Description

Method for the synthesis of organo element compounds

The present invention refers to the preparation of organo element compounds starting from organo halogen compounds, to the organo element compounds themselves as well as to the use of these organo element compounds.

Hereinafter, the basic principle of the invention shall be explained by use of organo zinc compounds. However, the invention shall not be limited to organo zinc compounds but can be carried out with a lot of other metals or semimetals (metalloids).

Due to their specific reactivity and tolerance for many functional groups, organo zinc compounds are important starting or intermediate products in organic chemistry. The direct preparation of, for example, organo zinc bromides directly from aryl and alkyl bromides has, however, been largely limited by the use of the comparatively expensive and less stable Rieke zinc or by a reaction procedure in pure dimethylacetamide (DMAC) as solvent hitherto.

For preparing Rieke zinc, zinc chloride is reduced with lithium naphthaline to a fine dispersed zinc powder. Due to its large surface, this zinc powder is highly reactive. It can be inserted in a carbon-halogen bond. Due to its high reactivity, it can, however, also react with other functional groups that are present in a molecule and can thus cause undesired side reactions and by-products. Hitherto, an isolation of the organo zinc compounds has not been possible.

The insertion of magnesium in carbon-halogen bonds is known as the Grignard reaction. The solubility of Grignard compounds can be enhanced by adding lithium ions, as it is, for example, disclosed in EP 1 582 524. In EP 1 582 524, there is disclosed a method for replacing an organic moiety at a magnesium ion. Similar methods for the preparation of organo element compounds do not exist for other metals or metalloids.

It is therefore an object of the present invention to provide a simplified method for the synthesis of organo element compounds starting from organo halogen compounds. Furthermore, it is an object of the present invention to provide novel organo element compounds as pure chemical substances or in solution, respectively. Another object of the

present invention is to provide methods for reacting the novel organo element compounds as well as the reaction products themselves.

According to the invention, these objects are solved by the features of the independent claims.

As the inventors of the present invention recently found out, a reaction between a metallic element and organo halogen compounds can efficiently be carried out in a solution containing lithium ions. Functional groups as, for example, esters or nitriles, are tolerated in this method. The method is thus applicable to a number of organic compounds which are also able to carry different functional groups.

The present invention discloses a method for preparing a compound having the general formula

$$R^1\text{-}M^1\text{-}A_d \quad zLiX \qquad \textbf{(I)}$$

by reacting a compound R^1-A (**III**) with an element M^1 in presence of LiX,
wherein

R^1 is a substituted or un-substituted C_3-C_{24} aryl or C_3-C_{24} heteroaryl containing one or more heteroatoms like B, O, N,S, Se, P or Si, a linear or branched, substituted or un-substituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl or C_2-C_{20} alkynyl or a substituted or un-substituted C_3-C_{20} cycloalkyl or a derivative thereof;

M^1 is an element selected from Mn, Cu, Zn, Sn, In, La, Ce, Nd, Y, Li, Sm, Na, K and Bi;

A is a halogen selected from F, Cl, Br, I; a sulphonate (RSO_3-) or a phosphonate (-$OP(O)(OR)_2$) wherein R is defined like R^1;

d is 0 or 1;

z is > 0; and

X is selected from the group consisting of F; Cl; Br; CN; SCN; NCO; Hal^1O_k, wherein k=3 or 4 and Hal^1 is selected from Cl, Br and I; NO_3; BF_4; PF_6; H; a carboxylate having the general formula R^xCO_2; a disilazide having the general formula $(R^x{}_3Si)_2N$; a thiolate having the general formula SR^x; an alcoholate having the general formula OR^x; $R^xP(O)O_2$; or $SCOR^x$; an amine having the general formula R^xNH; a dialkyl- or diaryl amine having the general formula $R^x{}_2N$, wherein R^x is defined as below or $R^x{}_2N$ represents a cyclic alkylamine; a phosphine having the general formula $PR^x{}_2$, wherein R^x is defined as below or $PR^x{}_2$

represents a cyclic phosphine; O_jSR^x, wherein j = 2 or 3; or NO_r, wherein r = 2 or 3; and derivatives thereof; wherein R^x is a substituted or un-substituted C_4-C_{24} aryl or a C_3-C_{24} heteroaryl containing one or more heteroatoms like B, O, N, S, Se, P or Si; a linear or branched, substituted or un-substituted C_1-C_{20} alkyl; C_2-C_{20} alkenyl or C_2-C_{20} alkynyl; or a substituted or un-substituted C_3-C_{20} cycloalkyl; or derivatives thereof; or H. Tosylate (p-toluene sulphonate) or mesylate (methane sulphonate) are preferably used as sulphonates.

The present method thereby has the advantage that an element, especially an elementary metal, can be used in any form. The element or metal can, for example, be used in form of granules, swarf, bars, sheets or as a powder. By the addition of a lithium salt, a reaction is facilitated or enabled. A highly fine dispersion as it is, for example the case for Rieke zinc, is not necessary. Any compound having a carbon-halogen bond can be used as the organic starting compound R^1-A (**III**). The metal is inserted in this carbon-halogen bond according to the method of the present invention. Other functional groups that are present in the molecule are not altered in the method and do not interfere with the reaction according to the invention. Thereby, multiply functionalised molecules can be used in the reaction according to the invention. This grants access to a plurality of differently functionalised molecules having a carbon element halogen group.

According to this aspect of the present invention, the number d is 0 or 1. The value of n thereby conforms to the valence of the element M^1. The valence of the element M^1 thereby corresponds to the valency or the oxidation number. If this valence is set to v, so d = v - 1. Hence, for example, the value of d = 0, for a monovalent metal M^1 like Li. For a bivalent metal such as Zn, the value of d = 1.

According to a second aspect of the invention, a compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad z\text{LiX} \qquad \textbf{(II)}$$

can be obtained by reacting a compound R^1-A (**III**) with a M^3-containing compound in the presence of LiX and in the presence of an elementary metal M^2. M^2 is thereby selected from Li, Na, K, Cs, Mg, Ca, Mn and Zn. R^1, z, A and X are as defined above and M^3 is defined as M^1 above, wherein M^3 can additionally be Al, Ti, Mg, B, Si and S. M^3 is also selected from

the group consisting of Al, Mn, Cu, Zn, Sn, Ti, In, La, Ce, Nd, Y, Li, Sm, Bi, Mg, B, Si and S. T is defined as A or X above, i.e. T can be selected from A and/or from X, wherein X and T can be identical or different. n is 0, 1, 2 or 3. m is 1, 2 or 3. If m = 2 or m = 3, there are several moieties R^1 bonded with a single element M^3. With respect to the definition of R^1 above, these moieties R^1 can be identical or different moieties.

According to this aspect of the present invention, an insertion and transmetalation reaction is performed in one single step. Thereby, the element M^3 of the M^3-containing compound is less reactive than the metal M^2. Thus, the M^3 elements which are otherwise not accessible for a direct reaction, can be inserted in the compound (**III**) under mild conditions. The insertion reaction can be carried out by using a reactive metal M^2 which can be easily activated. Subsequently, the element M^3 in form of a M^3-containing compound is inserted into the organic compound by a transmetalation reaction under mild conditions. It is therefore important that the element M^3 is less reactive than the element M^2.

The M^3-containing compound can be a salt, specifically a metal salt, an organo element compound, specifically an organo metal compound, or also an organo element salt compound, preferably an organo metal salt compound. As already noted above for M^1 and d, both n and m depend from the valency of the element M^3. In this context, the terms valency, valence and oxidation number are equivalently used. For the valence v of M^3 with the numbers n and m, the relation v = m+n applies.

According to another aspect of the present invention, there is provided a compound having the general formula R^1_m-M^3-T_n zLiX (**II**) wherein R^1, M^3, m, n, z, X and T are defined as above, wherein M^3 does not comprise Mg.

According to still a further aspect of the present invention, there is provided a solution of a compound having the general formula R^1_m-M^3-T_n zLiX (**II**) in a solvent, wherein R^1, M^3, m, n, z, X and T are defined as above and wherein M^3 does not comprise Mg. Or, in other words, the present invention relates to a composition in form of a solution containing a compound having the formula (**II**) in a solvent.

