5] The driving force of this exchange reaction is the formation of strong Li-O interactions.[14] Experiments by Lochmann and Bauer showed that in THF the exchange reaction between an alkyllithium base (trityllithium) and a heavier alkali metal alkoxide (cesium 3-ethyl-3-heptoxide) runs to completion.[11] We therefore assume that after mixing ^{n}BuLi and KO^{t}Bu in a 1:1 ratio mainly ^{n}BuK and LiO^{t}Bu are present in all solvents.

A number of experiments were done in order to gain evidence for the formation of mixed aggregates of the kind ^{n}BuK·(MO^{t}Alk)$_n$ (M=Li or K, n=1,2,3..) in solution. Upon addition of 1 equivalent of KO^{t}Am to a solution of ^{n}BuLi in hexane at 10°C a coarse, off-white, precipitate was formed. ^{n}BuLi as well as KO^{t}Am and LiO^{t}Am is soluble in hexane. The solid was expected to consist therefore only of ^{n}BuK, formed in the exchange reaction. Upon addition of a second equivalent of KO^{t}Am the suspension became somewhat finer of structure. Further additions did not change the constitution of the mixture, until a fifth equivalent was added: the initially formed suspension dissolved completely, to give a clear brownish solution.[15] Repetition of this experiment with KO^tBu instead of KO^tAm did not result in a clear solution, probably due to the insolubility of KO^tBu in hexane. Lithium *tert*-butoxide (which is soluble in hexane) had the same effect as potassium *tert*-amylate. A mixture of 1 equivalent of ^nBuLi and 1 equivalent of KO^tBu was prepared in pentane at 10°C, resulting in a slightly brownish precipitate, probably consisting of *n*-butylpotassium. LiO^tBu was subsequently added in portions of 1 equivalent. After addition of three equivalents the precipitate had completely dissolved (1 equivalent of LiO^tBu was formed in the exchange reaction).

These experiments show that strong interactions between *n*-butylpotassium and alkoxides take place in hexane. Probably these interactions also exist in THF and diethyl ether. The following reactions can be proposed on basis of the experiments with the base mixtures. The exchange reaction between *n*-butyllithium and potassium *tert*-butoxide, results in the formation of *n*-butylpotassium and lithium *tert*-butoxide and small quantities of a mixed aggregate:

$$^{n}BuLi + KO^{t}Bu \longrightarrow {}^{n}BuK + LiO^{t}Bu + \underset{\substack{\text{small amounts}\\ n=1,2,3..}}{{}^{n}BuK\cdot(LiO^{t}Bu)_n}$$

Scheme 6: Transmetallation reaction.

Upon addition of excess alkoxide larger quantities of mixed aggregates are formed, the alkoxides more or less solvatating the *n*-butylpotassium. Screttas *et al.* observed a similar effect with the in hexane insoluble *n*-butylsodium, which formed soluble complexes with magnesium ethoxyethoxide in various ratios.[16]

$$^{n}BuK + \underset{M=\text{ Li or K}}{\text{excess } MO^{t}Bu} \rightleftharpoons \underset{m=1,2,3..}{{}^{n}BuK\cdot(MO^{t}Bu)_m}$$

Scheme 7: Interaction between *n*-butylpotassium and alkoxides.

The crystal structure of 2-methylsodium-4,6-dimethyl-lithiumphenolate, elucidated by Harder *et al.*, shows an example of how such an aggregate could be build.[13] In figure 1 part of the interactions in this model are schematically shown. The structure of $[^nBuLi\cdot LiO^tBu]_4$, elucidated by Boche *et al.* showed a similar arrangement.[17] Both consist of a core of alkoxides, held together by strong Li-O contacts, with on the outer part of this core the alkyl alkali species interacting with alkoxide species.

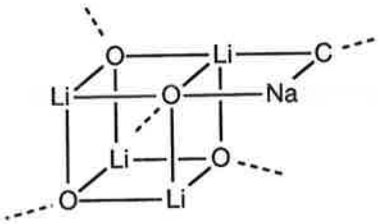
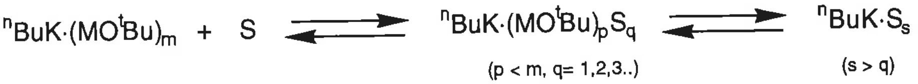


Figure 1: Schematic representation of interactions in the crystal structure of 2-methylsodium-4,6-dimethyl-lithiumphenolate, a model for superbases.[13]

In case of *potassium* alkoxides the formation of such a mixed aggregate results in the formation of a strong base as the anionic carbon atom of the butyl group is surrounded by potassium ions only. In the case of *lithium* alkoxides (as shown in figure 1), however, it results in the formation of a weaker base compared to 'single' *n*-butylpotassium as the anionic carbon atom of the butyl moiety is surrounded by potassium ions as well as lithium ions and this base can therefore be considered to consist partially of ^{n}BuK and partially of $^{n}BuLi$. This assumption is in accordance with results of thermodynamic measurements on organolithium compounds by Arnett *et al.*.[18] The reactivity of a 1:1 mixture of LiHMDS (= lithium bis(trimethylsilyl)amide) and $KO^{t}Bu$ was intermediate between the reactivities of the pure organolithium base (LiHMDS) and the pure organopotassium base (KHMDS). The reactivities of this 1:1 mixture and a 1:1 mixture of KHMDS and $LiO^{t}Bu$ proved to be similar, and it was concluded that the same species was formed in both cases,"whatever it may be". The reactivity of lithium bases was not affected by addition of $LiO^{t}Bu$.

Solvents can (partially) break down these aggregates, the species formed depending on the coordinating properties of the solvent:



$$^{n}BuK\cdot(MO^{t}Bu)_m + S \rightleftharpoons \underset{(p < m,\ q = 1,2,3..)}{^{n}BuK\cdot(MO^{t}Bu)_pS_q} \rightleftharpoons \underset{(s > q)}{^{n}BuK\cdot S_s}$$

Scheme 8: Interaction between base and solvent (S).

For THF and diethyl ether, both having good coordinating properties, one of the two species on the right side will be present. The fact that also in these solvents the influence of amount of and type of alkoxide is large indicates that the reactive species is rather a mixed aggregate, $^{n}BuK\cdot(MO^{t}Bu)_p\cdot(S)_q$, than the pure $^{n}BuK\cdot(S)_s$ species.

As hexane has no coordinating properties at all only the species on the left, $^{n}BuK\cdot(MO^{t}Bu)_n$, will presumably be present. This mixed aggregate may fall apart in ^{n}BuK and $MO^{t}Bu$ (due to the often large difference in solubility), but the fact that the amount of alkoxide and type of alkoxide has an influence on results suggests that also some mixed aggregate is present.

The performance of pure *n*-butylpotassium as a base is good even in absence of solvating alkoxides or solvents. This may be explained by the extremely high reactivity of the bare anionic carbon atom in *n*-butylpotassium. It is generally highly reactive as a precipitate (in hexane and diethyl ether) as well as dissolved (in THF *n*-butylpotassium is a monomeric species[5]). It is unlikely that ^{n}BuK in hexane and diethyl ether reacts in a solvatated state in a very low concentration (as is sometimes suggested in literature[2]) as the reactions proceed extremely rapidly. A base active only in a dissolved form at low concentration, can not account for the good results we obtained. Although pure ^{n}BuK is a very strong base practical problems put limitations on its use. The preparation of pure ^{n}BuK is time consuming and troublesome due to the high reactivity of the solid compound. Furthermore the high reactivity of the base towards solvents, especially THF, results in lower yields of metallation of substrate. Compared to base mixtures consisting of mixtures of *n*-butyllithium and potassium *tert*-alkoxides the pure *n*-butylpotassium base has no advantages in organic synthesis.

Some applications.

The good results obtained with the base mixture containing an excess of potassium alkoxide led us to investigate the applicability of this mixture on the metallation of other substrates. Some compounds that give low to moderate yields upon treatment with the standard 1:1 base mixture were treated with the new base mixture.

Ortho-methylthio-benzotrifluoride (**3**) was isolated in 52% yield after treatment of benzotrifluoride with 1 equivalent of ^{n}BuLi·KO^{t}Bu in THF at -80°C and subsequent quenching with dimethyl disulfide. When we performed the reaction with 1 equivalent of the ^{n}BuLi·3KO^{t}Bu mixture under the same conditions we obtained the desired product in 78% yield.[19]

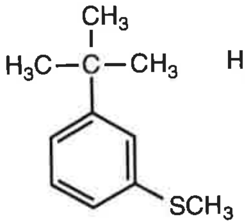
The results of the metallation of *tert*-butylbenzene with 1 equivalent of the various base mixtures in hexane and THF are shown in table 7. Steric effects and the positive inductive effect of the *tert*-butyl group direct this metallation to the *meta* and *para* positions. Product (**4**) was isolated after quenching with dimethyl disulfide.

Table 6: Metallation of *tert*-butylbenzene with various base mixtures in hexane and THF.

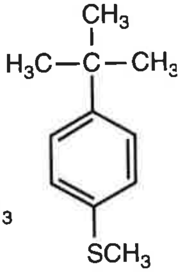
Base	solvent	Temp. (°C)	time (h)	yield of (4) (%)	ratio[a] *m* : *p*
^{n}BuLi·KO^{t}Bu	THF	-80	3	20	1 : 1
^{n}BuLi·3KO^{t}Bu	THF	-80	3	59	1 : 1
^{n}BuLi·KO^{t}Bu	hexane	RT	3	38	1 : 2
^{n}BuLi·3KO^{t}Bu	hexane	RT	3	73	1 : 2
^{n}BuLi·KO^{t}Am	hexane	RT	3	48	1 : 2
^{n}BuLi·3KO^{t}Am	hexane	RT	3	76	1 : 2

[a] The *meta/para* ratio of the product obtained after the metallation of *tert*-butylbenzene is strongly influenced by the base used.[20]

(3)



meta -**(4)**

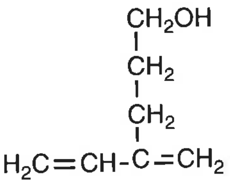


para -**(4)**

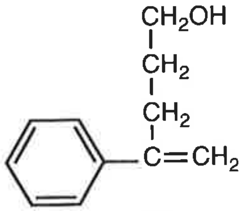
The improvement is not limited to base mixtures containing *n*-butyllithium. Also the performance of the base mixture containing lithium di*iso*-propylamide and potassium *tert*-butoxide (LDA·KO^{t}Bu[21]), usually applied in a 1:1 ration, is enhanced by adding excess alkoxide. This combination is especially useful for the metallation of unsaturated compounds, that are susceptible to addition of bases containing *n*-butyllithium.

The amount of product (5) obtained after metallation of isoprene in THF at -60°C and subsequent addition of ethylene oxide is improved from 50% with LDA·KO^{t}Bu to 70% with LDA·3KO^{t}Bu.[22]

After treatment of α-methylstyrene with LDA·KO^{t}Bu in THF at -90°C and subsequent quenching with ethyleneoxide, the alcohol 4-phenyl-pent-4-ene-1-ol (6) was isolated in 63% yield. The same reaction with LDA·3KO^{t}Bu gave the alcohol in 80% yield. (The analogous reaction with ^{n}BuLi·KO^{t}Bu and ^{n}BuLi·3KO^{t}Bu in THF at -80°C gave only 29% and 38%, respectively, of the desired product. Addition of base to the double bond and subsequent polymerization were the main reactions.)



(5)



(6)

The exchange reaction between alkyl amide bases and potassium alkoxides probably does not run to completion in THF. The excess potassium alkoxide may serve to shift the exchange equilibrium more to the right side, therefore making the base mixture thermodynamically more powerful:

$$\text{LDA} + \text{KO}^{t}\text{Bu} \rightleftharpoons \text{KDA} + \text{LiO}^{t}\text{Bu}$$

Scheme 8: Exchange equilibrium between LDA and KO^{t}Bu.

Conclusions.

The use of an excess potassium alkoxide in reactions with superbases, prepared by mixing *n*-butyllithium and potassium alkoxides, is especially useful for deprotonations of unactivated substrates and gives higher yields in all solvents than the conventional superbase mixture (^{n}BuLi·KO^{t}Bu). There probably is a very complicated interplay in solution between alkylpotassium and alkali metal alkoxide. Furthermore the solvent has a great influence on results. THF is most useful for metallations with superbasic mixtures, but diethyl ether can also be succesfully used. In hexane reactions can be performed at room temperature but side reactions occur easily in this solvent due to the insolubility of the superbases and metallated substrates in this solvent.

Experimental methods

General Conditions.

All reactions were carried out under nitrogen in a 250 mL three-necked round-bottomed flask, equipped with a thermometer-gas inlet combination, mechanical stirrer and dropping funnel-gas outlet combination. Solvents were dried before use. *n*-Butyllithium (1.6 Molar solution in hexane) and potassium *tert*-alkoxides were obtained commercially. All products were isolated by distillation and analyzed by NMR spectroscopy and GLC. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) using deuteriochloroform as solvent and internal standard. GLC analysis was carried out on a Varian 4400 gas chromatograph using a capillary silica-coated cloumn.

Preparation of LiOtBu.

To a mixture of 74 g (1.0 mol) of dry *tert*-butylalcohol and 100 mL of hexane was added 630 mL of a 1.6 M solution (1.0 mol) of ^{n}BuLi in hexane while cooling with an ice bath. When the addition was complete all hexane was removed by evaporation in an oil-pump vacuum using a bath at *ca.* 30°C. LiO^{t}Bu was obtained as a white solid.

Metallation Reactions.

Metallation of benzene with ^{n}BuLi·KOtBu in THF.

11.2 g (0.10 mol) of KOtBu and 7.8 g (0.10 mol) of benzene were dissolved in 65 mL of THF. The solution was stirred and cooled to -80°C, then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes while maintaining the temperature at -80°C. The clear orange solution was stirred for 30 minutes at -80°C, after which 20.0 g (0.16 mol) of diethyl disulfide, diluted with 10 mL of THF, was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at -20°C. The layers were separated and the water layer was extracted three times with 50 mL of diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, **ethylthiobenzene** (**1**) as a slightly yellow liquid, 5.79 g (42%). bp. 90-95°C (20 mm Hg).

^{13}C-NMR: δ= 14.5 (CH_3), 27.7 (SCH_2), 125.8 (C_p), 128.9 (C_o), 129.1 (C_m), 136.8 (C_i).

^{1}H-NMR: δ= 1.36 (t, CH_3, J= 7.4 Hz, 3H), 2.98 (t, SCH_2, J= 7.4 Hz, 2H), 7.18- 7.41 (m, phenyl, 5H).

Metallation of benzene with ^{n}BuLi·3KO^{t}Bu in THF.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. KOtBu (34.0 g (0.30 mol)) and a mixture of 7.8 g (0.10 mol) of benzene and 65 mL of THF were placed in the flask. Only part of the KO^{t}Bu dissolved. The mixture was stirred and cooled to -80°C, after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The clear orange solution was stirred for 30 minutes at -80°C. After the usual work-up (**1**) was obtained as a slightly yellow liquid, 8.15 g (59%).

Metallation of benzene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in THF.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KOtBu, 24.0 g (0.30 mol) of LiO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of THF was placed in the flask. A clear solution was formed. The mixture was stirred and cooled to -80°C after which 64 mL of a 1.6 M (0.10 mol) solution of ^{n}BuLi was added. The clear yellow solution was stirred for 30 minutes at -80°C. After the usual work-up (**1**) was obtained as a slightly yellow liquid, 5.14 g (37%).

Metallation of benzene with ^{n}BuK in THF.

First ^{n}BuK was prepared using standard Schlenk techniques. A stirred solution of 6.3 g (0.05 mol) of KO^{t}Am in 50 mL of hexane was cooled to -40°C. Subsequently 39 mL of a 1.6 M solution (0.05 mol) of ^{n}BuLi in hexane was added over a few minutes while stirring the mixture efficiently. A white suspension was formed immediately. The temperature was raised to room temperature over a few minutes. The suspension turned somewhat brown. The mixture was centrifuged and subsequently the brownish precipitate was washed twice with hexane. The precipitate was transferred into the 250 mL round-bottomed flask as a suspension in 32 mL of hexane. The stirred suspension was cooled to -90°C. A mixture of 3.9 g (0.05 mol) of benzene and 33 mL of THF was added dropwise while maintaining the temperature between -80°C and -90°C. The brown clear solution was stirred for 30 minutes at -80°C. A mixture of 10 g (0.08 mol) of diethyl disulfide and 10 mL of THF was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. Product (**1**) was obtained as a slightly yellow liquid, 3.00 g (43%).

Metallation of benzene with ^{n}BuLi·KO^{t}Bu in diethyl ether.

In the flask were placed 11.2 g (0.10 mol) of KOtBu, 7.8 g (0.10 mol) of benzene and 65 mL of diethyl ether. Only a very small part of the KO^{t}Bu dissolved. The suspension was stirred and cooled to -40°C. Then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes while maintaining the temperature at -40°C. The yellow suspension was stirred for 30 minutes at -40°C. Subsequently 20.0 g (0.16 mol) of diethyl disulfide, diluted with 10 mL of diethyl ether, was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at -20°C. The layers were separated and the water layer was extracted three times with 50 mL of diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, (**1**), as a slightly yellow liquid. 7.16 g (52%).