According to a further aspect of the present invention, there is provided a reaction of a compound having the general formula $R^1{}_m$-M^3-T_n zLiX (**II**) with an electrophile, wherein R^1, M^3, m, n, z, X and T are defined as above and wherein M^3 does not comprise Mg. In principle, there can be used many different types of electrophiles. For example, electrophiles that are mentioned in the following documents but are not limited thereto can be used:

a) Handbook of Grignard reagents; edited by Gary S. Silverman and Philip E. Rakita (Chemical Industries; v. 64).
b) Grignard reagents New Developments; edited by Herman G. Richey, Jr., **2000**, John Wiley & Sons Ltd.
c) Methoden der Organischen Chemie, Houben-Weyl, vol. XIII/2a, Metallorganische Verbindungen Be, Mg, Ca, Sr, Ba, Zn Cd. **1973**.
d) The chemistry of the metal-carbon bond, vol. 4. edited by Frank R. Hartley. **1987**, John Wiley & Sons.

A final aspect of the present invention relates to a product of a reaction of an electrophile with a compound having the general formula $R^1{}_m$-M^3-T_n zLiX (**II**) wherein R^1, M^3, m, n, z, X and T are defined as above, wherein M^3 does not comprise Mg. The possible electrophiles can again be selected from the documents mentioned under a) to d) but are not limited thereto. The compounds (**II**) thereby react as a nucleophile. They can thus be used in reactions, in which nucleophiles can be used.

The solvent for the methods of the present invention as well as for the solution and the reaction according to the present invention can be selected from the group consisting of cyclic, linear or branched mono- or polyethers, thioethers, amines, phosphines and derivatives thereof that contain one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofurane (THF), 2-methyltetrahydrofurane, dibutylether, diethylether, tert-butylmethylether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropylamine, dimethylsulphide, dibutylsulphide; cyclic and linear amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogen atoms are replaced by halogens, preferably dichloromethane, 1,2-dichloroethane, CCl_4; derivates of

urea, preferably N,N'-dimethylpropylene urea (DMPU), N,N,N'N'-tetramethyl urea; aromatic, heteroaromatic or aliphatic hydrocarbons, preferably, benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphortriamide (HMPA), CS_2; or combinations thereof.

The presence of lithium ions in the solution for preparing the compound having the general formula (**I**) or in the solution itself, enables the reaction or the dissolution of the compound, respectively. Thereby, a lithium salt can be used stoichiometrically in relation to the organo halogen compound (**III**), wherein z = 1. However, it is also possible to only use traces of lithium salt. Then z is > 0. On the other hand, it is also possible to introduce the lithium salt excessively when compared with the organo halogen compound, wherein z is then greater than 1. Within all aspects of the present invention, z is preferably within the range from 0.01 to 5, preferably from 0.5 to 2, more preferably from 0.9 to 1.2, and most preferably about 1.

The M^3-containing compounds being used according to the second aspect of the present invention are compounds which can contain a metal, a metalloid or a non-metal M^3, for example, in a salt, a covalent bond or a complex. Thereby, metal-halogen compounds, metal-alkyl-, metal-aryl-, metal-alkoxy or metal-aryloxy compounds are preferably used. More preferably used compounds that contain M^3 are $MgBr_2$, $MgCl_2$, $B(OMe)_3$, $B(i\text{PrO})_3$, BF_3, Et_2AlCl, $Si(OMe)_4$, $SiCl_4$, $MnCl_2$, $SnCl_2$, $ZnCl_2$, $ZnBr_2$, $TiCl(Oi\text{Pr})_3$, $Ti(Oi\text{Pr})_4$, $InCl_3$, $LaCl_3$, $CeCl_3$, $SmCl_3$ and $NdCl_3$. Thereby, Me represents methyl and *i*Pr *iso*-propyl.

The concentration of lithium chloride in the solution of the present invention is from 0.01 o 5 mol/l, preferably from 0.1 to 4 mol/l. A concentration of from 0.2 to 1.5 mol/l is most preferred. The concentration of the M^3-containing compound is preferably from 1 to 4 mol/l, more preferably 1.2 to 3 mol/l and most preferably about 1.4 mol/l.

The elementary metals being used in this reaction can be activated by known compounds. Thereby, there can be used all compounds known to activate elementary metals for a reaction. The elements M^1 and M^2 can, for example, be activated by compounds selected from the group consisting of copper salts such as, for example, $CuCl_2$, $CuBr_2$ or $CuSO_4$, nickel salts such as, for example, $NiCl_2$ or $NiSO_4$, iron compounds such as, for example, $FeCl_2$ or $FeCl_3$, cobalt compounds such as, for example, $CoCl_2$ or $CoSO_4$, I_2, $C_2H_4Br_2$, $Cl(CH_2)_2Br$, *t*-BuOLi,

BCl_3, BF_3, $LiBH_4$, $LiAlH_4$, $NaAlH_4$, Et_3Al, DIBAL-H (diisobutylaluminum hydride), $Na[H_2Al(OCH_2CH_2OCH_3]$, Me_3SiCl, Et_2Zn, ICl and $SnCl_2$. For example, magnesium swarf can be activated with 2 to 3 mol% Me_3SiCl. The reaction procedure can be carried out at room temperature.

When, in the context of the present invention, a metal is mentioned, those metalloids or non-metals that are accessible for the reaction such as, for example, boron, silicon or sulphur are also encompassed. The metals Zn, Mn, La, Ce, Nd and Sm are preferred for M^1, wherein zinc is specifically preferred. In the selection of M^2, Li, Mg and Na are preferred metals. Zn, B, Si and Sn are preferred elements in the selection of M^3.

The terms alkyl, alkenyl and alkynyl relate to linear, cyclic and branched, substituted and un-substituted C_1 or C_2 to C_{20} compounds, respectively. Preferred ranges for these compounds are C_1 to C_{10}, preferably C_1 to C_5 (lower alkyl), for alkyl or C_2 to C_{10}, preferably C_2 to C_5, for alkenyl or alkynyl, respectively. Linear or branched, substituted or un-substituted C_3 to C_{20} cycloalkanes are understood as cycloalkyl. A preferred range is C_3 to C_{15} and more preferably C_3 to C_8.

With aryl are meant substituted or un-substituted C_3 to C_{24} aryl compounds. Heteroaryls are substituted or un-substituted C_3 to C_{24} heteroaryl compounds containing one or more heteroatoms like B, O, N, S, Se, P or Si. Preferable ranges for both are C_4 to C_{15} or even more preferably C_4 to C_{10}.

Whenever any one of the moieties R, R^x or R^I is substituted with a substituent, the substituent can be selected from any substituent known to a person skilled in the art. A person skilled in the art will select a possible substituent in accordance with his expertise and he will be able to select a substituent that will not interact with other substituents that are present in the molecule and that will not interfere with reactions or interact in these reactions, specifically not in reactions being described in this application. Possible substituents include the following, without being limited thereto:

- halogens, preferably fluorine, chlorine, bromine and iodine;

- aliphatic, alicyclic, aromatic and heteroaromatic hydrocarbons, specifically alkanes, alkenes, alkynes, aryls, arylidenes, heteroaryls and heteroarylidenes;
- carboxylic acids including salts and esters thereof;
- carboxylic acid halides
- aliphatic, alicyclic, aromatic or heteroaromatic carboxylic acid esters;
- aldehydes;
- aliphatic, alicyclic, aromatic or heteroaromatic ketones;
- alcohols and alcoholates including hydroxyl groups;
- phenols and phenolates;
- aliphatic, alicyclic, aromatic or heteroaromatic ethers;
- aliphatic, alicyclic, aromatic or heteroaromatic peroxides;
- hydroxy peroxides;
- aliphatic, alicyclic, aromatic or heteroaromatic amides or amidines;
- nitriles;
- aliphatic, alicyclic, aromatic or heteroaromatic amines;
- aliphatic, alicyclic, aromatic or heteroaromatic imines;
- aliphatic, alicyclic, aromatic or heteroaromatic sulphides, and a thiol group;
- sulfonic acids including salts and esters thereof;
- thiols and thiolates;
- phosphonic acids including salts and esters thereof;
- phosphinic acids including salts and esters thereof;
- phosphorous acids including salts and esters thereof;
- phosphinous acids including salts and esters thereof.

The substitutents can be bonded to the moieties via a carbon atom, an oxygen atom, a nitrogen atom, a sulphur atom or a phosphorus atom. N, O, S and P are preferably used as heteroatoms in e.g. heteroaromates.