Metallation of benzene with ^{n}BuLi·3KO^{t}Bu in diethyl ether.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 34.0 g (0.30 mol) KO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of diethyl ether was placed in the flask. Only a very small part of the KO^{t}Bu dissolved. The suspension was stirred and cooled to -40°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The yellow suspension was stirred for 30 minutes at -40°C. After the usual work-up (**1**) was obtained as a slightly yellow liquid, 6.73 g (49%).

Metallation of benzene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in diethyl ether.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 24.0 g (0.30 mol) of LiO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of diethyl ether was placed in the flask. A clear yellow solution was formed. The mixture was stirred and cooled to -40°C after which 64 mL of a

1.6 M solution (0.10 mol) of ^{n}BuLi was added. The clear yellow solution was stirred for 30 minutes at -40°C. After the usual work-up (**1**) was isolated as a slightly yellow liquid, 3.80 g (28%).

Metallation of benzene with ^{n}BuK in diethyl ether.

^{n}BuK was prepared as described for the reaction in THF. The precipitate of 0.05 mol of ^{n}Buk was transferred into the 250 mL round-bottomed flask as a suspension in 32 mL of hexane. The stirred suspension was cooled to -50°C. A mixture of 3.9 g (0.05 mol) of benzene and 33 mL of diethyl ether was added dropwise while maintaining the temperature between -40°C and -50°C. The brown suspension was stirred for 30 minutes at -40°C. A mixture of 10 g (0.08 mol) of diethyl disulfide and 10 mL of diethyl ether was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. No ethylthiobenzene was obtained.

Metallation of benzene with ^{n}BuLi·KO^{t}Bu in hexane.

In the reaction flask was placed a mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of hexane. The KO^{t}Bu did not dissolve. The suspension was stirred and cooled to *ca.* -20°C. Then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes. The cream-colored suspension was stirred for 30 minutes at room temperature. The suspension was cooled to -40°C. Subsequently 20.0 g (0.16 mol) of diethyl disulfide, diluted with 10 mL of hexane, was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at -20°C. The layers were separated and the water layer was extracted three times with 50 mL of diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, (**1**), as a slightly yellow liquid. 4.46 g (32%). A second fraction, bp. 110-120°C (1 mm Hg), proved to be bis(ethylthio)benzene (*m*:*p* = ~1:1), 1.50 g (8%). This second fraction partially solidified due to the presence of the *para* isomer.

1,3-bis(ethylthio)benzene:

^{13}C-NMR: δ= 14.3 (SCH_2CH_3), 28.0 (SCH_2CH_3), 128.7 (C_4/C_6), 129.1 (C_5), 129.8 (C_2), 134.2 (C_1/C_3).

^{1}H-NMR: δ= 1.30 (t, SCH_2CH_3, *J*= 6.1 Hz, 3H), 2.93 (q, SCH_2CH_3, *J*= 6.1 Hz, 2H), 7.08- 7.30 (m, phenyl, 4H).

1,4-bis(ethylthio)benzene:

^{13}C-NMR: δ= 14.4 (SCH_2CH_3), 27.5 (SCH_2CH_3), 126.1 ($C_2/C_3/C_5/C_6$), 137.6 (C_1/C_4).

^{1}H-NMR: δ= 1.29 (t, SCH_2CH_3, *J*= 7.3 Hz, 3H), 2.90 (q, SCH_2CH_3, *J*= 7.3 Hz, 2H), 7.24 (s, phenyl, 4H).

Metallation of benzene with ^{n}BuLi·3KO^{t}Bu in hexane.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 34.0 g (0.30 mol) of KO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of hexane was placed in the flask. The KO^{t}Bu did not dissolve. The suspension was stirred and cooled -20°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The brown suspension was stirred for 30 minutes at room temperature. After the usual work-up (**1**) was obtained as a slightly yellow liquid, 5.66 g (41%). As a by product bis(ethylthio)benzene (*m*/*p*= ~ 1:1), 2.00 g (10%), was obtained. This product partially solidified due to the presence of the *para* isomer.

Metallation of benzene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in hexane.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 24.0 g (0.30 mol) of LiO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of hexane was placed in the flask. A large part of the alkoxide dissolved. The mixture was stirred and cooled to -20°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The cream-colored suspension was stirred for 30 minutes at room temperature. After the usual work-up (**1**) was isolated as a slightly yellow liquid, 4.30 g (31%). As a by product bis(ethylthio)benzene (*m*/*p*= ~ 1:1), 1.20 g (6%), was obtained. This by product partially solidified due to the presence of the *para* isomer.

Metallation of benzene with ^{n}BuK in hexane.

^{n}BuK was prepared as described for the reaction in THF. The precipitate of 0.05 mol of ^{n}Buk was transferred into the 250 mL round-bottomed flask as a suspension in 50 mL of hexane. A mixture of 3.9 g (0.05 mol) of benzene and 15 mL of hexane was added dropwise to the stirred suspension at room temperature. The brown suspension was stirred for 30 minutes at room temperature. A mixture of 10 g (0.08 mol) of diethyl disulfide and 10 mL of diethyl ether was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. **(1)** was isolated as a slightly yellow liquid, 1.86 g (27%). As a by product bis(ethylthio)benzene (*m/p*= ~ 1:1), 0.99 g (10%), was obtained. This by product partially solidified due to the presence of the *para* isomer.

Metallation of toluene with ^{n}BuLi·KO^{t}Bu in THF.

In the reaction flask was placed a mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of THF. The clear solution was stirred and cooled to -80°C. Then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes while maintaining the temperature at -80°C. The immediately formed red suspension was stirred for 30 minutes at -80°C, after which a mixture of 15.0 g (0.16 mol) of dimethyl disulfide and 10 mL of THF was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at -20°C. The layers were separated and the water layer was extracted three times with 50 mL diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, **methylbenzylthioether (2)**, as a slightly yellow liquid, 9.95g (72%). bp. 100-105°C (20 mm Hg).[23]

^{13}C-NMR: δ= 14.7 (SCH_3), 38.1 (CH_2S), 126.7 (C_p), 128.2 (C_m), 128.7 (C_o), 138.0 (C_i).

^{1}H-NMR: δ= 2.00 (s, SCH_3, 3H), 3.69 (s, CH_2S, 2H), 7.22- 7.35 (m, phenyl, 5H)

Metallation of toluene with ^{n}BuLi·3KO^{t}Bu in THF.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 34.0 g (0.30 mol) of KO^{t}Bu, 9.2g (0.10 mol) of toluene and 65 mL of THF was placed in the flask. The KO^{t}Bu dissolved poorly. The mixture was stirred and cooled to -80°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The orange suspension was stirred for 30 minutes at -80°C. After the usual work-up **(2)** was obtained as a slightly yellow liquid, 12.42 g (90%).

Metallation of toluene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in THF.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 24.0 g (0.30 mol) of LiO^{t}Bu, 7.8 g (0.10 mol) of benzene and 65 mL of THF was placed in the flask. A clear solution was formed. The mixture was stirred and cooled to -80°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The slightly orange suspension was stirred for 30 minutes at -80°C. After the usual work-up **(2)** was obtained as a slightly yellow liquid, 9.44 g (68%).

Metallation of toluene with ^{n}BuK in THF.

^{n}BuK was prepared as described for the reaction of benzene in THF. The precipitate of 0.05 mol of ^{n}Buk was transferred into the 250 mL round-bottomed flask as a suspension in 32 mL of hexane. The stirred suspension was cooled to -90°C. A mixture of 4.6 g (0.05 mol) of toluene and 33 mL of THF was added dropwise while maintaining the temperature between -80°C and -90°C. The red suspension was stirred for 30 minutes at -80°C. A mixture of 8 g (0.08 mol) of dimethyl disulfide and 10 mL of THF was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. **(2)** was obtained as a slightly yellow liquid, 3.92 g (68%).

Metallation of toluene with ^{n}BuLi·KO^{t}Bu in diethyl ether.

In the flask were placed 11.2 g (0.10 mol) of KO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of diethyl ether. Only a very small part of the KO^{t}Bu dissolved. The suspension was stirred and cooled to -40°C. Then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes while maintaining the temperature at -40°C. The orange suspension was stirred for 30 minutes at -40°C. Subsequently a mixture of 15.0 g (0.16 mol) of dimethyl disulfide and 10 mL of diethyl ether was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at

-20°C. The layers were separated and the water layer was extracted three times with 50 mL diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, (**2**), as a slightly yellow liquid, 7.87 g (57%).

Metallation of toluene with ^{n}BuLi·3KO^{t}Bu in diethyl ether.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 34.0 g (0.30 mol) of KO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of diethyl ether was placed in the flask. Only a very small part of the KO^{t}Bu dissolved. The suspension was stirred and cooled to -40°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The orange suspension was stirred for 30 minutes at -40°C. After the usual work-up (**2**) was obtained as a slightly yellow liquid, 12.14 g (88%).

Metallation of toluene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in diethyl ether.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 24.0 g (0.30 mol) of LiO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of diethyl ether was placed in the flask. A clear yellow solution was formed. The mixture was stirred and cooled to -40°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The clear orange solution was stirred for 30 minutes at -40°C. After the usual work-up (**2**) was isolated as a slightly yellow liquid, 2.8 g (20%).

Metallation of toluene with ^{n}BuK in diethyl ether.

^{n}BuK was prepared as described for the reaction of benzene in THF. The precipitate of 0.05 mol of ^{n}Buk was transferred into the 250 mL round-bottomed flask as a suspension in 32 mL of hexane. The stirred suspension was cooled to -50°C. A mixture of 4.6 g (0.05 mol) of benzene and 33 mL of diethyl ether was added dropwise while maintaining the temperature between -40°C and -50°C. The orange-brown suspension was stirred for 30 minutes at -40°C. A mixture of 8 g (0.08 mol) of dimethyl disulfide and 10 mL of diethyl ether was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. (**2**) was obtained as a slightly yellow liquid, 4.13 g (60%).

Metallation of toluene with ^{n}BuLi·KO^{t}Bu in hexane.

In the flask were placed 11.2 g (0.10 mol) of KO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of hexane. The KO^{t}Bu did not dissolve. The suspension was stirred and cooled to *ca.* -20°C. Then 63 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi in hexane was added over a few minutes. The orange suspension was stirred for 30 minutes at room temperature. The suspension was cooled to -40°C. Subsequently a mixture of 20.0 g (0.16 mol) of diethyl disulfide and 10 mL of hexane was added in one portion with vigorous stirring. After stirring for an additional 5 minutes 100 mL of water was added at -20°C. The layers were separated and the water layer was extracted three times with 50 mL diethyl ether. The combined organic layers were dried over magnesium sulfate and concentrated at reduced pressure. Distillation of the remaining liquid through a short Vigreux column gave the product, (**2**), as a slightly yellow liquid, 6.55 g (47%). A second fraction proved to be **α, α-bis(methylthio)toluene**, 2.1 g (11%). bp. 150-155°C (1 mm Hg).

α, α-bis(methylthio)toluene:

^{13}C-NMR: δ= 15.1 (SCH$_3$), 56.6 (CH(SCH$_3$)$_2$), 126.9 (C$_m$), 127.7 (C$_o$), 125.7 (C$_p$), 139.8 (C$_i$).

^{1}H-NMR: δ= 2.12 (s, (SCH$_3$)$_2$, 6H), 4.83 (s, CH(SCH$_3$)$_2$, 1H), 7.20- 7.50 (m, phenyl, 5H)

Metallation of toluene with ^{n}BuLi·3KO^{t}Bu in hexane.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 34.0 g (0.30 mol) of KO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of hexane was placed in the flask. The KO^{t}Bu did not dissolve. The suspension was stirred and cooled -20°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The orange suspension was stirred for 30 minutes at room temperature. After the usual work-up (**2**) was obtained as a slightly yellow liquid, 7.00 g (51%). As a by product α, α-bis(methylthio)toluene, 2.5 g (13%), was obtained.

Metallation of toluene with ^{n}BuLi·KO^{t}Bu·3LiO^{t}Bu in hexane.

The reaction was performed as described for ^{n}BuLi·KO^{t}Bu. A mixture of 11.2 g (0.10 mol) of KO^{t}Bu, 24.0 g (0.30 mol) of LiO^{t}Bu, 9.2 g (0.10 mol) of toluene and 65 mL of hexane was placed in the flask. A large part of the alkoxide dissolved. The mixture was stirred and cooled to -20°C after which 64 mL of a 1.6 M solution (0.10 mol) of ^{n}BuLi was added. The orange suspension was stirred for 30 minutes at room temperature. After the usual work-up (**2**) was obtained as a slightly yellow liquid, 6.20 g (45%). As a by product α, α-bis(methylthio)toluene, 2.0 g (10%), was obtained.

Metallation of toluene with ^{n}BuK in hexane.

^{n}BuK was prepared as described for the reaction with benzene in THF. The precipitate of 0.05 mol of ^{n}Buk was transferred into the 250 mL round-bottomed flask as a suspension in 50 mL hexane. A mixture of 4.6 g (0.05 mol) of toluene and 15 mL of hexane was added dropwise to the stirred suspension at room temperature. The orange suspension was stirred for 30 minutes at room temperature. A mixture of 8 g (0.08 mol) of dimethyl disulfide and 10 mL of hexane was added in one portion. Work-up was performed as described for the reaction with ^{n}BuLi·KO^{t}Bu. (**2**) was obtained as a slightly yellow liquid, 2.87 g (42%). As a by product α, α-bis(methylthio)toluene, 0.9 g (10%), was obtained.

Metallation of benzotrifluoride with ^{n}BuLi·KO^{t}Bu in THF.

The base was prepared as described for the reaction of benzene with ^{n}BuLi·KO^{t}Bu in THF. The substrate, 14.6 g (0.10 mol) of benzotrifluoride, was added in one portion at -80°C. The dark colored mixture was stirred for one hour at -80°C. After quenching with dimethyl disulfide and work-up the product, *ortho*-methylthiobenzotrifluoride (**3**), was obtained as a slightly yellow liquid, 9.92 g (52%). bp. 105-110°C (20 mm Hg) (the product conatined *ca.* 10% of the *meta* isomer).

2-methylthiobenzotrifluoride:

^{13}C-NMR: δ= 16.2 (q, SCH_3, *J*= 1.7 Hz), 124.0 (q, CF_3, *J*= 271.8 Hz), 124.7 (s, C_5), 126.6 (s, C_3), 127.4 (s, C_4), 127.9 (q, C_1, *J*= 61.3 Hz), 132.0 (q, C_6, *J*= 1.1 Hz), 138.3 (q, C_2, *J*= 1.0 Hz).

^{1}H-NMR: δ= 2.50 (s, SCH_3, 3H), 7.22 (bt, H_4, 1H), 7.37 (bd, H_3, 1H), 7.47 (bt, H_5, 1H), 7.62 (bd, H_6, 1H).

Metallation of benzotrifluoride with ^{n}BuLi·3KO^{t}Bu in THF.

The base was prepared as described for the reaction of benzene with ^{n}BuLi·3KO^{t}Bu in THF. The substrate, 14.6 g (0.10 mol) of benzotrifluoride, was added in one portion at -80°C. The dark colored mixture was stirred for one hour at -80°C. After quenching with dimethyl disulfide and work-up the product, *ortho*-methylthiobenzotrifluoride (**3**), was obtained as a slightly yellow liquid, 15.00 g (78%) (the product conatined *ca.* 10% of the *meta* isomer).

Metallation of tert-butylbenzene with ^{n}BuLi·KO^{t}Bu in THF.

The reaction was performed similarly to the reaction of benzene with ^{n}BuLi·KO^{t}Bu in THF using 13.4 g (0.10 mol) of *tert*-butylbenzene. After addition of the ^{n}BuLi a clear orange soltution was formed, which was stirred for three hours at -80°C. After quenching with dimethyl disulfide and work-up a 1:1 mixture of *meta*- and *para*-(methylthio)*tert*-butylbenzene (**4**) was obtained, 3.60 g (20%). bp. 110-120°C (20 mm Hg).

meta-**4** (**3-methylthio-*tert*-butylbenzene**):

^{13}C-NMR: δ= 16.3 (SCH_3), 31.4 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 122.5 (C2), 123.8 (C6), 124.2 (C4), 126.0 (C5), 138.0 (C3), 151.8 (C1).

^{1}H-NMR: δ= 1.44 (s, $C(CH_3)_3$, 9H), 2.58 (s, SCH_3, 3H), 7.19 (ddd, H4, *J*= 7.2, 1.8, 1.8 Hz, 1H), 7.30 (ddt, H5, *J*= 7.8, 7.8, 1.6 Hz, 1H), 7.34 (dd, H2, *J*= 2.1, 2.1 Hz, 1H), 7.43 (ddd, H6, *J*= 8.8, 2.1, 2.1 Hz, 1H)

para-**4**: (**4-methylthio-*tert*-butylbenzene**):

^{13}C-NMR: δ= 16.1 (SCH_3), 31.5 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 127.0 (C2), 128.8 (C3), 135.1 (C4), 148.3 (C1).