The principle underlying all aspects of the present invention is the preparation or use of organo element compounds in the presence of lithium ions. These lithium ions enable or facilitate the reaction of the elementary metals M^1 and M^2. Moreover, due to the presence of lithium salts in the reaction solution or the compound according to formula (**I**), the solubility is enhanced and the further reaction is enabled or facilitated.

The compounds having the general formula (**I**) all share the general formula (**II**). The method for preparing the compounds having the general formula (**II**) shall thereby encompass Mg, B, Si and S for the element M^3, wherein Mg shall be excluded in the selection of the elements for M^3 for the compound according to formula (**II**) or for the solution of the compound according to formula (**II**).

For the preparation of organo element compounds according to the general formula R^1-M^1-A_d zLiX (**I**) according to the invention, an organo compound R^1-A is reacted in a solvent with an element, specifically a metal, in the presence of a lithium salt. Thereby, the metal can be used stoichiometrically in relation to the organo compound or preferably excessively. The reaction can be carried out within a temperature range of from -90°C to 100°C, preferably from 0°C to 80°C and most preferably between 15°C and 60°C. Preferably, a reaction is carried out in an inert gas atmosphere. As the inert gas, for example, nitrogen or Argon can, be used.

In the reaction with elementary metals, the organo element compound according to formula (**I**) or (**II**) can further be reacted with an electrophile *in situ*. However, it is also possible to isolate the organo element compound (**I**) or (**II**) and thus, to separate it from excessive elementary metal. If excessive metal is not separated in advance of a further reaction with an electrophile, the metal could react with another carbon-halogen bond that is present in the organic compound. By using a corresponding processing, it is thus possible to selectively react one carbon-halogen group or several carbon-halogen groups that are present in an organic compound.

In the compounds having the formula (**II**), it is possible that n = 2. If this is the case, T_2 could be a bivalent anion being selected from the group consisting of diamines, dialkoxides or dithiols. Thereby, the diamine can preferably have the general formula R'NH-R-NHR', the dialkoxide can have the general formula HO-R-OH and the dithiol can have the general formula HS-R-SH, wherein R' and R are independently selected from the same group as R^x, wherein R is a bivalent moiety. The limitation for R shall be applied insofar as that no chemically nonsensical compounds will result. Accordingly, the moiety referred to as an alkyl moiety in the selection of R^x is an alkanediyl in the selection of R, the alkenyl is an alkenediyl and the alkynyl is an alkynediyl. A preferred diamine is $CH_3NHCH_2CH_2NHCH_3$ and

preferred dialkoxides are the dialkoxides of the dioles $HOCH_2CH_2OH$, binole and 1,2-diaminocyclohexane.

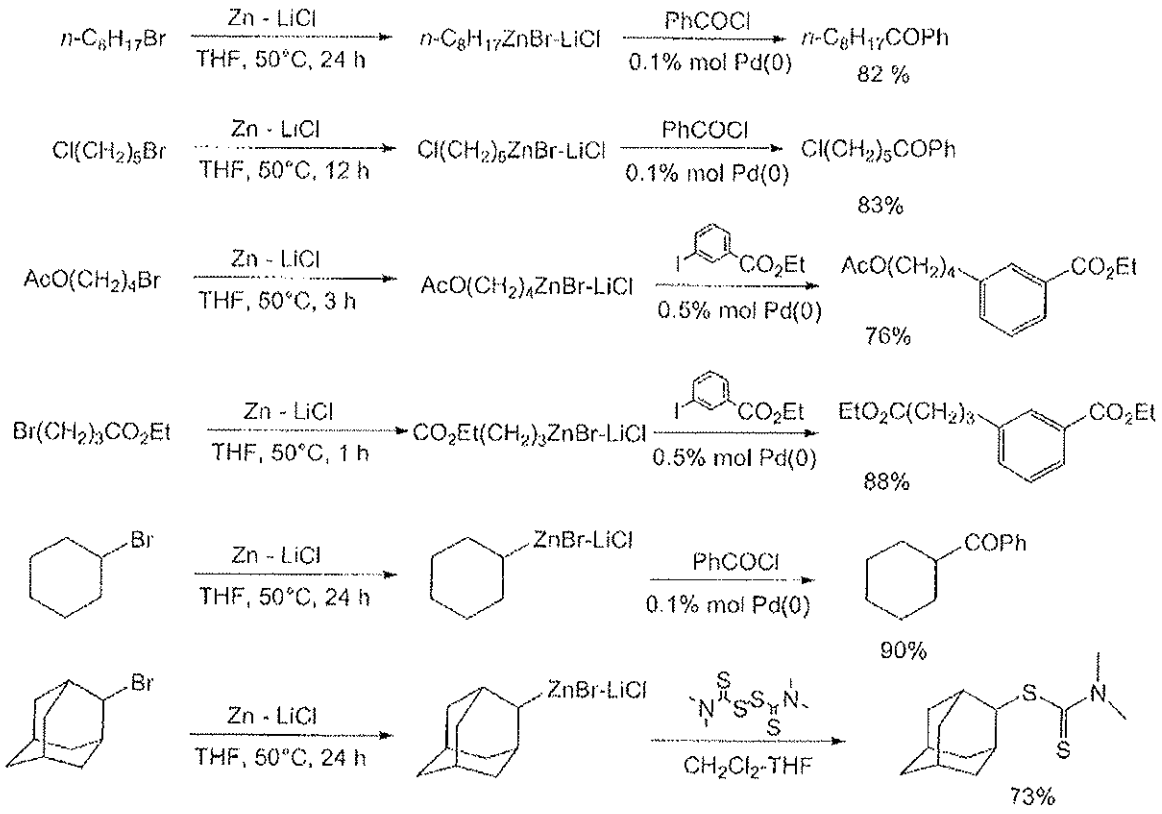
If there are several anions T present in the compound (**II**), these can be both identical or different. For example, one anion can be derived from the use of a compound (**III**) and another anion can be derived from the M^3-containing compound. Thus, the anions T can be independently selected from each other.

The reaction of organo halogen compounds with a metal M^2 in the presence of a lithium salt and a M^3-containing compound *in situ* enables an easy access to compounds (**II**) with metals M^3 that are otherwise only preparable under harder conditions. Thus, an easy access to compounds (**II**) is enabled which are otherwise only available under more difficult conditions.

With the methods of the present invention, accesses to organo element compounds (**II**) are provided which have previously not been accessible.

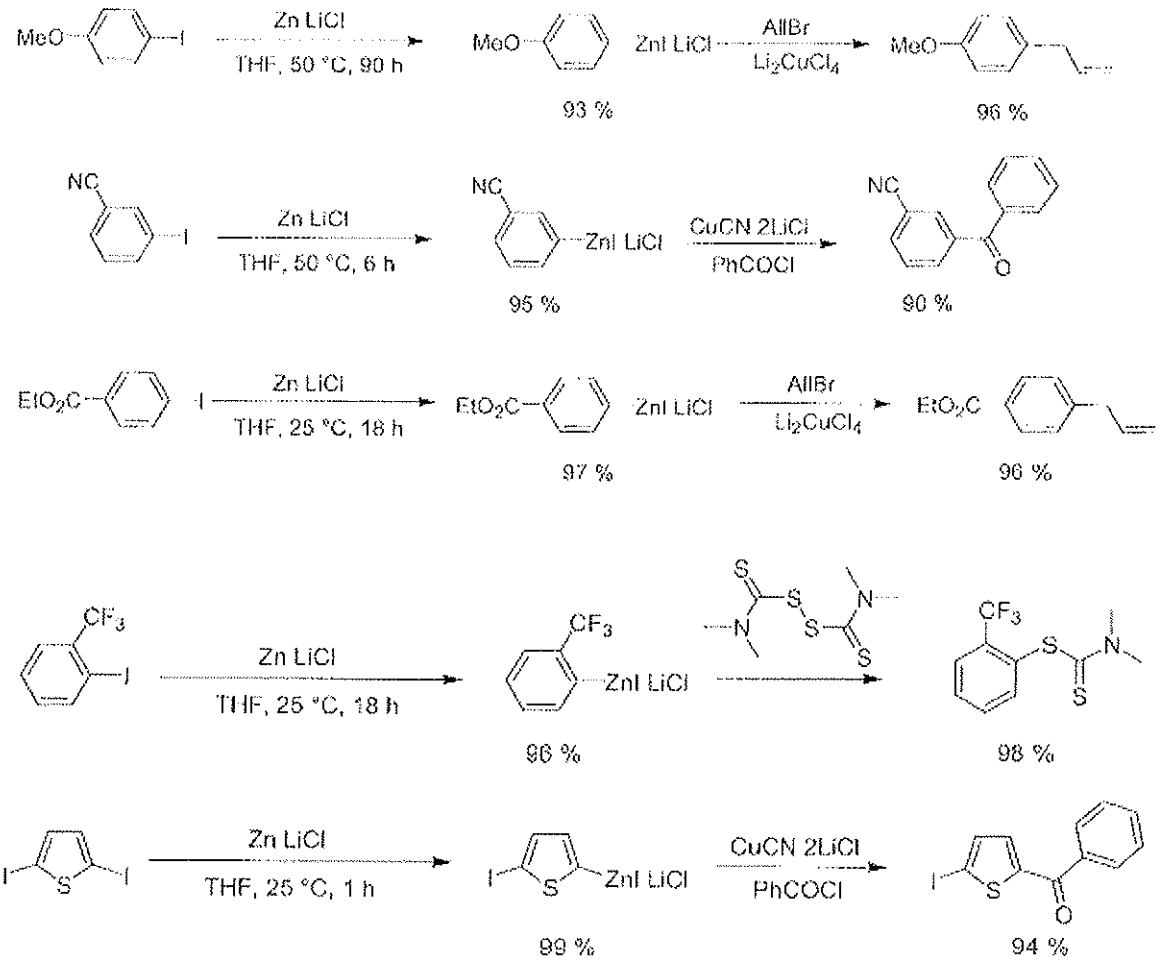
In the following, the reaction of the invention shall be illustrated by use of general examples, however, without being limited to these examples.