^{1}H-NMR: δ= 1.42 ($C(CH_3)_3$, 9H), 2.55 (SCH_3, 3H), 7.33 (d, H3, *J*= 8.6 Hz, 2H), 7.43 (d, H2, *J*= 8.6 Hz, 2H).

Metallation of tert-butylbenzene with ^{n}BuLi·3KO^{t}Bu in THF.

The reaction was performed similarly to the reaction of benzene with ^{n}BuLi·3KO^{t}Bu in THF using 13.4 g (0.10 mol) of tert-butylbenzene. After addition of the ^{n}BuLi a clear orange soltution was formed, which was stirred for three hours at -80°C. After quenching with dimethyl disulfide and work-up a 1:1 mixture of meta- and para-(methylthio)tert-butylbenzene (4) was obtained, 10.65 g (59%).

Metallation of tert-butylbenzene with ^{n}*BuLi·KO*^{t}*Bu in hexane*

The reaction was performed in the same way as the reaction of benzene with ^{n}BuLi·KO^{t}Bu in hexane using 13.4 g (0.10 mol) of *tert*-butylbenzene. After addition of the ^{n}BuLi a brown suspension was formed, which was stirred for three hours at room temperature. After quenching with dimethyl disulfide and work-up a 1:2 mixture of *meta*- and *para*-(methylthio)*tert*-butylbenzene (4) was obtained, 6.88 g (38%).

Metallation of tert-butylbenzene with ^{n}*BuLi·3KO*^{t}*Bu in hexane*

The reaction was performed similarly to the reaction of benzene with ^{n}BuLi·3KO^{t}Bu in hexane using 13.4 g (0.10 mol) of *tert*-butylbenzene. After addition of the ^{n}BuLi a brown suspension was formed, which was stirred for three hours at room temperature. After quenching with dimethyl disulfide and work-up a 1:2 mixture of *meta*- and *para*-(methylthio)*tert*-butylbenzene (4) was obtained, 13.12 g (73%).

Metallation of tert-butylbenzene with ^{n}*BuLi·KO*^{t}*Am in hexane*

The reaction was performed in the same way as the reaction of benzene with ^{n}BuLi·KO^{t}Bu in hexane. A mixture of 12.4 g (0.10 mol) of potassium *tert*amylate and 13.4 g (0.10 mol) of *tert*-butylbenzene was dissolved in 65 mL of hexane. After addition of the ^{n}BuLi a fine brown suspension was formed, which was stirred for three hours at room temperature. After quenching with dimethyl disulfide and work-up a 1:2 mixture of *meta*- and *para*-(methylthio)*tert*-butylbenzene (4) was obtained, 8.62 g (48%).

Metallation of tert-butylbenzene with ^{n}*BuLi·3KO*^{t}*Am in hexane*

The reaction was performed analogous to the reaction of benzene with ^{n}BuLi·3KO^{t}Bu in hexane. A mixture of 37.2 g (0.30 mol) of potassium-*tert*amylate and 13.4 g (0.10 mol) of *tert*-butylbenzene was dissolved in 65 mL of hexane. After addition of the ^{n}BuLi a very fine brown suspension was formed, which was stirred for three hours at room temperature. After quenching with dimethyl disulfide and work-up a 1:2 mixture of *meta*- and *para*-(methylthio)*tert*-butylbenzene (4) was obtained, 13.70 g (76%).

Metallation of isoprene with LDA·KO^{t}*Bu.*

A mixture of 11.2 g (0.10 mol) of KO^{t}Bu and 10.1 g (0.10 mol) of di-*iso*propylamine was dissolved in 75 mL of THF. The solution was stirred and cooled to -60°C. Subsequently 64 mL of a 1.6 M solution (0.10 mol) of *n*-butyllithium in hexane was added over a few minutes, a clear yellow solution was formed. A solution of 6.8 g (0.10 mol) of isoprene in 10 mL of THF was added dropwise over 10 minutes. Instantaneously a red solution was formed. The mixture was stirred for 15 minutes at -60°C, after which 14 g (0.30 mol) of ethylene oxide in 10 mL of THF was added in one portion. The red color disappeared and a rising of the temperature was observed. The mixture was allowed to rise over 30 minutes to room temperature. 100 mL of water was added at -20°C. Work-up was done as usual. Distillation afforded the product (5) as a colorless liquid, 5.60 g (50%). bp. 75-80°C (1 mm Hg).

^{13}C-NMR: δ= 27.3 ($CH_2CH_2CH_2OH$), 30.8 ($CH_2CH_2CH_2OH$), 62.1 ($CH_2CH_2CH_2OH$), 113.2 ($C{=}CH_2$), 115.7 ($H_2C{=}CH$-), 138.6 ($H_2C{=}CH$-), 145.7 ($C{=}CH_2$).

^{1}H-NMR: δ= 1.70 (tt, $CH_2CH_2CH_2OH$, *J*= 6.7, 7.5 Hz, 2H), 2.24 (t, $CH_2CH_2CH_2OH$, *J*= 7.5 Hz, 2H), 3.16 (b, OH, 1H), 3.62 (t, $CH_2CH_2CH_2OH$, *J*= 6.5 Hz, 2H), 4.95- 5.00 (m, $C{=}CH_2$, 2H), 5.07 (d, HHC=CH- (*cis*), *J*= 10.8, 1H), 5.25 (d, HHC=CH- (*trans*), *J*= 17.6, 1H), 6.38 (dd, HHC=CH-, *J*= 17.6, 10.8 Hz, 1H).

Metallation of isoprene with LDA·3KO^{t}*Bu.*

The reaction was performed as described above, 33.6 g (0.30 mol) of KO^{t}Bu was used. Distillation afforded the product (5) as a colorless liquid, 7.84 g (70%). bp 75-80°C (1 mm Hg).

Metallation of α-methylstyrene with LDA·KO^{t}*Bu.*

The base-mixture was prepared as described for isoprene. To the base-mixture was added dropwise over 5 minutes a mixture of 11.8 g (0.10 mol) of α-methylstyrene and 10 mL of THF while maintaining the temperature at -70°C. A clear red solution was immediately formed. The solution was stirred for 10 minutes at -70°C. To the red solution was added in one portion a mixture of 10 g (0.22 mol) of ethylene oxide and 10 mL of THF. The red color disappeared and a rising of the temperature was observed. The well stirred mixture was allowed to rise over 15 minutes to room temperature. At -20°C 100 mL of water was added. Work-up was done as usual. Distillation afforded the product (**6**) as a colorless liquid, 10.25 g (63%). bp. 110° (1 mm Hg).

^{13}C-NMR: δ= 31.2, 31.6, 62.2, 112.5 ($C=CH_2$), 126.2 (C_o), 127.5 (C_p), 128.4 (C_m), 141.1 (C_i), 148.0 ($C=CH_2$).

^{1}H-NMR: δ= 1.73 (tt, $CH_2CH_2CH_2OH$, *J*= 6.4, 6.6 Hz, 2H), 2.62 (t, $CH_2CH_2CH_2OH$, *J*= 6.5 Hz, 2H), 3.64 (t, $CH_2CH_2CH_2OH$, *J*= 6.5 Hz, 2H), 5.13 (d, C=CHH, *J*= 1.1 Hz, 1H), 5.33 (d, C=CHH, *J*= 1.0 Hz, 1H), 7.29- 7.46 (m, phenyl, 5H).

Metallation of α-methylstyrene with LDA·3KO^{t}Bu.

The reaction was performed as described above, 33.6 g (0.30 mol) of KO^{t}Bu was used. Distillation afforded the product (**6**) as a colorless liquid, 13.00 g (80%).

References

1 Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol I* Springer-Verlag, Heidelberg (1987); Brandsma, L.; Verkruijsse H. D. *Preparative Polar Organometallic Chemistry Vol II* Springer-Verlag, Heidelberg (1990).

2 Lochmann, L. *J. Organomet. Chem.* **376** (1989) 1; Lochmann, L.; Petránek, J. *Tetrahedron Lett.* **32** (1991) 1483.

3 Solvent not stated, probably THF was used. Schlosser, M. *Pure & Appl. Chem.* **60** (1988) 1627.

4 The amount of solvent used in reactions with the 3:1 and 4:1 mixtures is equal to the amount used for the 1:1 mixture.

5 Modified procedure from: Pi, R.; Bauer, W.; Brix, B.; Schade, C.; von Ragué Schleyer, P. *J. Organomet. Chem.* **306** (1986) C1. The ^{n}BuK prepared in this way is off-white in dry form and extremely reactive upon air. A suspension in pentane is dark brown. After evaporation of the pentane the original off-white color returns. Von Ragué Schleyer *et al.* showed that this precipitate consists of almost pure *n*-butylpotassium.