It is, for example, possible, to react metallic zinc with alkyl bromides in THF in the presence of LiCl at 50°C to the corresponding alkyl zinc bromides with a high yield. A general work instruction includes heating an alkyl bromide in a 0.7 M (saturated at room temperature) solution of lithium chloride in THF with three equivalents of zinc powder. Zinc powder is thereby activated with 2 mol% CH_2Br_2 and 2-5 mol% Me_3SiCl. The reaction is carried out at 50°C in 2-48 hours. The alkyl zinc bromides obtained thereby can be scavenged with different electrophiles. Additionally, there can be used catalysts such as, for example, palladium for accelerating the reaction. The structures and the yield of some products which can be synthesised in this way are summarised in scheme 1 below.



Scheme 1: Reaction of alkyl bromides with zinc

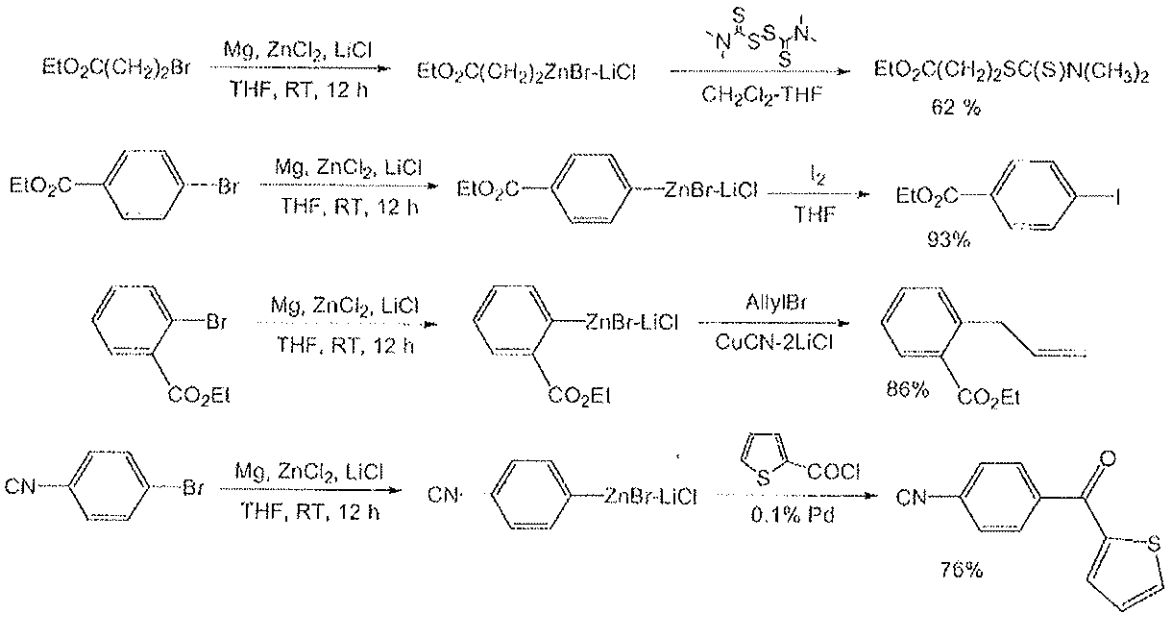
It is also possible to use aryl iodides as starting compounds. Thereby, zinc is inserted in the aryl-iodine bond in the presence of LiCl. A selection of compounds that can be synthesised in accordance with the present invention is given in scheme 2. Subsequently, the zinc organic compounds are reacted with an electrophile. This reaction is carried out quantitatively or mostly approximately quantitatively.



Scheme 2: Reaction of aryl iodides with zinc

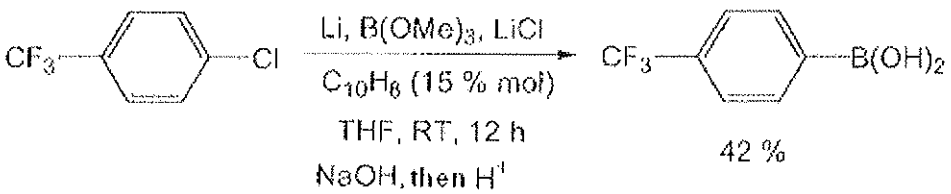
Furthermore, it is possible to prepare the compounds of the present invention starting from metal-containing compounds such as metal-containing salts or organo metal compounds. So, for example, aryl or alkyl bromides can be directly reacted with metallic magnesium and $ZnCl_2$ in THF in the presence of lithium chloride to aryl or alkyl zinc compounds. The concentration of lithium chloride in the solution is thereby from 1 to 5 mol/l, preferably from 2 to 4 mol/l. A concentration of 2.2 mol/l is especially preferred. The concentration of the M^3 containing compound is preferably 1 to 4 mol/l, more preferably 1.2 to 3 mol/l, and most preferably about 1.4 mol/l. The metals used can be activated. For example, magnesium swarf can be activated with 2 to 3 mol% Me_3SiCl. The reaction procedure can be carried out at room temperature. A summary of possible reactions is given in scheme 3. Here, the intermediate zinc organic compounds are again reacted with an electrophile. Thereby, the

electrophile can again be a halogen whereby a re-halogenation can result as illustrated in the second example in scheme 3.



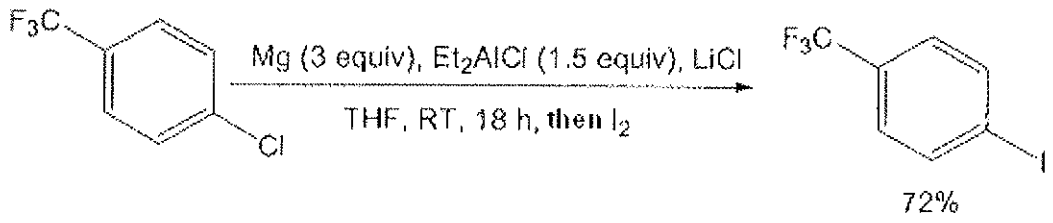
Scheme 3: Reaction of aryl and alkyl bromides with magnesium and $ZnCl_2$ in the presence of LiCl

According to another embodiment of the present invention, it is possible to prepare organo element compounds in the presence of LiCl starting from organo halogen compounds and to scavenge these compounds with an electrophile *in situ*. For example, 4-chloro-benzotrifluoride reacts with lithium in THF in the presence of naphthalene (15 mol%), LiCl and boron acid trimethylester to 4-trifluoromethylphenyl boron acid (see scheme 4). The post-processing of the product is at first carried out in basic medium, then in acid medium, wherein the yield is 42%.