6 Fraenkel, G.; Dayagi, S.; Kobayashi, S. *J. Phys. Chem.* **72** (1968) 953; Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **25** (1984) 745; see also ref [22].

7 All three isomers of ring functionalized product have been reported as side products in the metallation of toluene (major product in all cases was the benzyl-functionalized product). The *meta* and *para* metallation of toluene was reported after treatment with *n*-butylsodium (4% and 4% ring metallation respectively): Broaddus, C. D. *J. Am. Chem. Soc.* **88** (1966) 4174. Metallation of toluene with ^{n}BuLi·TMEDA gave 3% *ortho* and 9% *meta* functionalization: Broaddus, C. D. *J. Org. Chem.* **35** (1970) 10. Reaction of toluene with ^{n}BuLi·KO^{t}Bu in THF gave *ca.* 2% *ortho*-functionalized product: Guggisberg, Y.; Faigl, F.; Schlosser, M. *J. Organomet. Chem.* **415** (1991) 1. When applying prolonged reaction times and excess (300 mol%) toluene no ring metallated product is found (see also ref [20]). The ring metallated species then isomerize to the benzyl metallated species.

8 Lochmann, L.; Pospísil, J.; Vodnansky, J.; Trekoval, J.; Lím, D. *Coll. Czech. Chem. Commun.* **30** (1965) 2187.

9 Gilman, H. *Org. React.* **6** (1951) 339.

10 Lochmann, L.; Lím, D. *J. Organomet. Chem.* **28** (1971) 153; Boche, G.; Etzrodt, H. *Tetrahedron Lett.* **24** (1983) 5477; Pi, R.; Bauer, W.; von Ragué Schleyer, P. *J. Organomet. Chem.* **306** (1986) C1; Lochmann, L. *Coll. Czech. Chem. Commun.* **52** (1987) 2710; Lochmann, L.; Trekoval, J. *J. Organomet. Chem.* **326** (1987) 1.

11 Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **114** (1992) 7482 (contains a discussion on the topic of the structure of the superbases).

[12] Williard, P. G.; MacEwen, G. J. *J. Am. Chem. Soc.* **111** (1989) 7671; Marsch, M.; Harms, K.; Lochmann, L.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **29** (1990) 308.

[13] Harder, S.; Streitwieser, A. *Angew. Chem., Int. Ed. Engl.* **32** (1993) 1066.

[14] The ΔG for the exchange reactions between ^{n}BuLi and MO^{t}Bu are calculated to be -8.4 kcal/mol (M=Na), -14.2 kcal/mol (M=K), -15.8 kcal/mol (M=Rb) and -17.8 kcal/mol (M=Cs). Grovenstein jr., E. *Recent Advances in Anionic Polymerization*, Eds. Hogen-Esch, T. E.; Smid, J. Elsevier Science Publishing Co. (1987).

[15] Reverse addition gave the same results. Upon addition of ^{n}BuLi to a solution of KO^{t}Am in hexane at 10°C the solution remained clear until the ratio KO^{t}Am: ^{n}BuLi had become 5: 1. When the amount of ^{n}BuLi was further increased a precipitate, probably ^{n}BuK, was formed.

[16] Screttas, C. G.; Micha-Screttas, M. *J. Organomet. Chem.* **316** (1986) 1.

[17] Marsch, M.; Harms, K.; Lochmann, L.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **29** (1990) 308.

[18] Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **113** (1991) 7068.

[19] The metallation of benzotrifluoride does not proceed completely regioselective. The product contained *ca.* 10% *meta*-methylthio-benzotrifluoride. Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **68** (1946) 1658; Shirley, D. A.; Johnson Jr, J. R.; Hendrix, J. P. *J. Organomet. Chem.* **11** (1968) 209.

[20] For example, after treatment of *tert*-butylbenzene with ^{n}BuLi·KO^{t}Bu·TMEDA in hexane at -20°C and subsequent quenching with trimethylchlorosilane silylated product was obtained in 50% yield in a *meta/para* ratio of 2:1. Klusener, P. A. A.; Hanekamp, J. C.; Brandsma, L. *J. Org. Chem.* **55** (1990) 1311; Thesis P. A. A. Klusener; Department of Preparative Organic Chemistry, University of Utrecht (1989). For the reaction with some other bases see: Bryce-Smith, D. *J. Chem. Soc.* (1954) 1079; Morton, A. A.; Claff Jr., C. E.; Collins, F. W. *J. Org. Chem.* **20** (1955) 428; Benseker, R. A.; Foster. D. J.; Sauve, D. M.; Nobis, J. F. *Chem. Rev.* **57** (1957) 867.

[21] Lochmann, L. Trekoval, J. *J. Organomet. Chem.* **179** (1979) 123.

[22] When the metallation mixture was quenched with pivaldehyde, the amount of product obtained after work-up increased from 39% (^{n}BuLi·KO^{t}Bu) to 62% (^{n}BuLi·3KO^{t}Bu).

[23] All products obtained after metallation of toluene contained *ca.* 5% of ring-functionalized product, as the result of ring metallation and subsequent functionalization. We were unable to establish whether the *o*, *m* or *p* isomer was formed. See ref[7] and text.

Summary

The high reactivity of organoalkali compounds with regard to a variety of electrophiles was recognized already long ago and many organic chemists use this property for the synthesis of compounds. Most important starting materials for the preparation of these compounds are the very strong bases *n*-butyllithuim, -sodium, -potassium and, to a lesser extent, -cesium. In the past the preparation of organoalkali compounds, and especially the more reactive heavier alkali metal compounds, gave a lot of practical problems. A number of developments around 1960 increased the accessibility of these compounds. *n*-Butyllithium became commercially available, and it was found that the solubilities of organoalkali compounds in THF was better than in the so far used diethyl ether and alkanes. Finally, Lochmann and Schlosser found, independently from each other, that n-butylpotassium in hexane was easily formed by mixing *n*-butyllithium and potassium *tert*-butoxide. Since then organoalkali compounds are reagents that are relatively easily available. New applications and properties of this class of reactive compounds are still found. In this thesis some of these new developments are described.

In chapter 1 the dimetallation of conjugated enynes $HC^4{\equiv}C^3\text{-}C^2H{=}C^1H\text{-}R$ (in which R is a variety of groups) with mixtures of super bases, consisting of *n*-butyllithium and potassium *tert*-butoxide, are described. The regioselectivity of the metallation at the vinylic system is determined by the combination of the (de-)activating properties of the groups $\text{-}C{\equiv}CK$ (activates the proton at C^2) and R. It is shown that the activating properties of the acetylide group $\text{-}C{\equiv}CK$ is comparable in strength to those of known α-activators OCH_3, SCH_3, $N(CH_3)_2$.

Chapter 2 describes new synthetic routes for functionalized conjugated enynes and diynes. Starting material is the easily accessible $HC{\equiv}C\text{-}CH{=}CH\text{-}SCH_2CH_3$. Functionalization of the acetylenic group can be performed either by successive metallation and addition of an electrophile (introduction of a sp^3-functionality) or by a palladium catalyzed reaction (introduction of a sp^2-functionality). A diyne can now be obtained in one step from the functionalized enyne sulfide $RC{\equiv}C\text{-}CH{=}CH\text{-}SCH_2CH_3$ by treatment with the strong base sodium amide in liquid ammonia. Elimination of ethane thiolate affords the diyne $RC{\equiv}C\text{-}C{\equiv}CH$. Enynes can be prepared in two steps. First the acetylenic group of the functionalized enyne sulfide is selectively reduced with activated zinc or the couple zinc/copper(I) bromide in refluxing ethanol to afford a diene $RCH{=}CH\text{-}CH{=}CH\text{-}SCH_2CH_3$ (new double bond *cis*/*trans*= 100/0). Subsequent treatment of this diene with sodium amide in liquid ammonia gives elimination of ethane thiolate with formation of the enyne $RCH{=}CH\text{-}C{\equiv}CH$. All enynes and diynes are obtained in reasonable to good yields.

Fluorobenzene can be effectively metallated at the *ortho* position with a mixture consisting of *n*-butyllithium and potassium *tert*-butoxide in THF at -100°C. After addition of an electrophile and work-up the *ortho*-functionalized fluorobenzene can be obtained in high yield, as is shown in chapter 3.

In chapter 4 the stability of *ortho*-metallated fluorobenzene is investigated. Decomposition and synthetic experiments led to a stability order of: Na < K ~ Li < Cs. These results can be explained by assuming that electrostatic interactions in the *ortho*-metallated fluorobenzene lead to elimination of metal halogenide. The strength of this electrostatic interaction determines the stability. The crystal structure of [3-bromo-2-lithio-thiophene·TMEDA]$_2$ shows that in this model compound no halogen-metal interactions are present.

During the metallation and decomposition experiments with fluorobenzene it was discovered that in the decomposition of *o*-sodiumfluorobenzene appreciable amounts of the polycyclic compound triphenylene are formed, whereas in the case of the other alkali metal derivatives only traces of this compound are formed. Chapter 5 describes how triphenylene can thus be obtained in a yield as high as 66%.

Chapter 6 describes the preliminary results of investigations on the stability of carbenoïds RR'CXM, in which X= halogen and M= alkali metal. The investigated carbenoïds $MCHCl_2$, $MCCl_3$, $MCBr_3$ and $MCBr_2Ph$ show a stability order of Cs < K < Na < Li. This can be explained by assuming that the carbenoïds transform into a structure $[RR'CM]^+ X^-$ before decomposition, the stability is then determined by the strength of the C-M bond.

In chapter 7 it is shown that the reaction between dibromothiophenes and *n*-butyllithium in diethyl ether at -55°C leads to dimetallation only in the case of 2,5-dibromothiophene, which is proven by quench experiments with dimethyl disulfide. In the other cases only monoanions are formed. Diiodothiophenes are completely dimetallated under the same conditions. The dimetallation of all dibromothiophenes under similar conditions is described in the literature, but the authors of these publications were misled by the results of quench experiments. The presence of QUADAC's (quasi dianion complexes), complexes of monometallated thiophene and excess base, in solution can explain the results.

The dimetallation of benzene is the subject of chapter 8. Treatment of benzene with a mixture of *n*-butyllithium and potassium *tert*-alkoxide in hexane at room temperature gives a *ca.* 1:1 mixture of *meta*- and *para*-dipotassiumbenzene. After treatment of benzene with 8 equivalents of the mixture of *n*-butyllithium and potassium *tert*-amylate, followed by quenching with dimethyl disulfide, difunctionalized benzene can be isolated in 81% yield.

Although super bases consisting of mixtures of *n*-butyllithium and potassium *tert*-butoxide have proven their usefulness in many deprotonation reactions, there is a number of substrates with which the reaction proceeds less satisfactorily. In chapter 9 the attempts to increase the strength of these base mixtures by addition of an excess of alkoxide are described. Model reactions of various base mixtures with the substrates benzene and toluene in THF, diethyl ether and hexane show that an excess of alkoxide gives better results. The applicability is tested on some other substrates. Furthermore it is shown that also the reactivity of of the base mixture consisting of lithium di-*iso*-propylamide and potassium *tert*-butoxide is increased by addition of an excess of alkoxide.

Samenvatting

De hoge reactivteit van organoalkalimetaalverbindingen ten aanzien van diverse electrofielen werd reeds lange tijd geleden ontdekt en vele organisch chemici maken gebruik van deze eigenschap bij de synthese van verbindingen. Belangrijkste uitgangsstoffen voor de bereiding van deze verbindingen zijn de zeer sterke basen *n*-butyllithium, -natrium, -kalium en in mindere mate -cesium. De bereiding van organoalkaliverbindingen, en in het bijzonder de zwaardere alkalimetaalverbindingen, leverde vroeger echter grote praktische problemen op. Een aantal ontwikkelingen rond 1960 zorgden voor een grotere toegankelijkheid van deze verbindingen. *n*-Butyllithium werd commercieel verkrijgbaar, en gevonden werd dat de oplosbaarheid van organoalkaliverbindingen in THF beter is dan in de tot dusver gebruikte oplosmiddelen diethylether en alkanen. Tenslotte vonden Lochmann en Schlosser onafhankelijk van elkaar dat *n*-butylkalium in hexaan eenvoudig kan worden bereid door mengen van *n*-butyllithium en kalium *tert*-butoxide. Sindsdien zijn organoalkaliverbindingen reagentia die voor iedere organisch chemicus relatief eenvoudig beschikbaar zijn. Nog steeds echter worden nieuwe toepassingen en eigenschappen van deze reactieve verbindingen ontdekt. In dit proefschrift worden enige van deze nieuwe ontwikkelingen beschreven.

In hoofdstuk 1 wordt de dimetallering van geconjugeerde enynen $HC^4{\equiv}C^3\text{-}C^2H{=}C^1H\text{-}R$ (waarin R een variëteit aan groepen is) met mengsels van superbasen, bestaande uit *n*-butyllithium en kalium *tert*-alkoxide beschreven. De regioselectivteit van de metallering van het vinylisch systeem wordt bepaald door de combinatie van (de-)activerende effecten van groepen $\text{-}C{\equiv}CK$ (activeert het proton op C^2) en R. Aangetoond wordt dat de activerende eigenschappen van de acetylide groep $\text{-}C{\equiv}CK$ vergelijkbaar zijn met die van bekende α-activatoren OCH_3, SCH_3 en $N(CH_3)_2$.

Hoofdstuk 2 beschrijft nieuwe syntheseroutes voor gefunctionaliseerde geconjugeerde enynen en diynen. Uitgangsstof is het eenvoudig te bereiden $HC{\equiv}C\text{-}CH{=}CH\text{-}SCH_2CH_3$. Functionalisering van de acetyleengroep kan plaatsvinden door metallering en daarop volgend additie van een electrofiel (invoering sp^3-functionaliteit) of door een palladium-gekatalyseerde reactie (invoering sp^2-functionaliteit). Uit het zo gevormde $RC{\equiv}C\text{-}CH{=}CH\text{-}SCH_2CH_3$ kan in één stap een diyn verkregen worden: behandeling van het enyn met de sterke base natriumamide in vloeibare ammoniak geeft eliminatie van natriumethaanthiolaat onder vorming van een diyn $R\text{-}C{\equiv}C\text{-}C{\equiv}CH$. Enynen kunnen in 2 stappen bereid worden. Eerst wordt de acetyleengroep van het gefunctionalisserde enynsulfide selectief gereduceerd met geactiveerde zink of het koppel zink/koper(I)bromide in refluxende ethanol tot $R\text{-}CH{=}CH\text{-}CH{=}CH\text{-}SCH_2CH_3$ (nieuwe dubbele binding: *cis*/*trans* = 100/0). Behandeling van dit dieen met natriumamide in vloeibare ammoniak geeft eliminatie van natriumethaanthiolaat onder vorming van enyn $R\text{-}CH{=}CH\text{-}C{\equiv}CH$. Alle enynen en diynen worden in redelijke tot goede opbrengst verkregen.

Fluorbenzeen kan zeer effectief op de *ortho*-plaats gemetalleerd worden met een mengsel van ^{n}BuLi en KO^{t}Bu in THF bij -100°C. Na toevoeging van een electrofiel en opwerken kan *ortho*-gefunctionaliseerd fluorbenzeen in hoge opbrengst verkregen worden, zoals aangetoond wordt in hoofdstuk 3.

In hoofdstuk 4 wordt ingegaan op de stabiliteit van *ortho*-gemetalleerd fluorbenzeen. Ontledings- en syntheseexperimenten geven een stabiliteitsvolgorde van: Na < K ~Li < Cs. Deze resultaten kunnen verklaard worden door aan te nemen dat electrostatische interacties in het *ortho*-gemetalleerde fluorbenzeen leiden tot eliminatie van metaalhalogenide. De sterkte van deze electrostatische interactie bepaalt de stabiliteit. De kristalstructuur van [3-bromo-2-lithio-thiopheen·TMEDA]$_2$ toont aan dat in deze modelverbinding geen halogeen-metaal interacties aanwezig zijn.

Gedurende de metallerings en stabiliteitsexperimenten met fluorbenzeen werd ontdekt dat tijdens de ontleding van *o*-natriumfluorbenzeen aanzienlijke hoeveelheden van de polycyclische verbinding triphenyleen gevormd worden. Bij de ontleding van de andere alkalimetaalderivaten worden slechts sporen van deze verbinding gevormd. In hoofdstuk 5 wordt beschreven hoe op efficiënte wijze triphenyleen in 66% opbrengst kan worden verkregen.

Hoofdstuk 6 beschrijft de eerste resultaten van onderzoek naar de stabiliteit van carbenoïden RR'XCM, waarbij X= halogeen en M= alkalimetaal. Voor de onderzochte carbenoïden $MCHCl_2$, $MCCl_3$, $MCBr_3$ en $MCBr_2Ph$ geldt dat de stabiliteit toeneemt in de volgorde Cs < K < Na < Li. Dit kan verklaard worden door aan te nemen dat de carbenoïden voor ontleding een structuur $[RR'CM]^+ X^-$ aannemen, de stabiliteit wordt dan bepaald door de sterkte van de binding C-M.