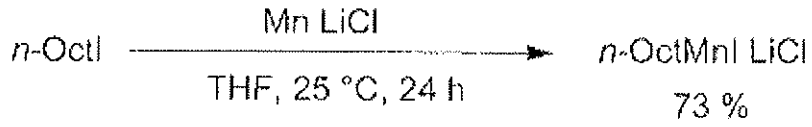
Scheme 4: Reaction of 4-chloro-benzotrifluoride with lithium and boron acid trimethylester

A reaction of 4-chloro-benzotrifluoride with magnesium in THF in the presence of LiCl and Et_2AlCl yields 72% of the corresponding aryl aluminum compound which can then be scavenged with iodine or another electrophile *in situ* such as illustrated in scheme 5.



Scheme 5: Reaction of 4-chloro-benzotrifluoride with magnesium, Et_2AlCl and iodine

Manganese can also be inserted in a halogen-carbon bond. For example, elementary manganese reacts with *n*-octyl iodide under mild reaction conditions at room temperature in the presence of lithium chloride to the corresponding insertion product as illustrated in scheme 6.



Scheme 6: Reaction of octyl iodide with manganese

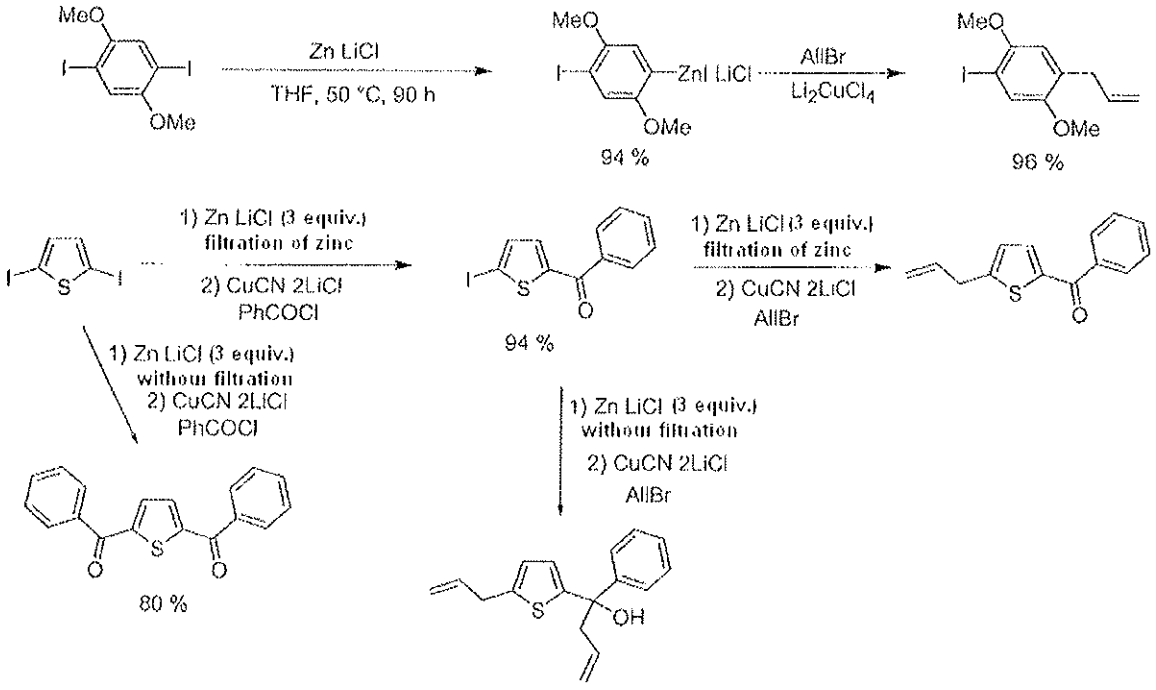
The method illustrated above can analogously be applied to the metals Cu, Bi, Al and In.

The reaction of multiply halogenated organic compounds can be selectively carried out at one or all carbon-halogen bonds. A selective insertion of zinc into a single carbon-iodine bond can, for example, be carried out by using zinc, as illustrated in the following scheme 7. The subsequent transmetalation with a copper species and the reaction with allyl bromide (AllBr) results in the single allylated product with high yield.

2,5-diiodothiophene can be reacted to the mono-substituted product with an excessive of zinc and by subsequently decanting for separating the solution from the remaining zinc. The second substitution of iodine of the thiophene can then result in a thiophene that is differently

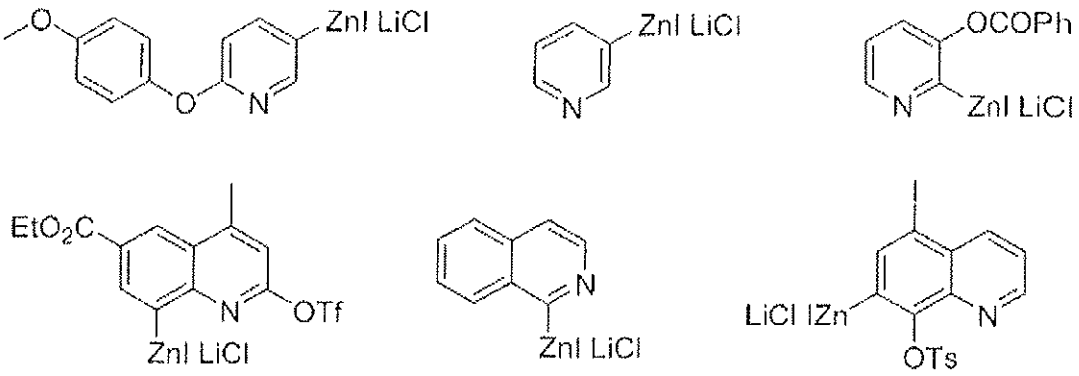
substituted in the 2- and 5-positions in a further reaction with zinc. However, if the zinc is not decanted or filtered, i.e. removed from the reaction mixture, after the first reaction, the carbonyl group will also be attacked by the alkyl bromide. Thus, the bi-allylated product results.

If, starting with 2,5-diiodothiophene, the solution of zinc is not decanted or filtered in the subsequent reaction, i.e. the zinc is present in the reaction mixture during the whole reaction procedure, the thiophene will be directly bi-substituted.



Scheme 7: Reaction of multiply iodated educts with zinc

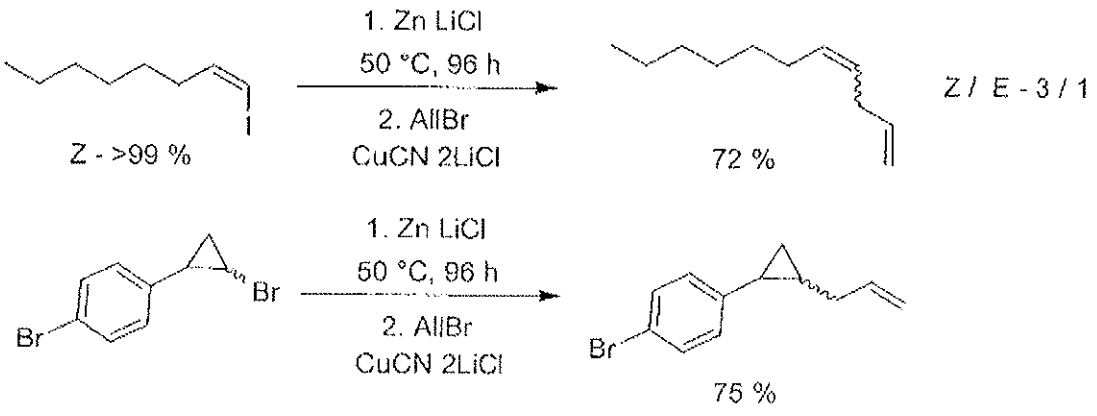
It is also possible to insert zinc in carbon-halogen bonds of aza heterocycles such as, for example, pyridine, quinoline and isoquinoline. The corresponding reactions can be carried out at room temperature and result in, for example, 24 hours in the desired organo zinc compounds with yields of more than 95%. Exemplary compounds obtainable in this way are presented in scheme 8.



Scheme 8: Aza heterocycles as the organo zinc compounds

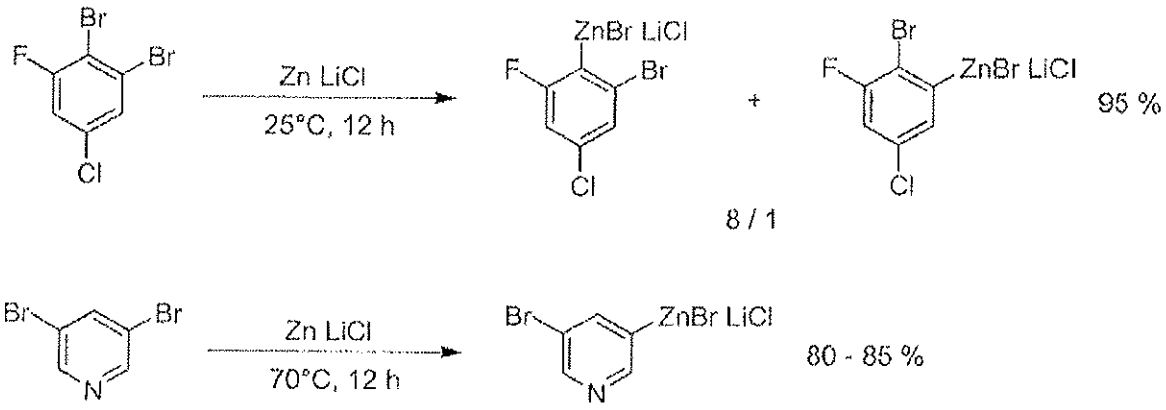
The new method according to the invention can also be used for the synthesis of alkenyl zinc compounds. In the case of Z-iodooctene, the corresponding octenyl zinc iodide has been obtained with a yield of more than 80%. The following reaction with allyl bromide (AllBr) is carried out after a transmetalation with copper with a yield of 72% as illustrated in the upper chemical equation in scheme 9. There, the ratio of the Z- to the E-isomer is 3 to 1.

An insertion of cyclopropyl derivatives in carbon-halogen bonds can also be carried out in accordance with the present invention. While a partial inversion of the configuration can be observed in both cases illustrated in scheme 9 below, these examples are of large interest as such an insertion has been carried out in those systems for the first time. Analogously to the example of iodooctene given above, the reaction of the organo zinc compound with allyl bromide is carried out after a transmetalation with copper with a yield of 75% (see scheme 9).



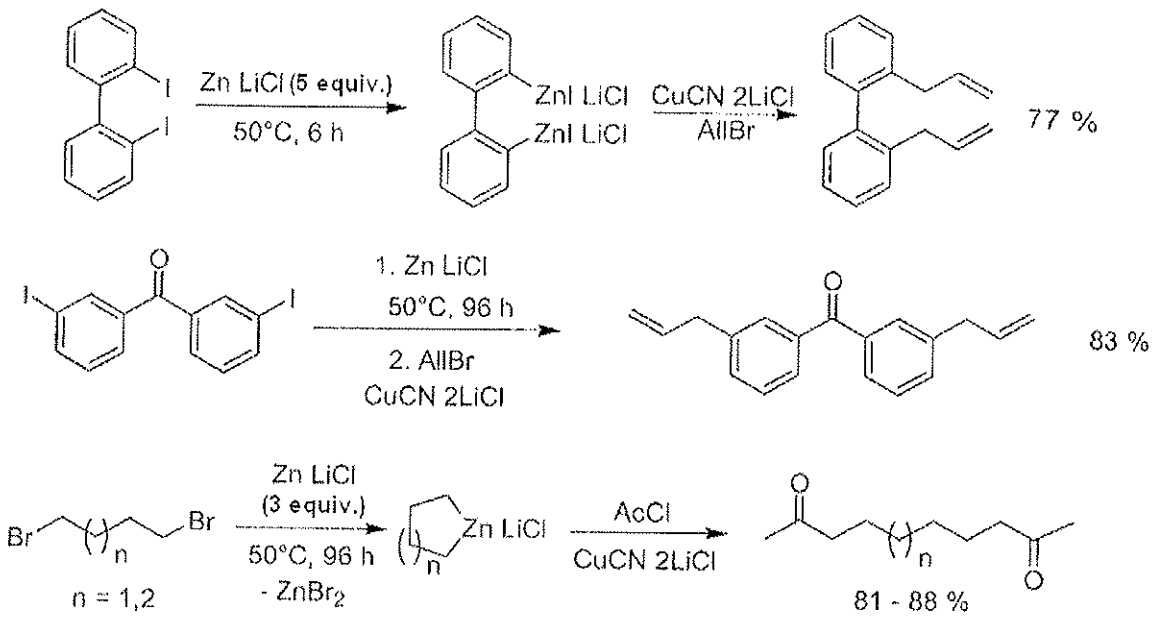
Scheme 9: Alkenyl zinc and cyclopropyl zinc compounds

In activated systems, it is also possible to use bromides as starting materials instead of the more expensive iodides. In asymmetrical substrates, a regioselective insertion can be carried out as illustrated in the following example in scheme 10.



Scheme 10: Regioselective insertion in multiply halogenated systems

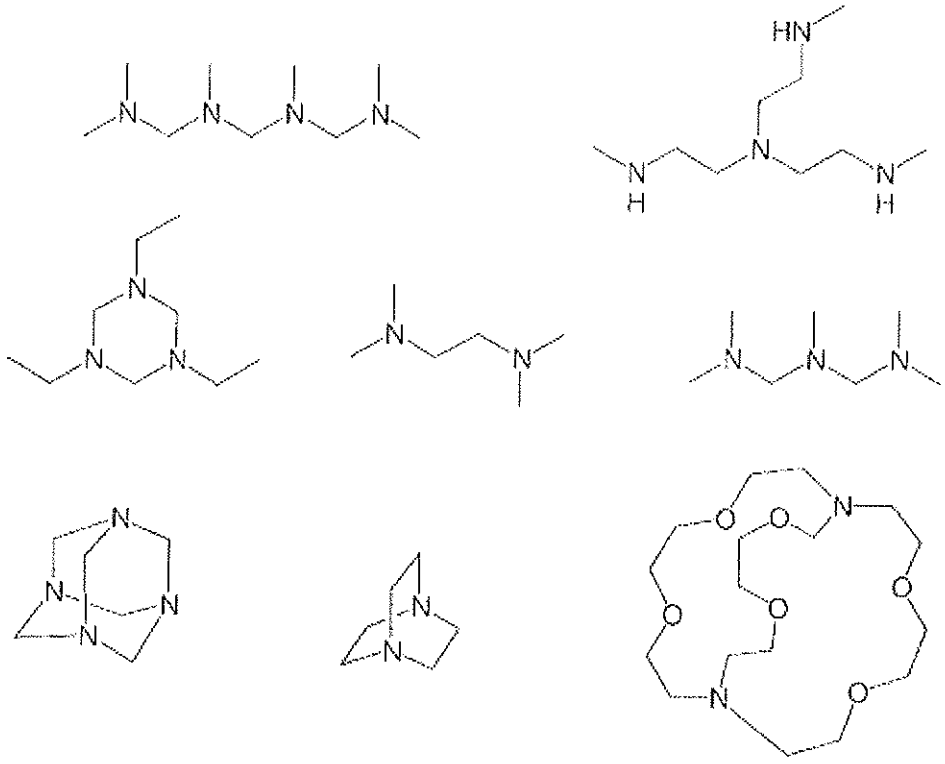
A number of di-zinc organo compounds can be prepared by the insertion of Zn in the presence of Li ions. Thereby, zinc is inserted in several iodine-carbon bonds such as illustrated in the examples in scheme 11. On the other hand, it is also possible to prepare di- or tri-organo element compounds with multivalent metals such as, for example, zinc. As shown in the third example of scheme 11, a dibromine compound can react with a single metal, for example, zinc. For example, the cyclic zinc pentane-1,5-diyl thus results from linear 1,5-dibromopentane which can be further reacted with an electrophile such as, for example, acetylchloride (AcCl). Thereby, two arms of the linear pentane are coordinated at a single zinc atom. From this example, there can be seen that also several mono-halogen compounds can be reacted with a single metal to di- or tri-organo element compounds.



Scheme 11: Di-zinc organo compounds and di-organo zinc compound

According to another embodiment of the present invention, the insertion reaction can be accelerated by the addition of amines. Thus, compounds which could originally not be reacted under conventional reaction conditions can now be made accessible to a reaction procedure according to the invention. In a preferred further embodiment, the insertion of zinc is accelerated by the addition of amines.

Any amines known to a person skilled in the art can be used as amines. These include primary, secondary and tertiary amines. Oligo- and polyamines are most preferably used. Most preferred amines are shown in scheme 12 below.