In hoofdstuk 7 wordt beschreven dat de reactie van dibroomthiofenen met een overmaat *n*-butyllithium in diethylether op -55°C alleen in het geval van 2,5-dibroomthiofeen leidt tot dimetallering, hetgeen aangetoond is door quenchexperimenten met dimethyldisulfide. In de overige gevallen worden alleen monoanionen gevormd. Dijoodthiofenen worden wel volledig digemetalleerd onder soortgelijke reactiecondities. In de literatuur wordt onder dezelfde reactie-omstandigheden dimetallering van alle dibroomthiofenen beschreven maar de auteurs van deze experimenten hebben zich laten misleiden door de uitkomst van resultaten van quenchexperimenten. De aanwezigheid van QUADAC's (quasi-dianioncomlexen), complexen van monogemetalleerd thiofeen en overmaat base, in oplossing vormt een verklaring voor de resultaten.

De dimetallering van benzeen wordt beschreven in hoofdstuk 8. Behandeling van benzeen met een mengsel van *n*-butyllithium en een kalium *tert*-alkoxide in hexaan op kamertemperatuur geeft een *ca.* 1:1 mengsel van *meta*- en *para*-dikaliumbenzeen. Na behandeling van benzeen met 8 equivalenten van het superbase mengsel van *n*-butyllithium en kalium *tert*-amylaat, gevolgd door quenchen met dimethyldisulfide, kon digefunctionaliseerd benzeen in 81% opbrengst geïsoleerd worden.

Hoewel de superbasen bestaande uit mengsels van *n*-butyllithium en kalium *tert*-butoxide hun nut hebben bewezen in vele deprotoneringsreacties, is er een aantal substraten waarbij de reactie minder bevredigend verloopt. In hoofdstuk 9 worden pogingen beschreven de sterkte van deze basemengsels te vergroten door een overmaat van het alkoxide te gebruiken. Modelreacties van verschillende basemengsels met de substraten benzeen en tolueen in THF, diethylether en hexaan tonen aan dat een overmaat alkoxide tot betere resultaten leidt. De toepasbaarheid wordt getoetst aan een aantal andere substraten. Bovendien wordt aangetoond dat ook de reactiviteit van het basemengsel bestaande uit lithium di-*iso*-propylamide en kalium *tert*-butoxide vergroot wordt door toevoeging van een overmaat alkoxide.

Dankwoord.

Mijn eerste kennismaking met de vakgroep organische synthese was nogal drastisch. Ik kwam, als vierdejaars student, even informeren naar de mogelijkheid er een hoofd- of keuzevak te doen. Na enige tijd raakte ik in gesprek met de 'baas', prof. dr. L. Brandsma. Op een gegeven moment vroeg hij mij de reactie tussen aniline en broom op te schrijven, wat mij (met enige moeite, moet ik toegeven) lukte. Toen werd ik meegetorst naar een zuurkast en waarna een reageerbuis gevuld met aniline en een literfles broom in mijn handen geduwd werden onder de woorden "ga je gang". Later zou blijken dat deze aanpak heel typerend was, en ik ben juist daarom blij dat ik in dit laboratorium zowel mijn hoofdvak als promotieonderzoek heb kunnen doen. Nergens anders had ik op zo'n mooie manier de organische synthese kunnen leren.

Tijdens mijn eerste jaren ben ik opgeleid door twee oudgedienden: Peter A. A. Kluus Klusener, leermeester in synthese en grootmeester in hamsteren; en goeroe Sjoerd Harder, die mij de meer fijne kneepjes leerde en aantoonde dat zelfs basilicumbier lekker kan zijn. Onmisbaar was verder Hermann Verkruijsse, je was er altijd als ik weer eens iets nodig had, varierend van chemicaliën tot kleine medische ingrepen. De jaren op Trans 3 zijn er geweest van werk, maar ook veel lol en slappe humor. Collega's en studenten wil ik hiervoor bedanken, vooral ·–· · –– –·–· ––– ·–·–·– –·· · ·–– ·–·–·– –··· · ··· – · –· , qui radio Fossatelli alla frequenzione di 102 MHz, Onkel Theo Peters, Jaap van Soolingen (alias de fosfineman) en Robbert-Jan de Lang. De twee studenten die ik heb begeleid bij hun hoofd- respectievelijk keuzevak, Willem "Carbenoïd" Nissink (zie hoofdstuk 6) en Michiel "Ik heb een idee !!!" Hacking, wil ik bedanken voor hun inzet en enthousiasme.

Buiten de eigen groep zijn er natuurlijk nog vele mensen aan wie ik mijn plezierige verblijf op Trans 3 te danken heb. Alle collega's achter de diverse zuurkasten waren belangrijk als bron van kennis of om loze kwartiertjes te vullen. Han Haverkate, glasblazer, je was altijd bereid een snelle reparatie uit te voeren als ik mijn favoriete glaswerk weer eens gebroken had. Jan den Boesterd en medewerkers, omdat ik niet alleen met mijn werk goede sier maakte op congressen maar ook omdat mijn posters en dia's er altijd op en top uit zagen. Tost, zonder de vele kilo's chemicaliën die je voor me besteld hebt was dit boekje een stuk dunner geweest. Van de afdeling massaspectroscopie wil ik Anca van der Kerk bedanken. Hoewel je in mijn boekje weinig GC-MS gegevens terug zult vinden ben je onmisbaar geweest bij het oplossen van de puzzels die mijn producten soms waren. Ton Spek bedank ik voor het oplossen van mijn enige kristalstructuur.

I am indebted to Dr. W. Weis (Chemetall GmbH, Frankfurt am Main) for generous gifts of heavier alkali metal alkoxides.

Ook, of misschien wel vooral, buiten de Uithof zijn er mensen die een woord van dank verdienen. Zij zijn het die het leven buiten de chemie leuk maakten, en zij waren het die de stank moesten doorstaan die ik vaak met mij meetorste (veroorzaakt door alle S'sen die in dit boekje staan).

Pa, ma en Paola, jullie zijn meer dan familie, jullie zijn vrienden.

Anouk, ik kan je voor veel dingen bedanken maar de vlieglessen zijn van alles misschien wel het mooist.

Samen met Mark Swevels, Rudolph Valentino Overbeek, Frank de Bruijn en Ludo Boot heb ik sinds ik nog een broekie was heel wat meegemaakt, en zolang er voetbalwedstrijden zijn zullen we elkaar wel blijven zien denk ik.

Zonder al mijn overige vrienden (voor wie hier helaas geen plek genoeg is om ze allemaal met naam en toenaam te noemen), de vele bewoners van 21-1 die ik heb zien komen en gaan en de bezoekers van de Woo waar ik zovele (misschien wel té vele) nachtelijke uren heb doorgebracht zou het leven stukken saaier zijn geweest.

Dalla parte precedente probabilmente non capite niente, ma questa e un ringraziamento per tutte le persone che, in qualche modo, hanno significato qualcosa per me durante gli anni passati.

Nonno e nonna, grazie a voi Terni è per me come una seconda casa. Mancano parole per ringraziare la famiglia Goracci, sopratutto Silvano, Clara, Andrea e Simone, per tutto quello che avete fatto per me. Sono diventato un vero Ternano seguendo le vostre lezioni.

Le mie ferie in Italia sono sempre state mega-rilassanti (pieno di sole, vino e amici), e tante volte avevo veramente bisogno di scappare un momento dalla chimica. Mi sembra che ho sempre trovato i più bei posti: Ai ragazzi di Russi, Andrea e Claudio, vorrei dire soltanto una cosa: Forza Ternana! Il tempo che ho passato insieme con 'le tre ragazze dal Wilhelminapark coi zaini Invicta' e stato molto bello, sia qui in Olanda, sia giù in Sardegna. Finalmente vorrei ringraziare la famiglia Garolini per la loro ospitalita, c'era sempre posto per me nonostante il fatto che voi dovevate lavorare.

Curriculum Vitae

De schrijver van dit proefschrift werd 23 september 1966 geboren te Zeist. Na het behalen van zijn VWO diploma aan de Scholengemeenschap Schoonoord te Zeist (1978-1984) begon hij in augustus 1984 de studie Scheikunde aan de Rijks Universiteit Utrecht. De eerste fase van deze studie eindigde hij met keuzevakken biochemie en farmacologie en een hoofdvak organische synthese bij de groep van professor dr. L. Brandsma. Het doctoraal diploma werd behaald in augustus 1989. Aan de vakgroep organische synthese begon hij in datzelfde jaar onder begeleiding van prof. dr. L. Brandsma de tweede fase van zijn opleiding, het in dit proefschrift beschreven promotieonderzoek, in dienst van de Stichting Scheikundig Onderzoek Nederland (S.O.N./N.W.O.). Hij nam eind 1993 afscheid van de vakgroep synthese.

New Applications of Super Bases in Organic Synthesis - Marco Fossatelli

New Applications of Super Bases in Organic Synthesis

Marco Fossatelli