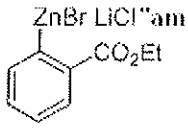
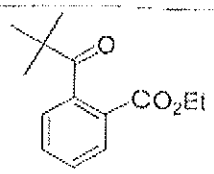
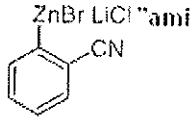
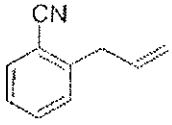
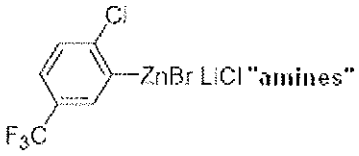
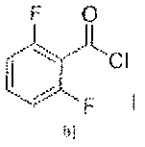
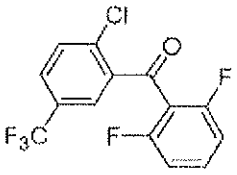
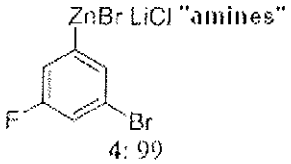
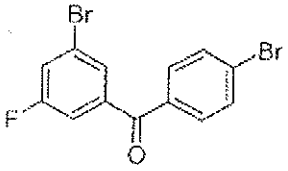
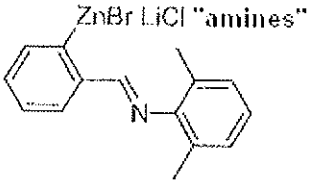
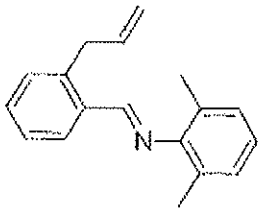
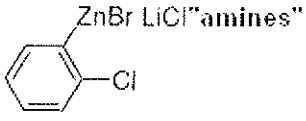
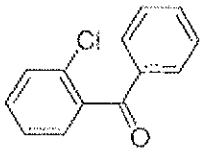
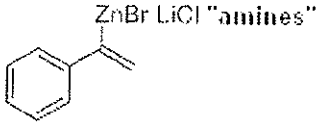
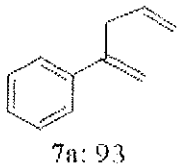


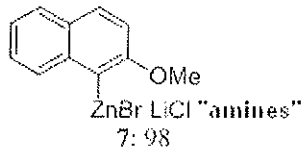
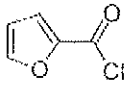
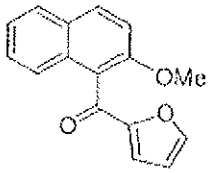
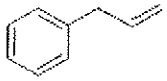
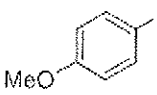
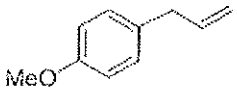
Scheme 12: Oligo- and polyamines

The amines can be added in any amount. Preferably, the amines are added in an amount of from 0.05 to 3 equivalents, more preferably in an amount of from 0.15 to 1.5 equivalents and most preferably from 0.2 to 1 equivalents in relation to the amount of the element M^1 and/or the metal M^2, specifically zinc, that is added.

In table 1 below, there are presented different reagents which have been reacted according to the general synthesis instruction for **3a**. Thereby, a good yield is shown after adding N,N,N',N'N''-pentamethyl diethylene triamine as the amine ("amines"). The addition of CuCN was carried out in order to react the zinc species into a more reactive Cu species catalytically.

Table 1. Preparation and reaction of aryl- and heteroaryl-functionalised zinc reagents in the presence of N,N,N',N'N''-pentamethyl diethylene triamine ("amines").

No.	zinc reagent, yield (%)[a]	temperature [°C]	time [h]	electrophile	product, yield (%)[b]
1	 1: 99	50	10	*t*-BuCOCl[b]	 1a: 94
2	 2: 96	50	24	AllBr[a]	 2a: 90
3	 3: 95	50	15		 3a: 89
4	 4: 99	50	12	4-BrPhCOCl[b]	 4a: 88
5	 5: 74	50	76	AllBr[a]	 5a: 56
6	 6: 99	50	170	PhCOCl[b]	 6a: 88
7	 7: 96	50	3,5	AllBr[a]	 7a: 93

No.	zinc reagent, yield (%)[a]	temperature [°C]	time [h]	electrophile	product, yield (%)[b]
8	 ZnBr LiCl "amines" 7: 98	50	48		 7a: 85
9	 ZnBr LiCl "amines" 8: 99	50	1	AllBr[a]	 8a: 91
10	 ZnBr LiCl "amines" 9: 99	50	3	AllBr[a]	 9a: 93

[a] 2 mol % CuCN 2LiCl has been added. [b] 30 mol % CuCN 2LiCl has been added.
(Bu = Butyl, All = Allyl, Ph = Phenyl)

Hereinafter, the reaction procedure shall be illustrated by use of typical synthesis instructions. These instructions shall serve as exemplary reaction procedures and can be modified by a person skilled in art in accordance with his expertise for preparing other reaction products. The reactions shall not limit the invention in any way.

Typical synthesis instructions

Preparation of 4-ethoxy-4-oxobutyl zinc bromide:

In a 25ml-Schlenk flask, LiCl (636 mg, 15 mmol) is provided and dried with a hot air blower at 140°C under high vacuum for 10 min. Zinc powder (981 mg, 15 mmol) as well as dry THF (12 ml) and 1,2-dibromomethane (20 µl, 0.225 mmol) are provided in a flask and carefully heated to 60°C for 1 min. under argon. After cooling to 35°C, Me_3SiCl (20 µl, 0.102 mmol) is added and vigorously stirred for 15 min. The reaction is tempered to 50°C in an oil bath and 4-bromobutane acid ethylester (975 mg, 5 mmol) is slowly added through a septum. The reaction control is carried out by the use of a GC. After 1 h, no educt is detected any more.

Preparation of [4-(ethoxycarbonyl)phenyl] zinc bromide:

In a 25ml-Schlenk flask, LiCl (636 mg, 15 mmol) is provided and dried with a hot air blower at 140°C under high vacuum for 10 min. Zinc powder (981 mg, 15 mmol) as well as dry THF (12 ml) and 1,2-dibromomethane (20 µl, 0.225 mmol) are provided in a flask and carefully heated to 60°C for 1 min. under argon. After cooling to 35°C, Me_3SiCl (20 µl, 0.102 mmol) is added and vigorously stirred for 15 min. The reaction is tempered to 50°C in an oil bath and 4-bromo benzoic acid ethylester (1145 mg, 5 mmol) is slowly added through a septum. The reaction control is carried out by the use of a GC. After 18 h, no educt is detected any more.

Preparation of [2-chloro-5-(trifluoromethyl)phenyl]-(2,6-difluorophenyl)methanone (3a):

Anhydrous LiCl (16 mol) is introduced in a 25ml-Schlenk flask having been rinsed with argon and dried under high vacuum (< 1 mbar) at 150-170°C for 5 minutes. Zinc powder (15 mmol) is added under argon and the flask is three-times evacuated and filled with argon. Then, dry THF (10 ml) is added and the zinc is activated with $BrCH_2CH_2Br$ (5 mol%) and Me_3SiCl (1 mol%). The mixture is heated to 50°C and then, 2-bromo-1-chloro-4-(trifluoromethyl)benzene (5 mmol) in 2 ml dry THF with an internal standard (n-tetradecane) of about 10% are added, followed by 5 mmol N,N,N',N',N''-pentamethyldiethylenetetramine. The insertion reaction is completed after 15 hours (control by use of an GC analysis of reaction aliquots wherein the reaction has proceeded for more than 99%). The solution of bromo-[2-chloro-5-(trifluoromethyl)phenyl] zinc (2.5 mmol, 5.5ml) is carefully separated from the remaining zinc powder by use of a syringe and transferred into another 10ml-Schlenk flask having been rinsed with argon. CuCN 2 LiCl (0.75 ml of a 1.0 M solution in THF, 0.75 mmol, 30 mol%) is added at -20°C, followed by 2,6-difluorobenzoylchloride (3.5 mmol). The reaction mixture is stirred over 1 hour at 0°C and then quenched with a saturated aequeous solution of NH_4Cl (5 ml). The aequeous phase is extracted with EtOAc (3 x 5 ml) and concentrated *in vacuo*. The raw product is purified via flash chromatography (PE : diethylether) whereby [2-chloro-5-(trifluoromethyl)phenyl]-(2,6-difluorophenyl)methanone (**3a**; 1.95 mmol, 625 mg, 78%) can be obtained as white needles.

While the invention has been described with the use of concrete embodiments hereinabove, it should not be limited thereto. It is apparent for a person skilled in the art that the above examples can be modified in many ways without departing from the scope of protection of the

claims. Thus, it is, for example, possible to multiply modify the reaction temperatures or times as well as the solvents or reagents. The scope of protection shall thus solely be defined by the claims.

CLAIMS

1. Method for preparing a compound having the general formula

$$R^1\text{-}M^1\text{-}A_d \; zLiX \qquad \textbf{(I)}$$

by reacting a compound R^1-A (**III**) with an element M^1 in presence of LiX,
wherein

R^1 is a substituted or un-substituted C_3-C_{24} aryl or C_3-C_{24} heteroaryl containing one or more heteroatoms like B, O, N, S, Se, P or Si, a linear or branched substituted or un-substituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl or C_2-C_{20} alkynyl or a substituted or un-substituted C_3-C_{20} cycloalkyl or a derivative thereof;

M^1 is an element selected from Mn, Cu, Zn, Sn, In, La, Ce, Nd, Y, Li, Sm, Na, K and Bi;

A is a halogen selected from F, Cl, Br, I; or a sulphonate (RSO_3-) or a phosphonate (-$OP(O)(OR)_2$) wherein R is defined as R^1;

d is 0 or 1;

z is > 0; and

X is selected from the group consisting of F; Cl; Br; CN; SCN; NCO; Hal^1O_k, wherein k=3 or 4 and Hal^1 is selected from Cl, Br and I; NO_3; BF_4; PF_6; H; a carboxylate having the general formula R^xCO_2; a disilazide having the general formula $(R^x{}_3Si)_2$; a thiolate having the general formula SR^x; an alcoholate having the general formula OR^x; $R^xP(O)O_2$; or $SCOR^x$; an amine having the general formula R^xNH; a dialkyl- or diarylamine having the general formula $R^x{}_2N$, wherein R^x is defined as below or $R^x{}_2N$ represents a cyclic alkylamine; a phosphine having the general formula $PR^x{}_2$, wherein R^x is defined as below or $PR^x{}_2$ represents a cyclic phosphine; O_jSR^x, wherein j = 2 or 3; or NO_r, wherein r = 2 or 3; and derivatives thereof; wherein R^x is a substituted or un-substituted C_4-C_{24} aryl or a C_3-C_{24} heteroaryl containing one or more heteroatoms like B, O, N, S, Se, P or Si; a linear or branched substituted or un-substituted C_1-C_{20} alkyl; C_2-C_{20} alkenyl or C_2-C_{20} alkynyl; or a substituted or un-substituted C_3-C_{20} cycloalkyl; or derivatives thereof; or H.

2. Method for preparing a compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad zLiX \qquad \textbf{(II)}$$

by reacting a compound R^1-A (**III**) with a M^3-containing compound in the presence of LiX and in the presence of an elementary metal M^2
wherein
R^1, z, A and X are defined as in claim 1;
T is defined as A or X in claim 1 and wherein X and T can be identical or different;
M^3 is defined as M^1 in claim 1 and additionally comprises Ti, Al, Mg, B, Si and S;
n is 0, 1, 2 or 3;
m is 1, 2 or 3;
M^2 is a metal being selected from Li, Na, K, Cs, Mg, Ca, Mn and Zn and the moieties R^1 can be identical or different, when m = 2 or m = 3.

3. Method according to claim 2, wherein the M^3-containing compound is selected from metal-halogen compounds, metal-alkyl compounds, metal-aryl compounds, metal-alkoxy compounds or metal-aryloxy compounds.

4. Method according to claim 2 or 3 wherein the M^3-containing compound is selected from $MgBr_2$, $MgCl_2$, $B(OMe)_3$, $B(i\text{PrO})_3$, BF_3, Et_2AlCl, $Si(OMe)_4$, $SiCl_4$, $MnCl_2$, $SnCl_2$, $ZnCl_2$, $ZnBr_2$, $TiCl(Oi\text{Pr})_3$, $Ti(Oi\text{Pr})_4$, $InCl_3$, $LaCl_3$, $CeCl_3$, $SmCl_3$ and $NdCl_3$.

5. Method according to one or more or the preceding claims, wherein the method is carried out in a solvent selected from cyclic, linear or branched mono- or polyethers, thioethers, amines, phosphines and derivatives thereof that contain one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofurane (THF), 2-methyltetrahydrofurane, dibutylether, diethylether, tert-butylmethylether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropylamine, dimethylsulfide, dibutylsulphide; cyclic and linear amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogen atoms are replaced by halogens, preferably dichlormethane, 1,2-dichlorethane, CCl_4;

derivatives of urea, preferably N,N'-dimethylpropylene urea (DMPU), N,N,N'N'-tetramethyl urea; aromatic, heteroaromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorotriamide (HMPA), CS_2; or combinations thereof.

6. Method according to one or more of the preceding claims characterised in that the elementary metal M^1 or M^2 is activated with a compound selected from the group consisting of copper salts, nickel salts, iron compounds, cobalt compounds, I_2, $C_2H_4Br_2$, $Cl(CH_2)_2Br$, *t*-BuOLi, BCl_3, BF_3, $LiBH_4$, $LiAlH_4$, $NaAlH_4$, Et_3Al, DIBAL-H, $Na[H_2Al(OCH_2CH_2OCH_3)]$ Me_3SiCl, Et_2Zn, ICl and $SnCl_2$.

7. Method according to one or more of the preceding claims characterised in that M^1 or M^2 is Zn.

8. Method according to one or more of the preceding claims characterised in that, when n 2, T_2 is a bivalent anion selected from the group consisting of diamines, dialkoxides or dithiols.

9. Method according to claim 8 characterised in that the diamine has the general formula R'NH-R-NHR', the dialkoxide has the general formula HO-R-OH and the dithiol has the general formula HS-R-SH, wherein R' and R are independently from each other selected from the same group as R^x, wherein R is a bivalent moiety and preferably $CH_3NHCH_2CH_2NHCH_3$, $HOCH_2CH_2OH$, binole, 1,2-diaminocyclohexane are used.

10. Method according to one or more of the preceding claims characterised in that an amine, preferably an oligo- or polyamine, is added additionally.

11. Method according to claim 10 characterised in that the amine is added in an amount of from 0.05 to 3 equivalents, preferably from 0.15 to 1.5 equivalents, more preferably from 0.2 to 1 equivalents, in relation to the element M^1 and/or the metal M^2.

12. Compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad zLiX \qquad \textbf{(II)}$$

wherein
R^1, z and X are defined as in claim 1 and n, m, T and M^3 are defined as in claim 2, but M^3 does not comprise Mg.

13. Solution of a compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad zLiX \qquad \textbf{(II)}$$

wherein R^1, z and X are defined as in claim 1 and n, m, T and M^3 are defined as in claim 2, but M^3 does not comprise Mg
in a solvent.

14. Solution according to claim 13 wherein the method is carried out in a solvent selected from cyclic, linear or branched mono- or polyethers, thioethers, amines, phosphines and derivatives thereof that contain one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofurane (THF), 2-methyltetrahydrofurane, dibutylether, diethylether, tert-butylmethylether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropylamine, dimethylsulfide, dibutylsulphide; cyclic and linear amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC); cyclic, linear and branched alkanes and/or alkenes wherein one or more hydrogen atoms are replaced by halogens, preferably dichlormethane, 1,2-dichlorethane, CCl_4; derivatives of urea, preferably N,N`-dimethylpropylene urea (DMPU), N,N,N`N`-tetramethyl urea; aromatic, heteroaromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorotriamide (HMPA), CS_2; or combinations thereof.

15. Use of a compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad zLiX \qquad \textbf{(II)}$$

wherein R^1, z and X are defined as in claim 1 and n, m, T and M^3 are defined as in claim 2, but M^3 does not comprise Mg
in a reaction with an electrophile.

16. Product of a reaction of an electrophile with a compound having the general formula

$$R^1{}_m\text{-}M^3\text{-}T_n \quad zLiX \qquad \textbf{(II)}$$

wherein R^1, z and X are defined as in claim 1 and n, m, T and M^3 are defined as in claim 2, but M^3 does not comprise Mg.