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Preparation of functionalized Zn and Mg-organometallics. Application to the performance of diastereoselective cross-couplings

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ABSTRACT

This review describes two general approaches for preparing functionalized Zn- and Mg-organometallics. The first method starts from unsaturated halides (X = Cl, Br, I) and involves a direct insertion of Zn or Mg powder in the presence of LiCl. The second method uses aromatic, heterocyclic or olefinic precursors and converts them with LiCl-solubilized bases directly via C–H activation to the corresponding organometallics.

1. Introduction

Zinc and magnesium organometallics have strongly influenced the development of organic synthesis over the last century [1]. In recent years, it became important to prepare highly functionalized organometallics for the construction of complex organic target molecules [2]. Zinc organometallics were especially well suited for such a purpose, due to the low reactivity of the carbon-zinc bond and to the excellent response of this carbon-metal bond for participating in various transition metal catalysis [3]. New preparation methods also allowed the synthesis of functionalized organomagnesium reagents [4]. Both of these metals display a low toxicity and are moderately priced. This short review describes two general methods for the synthesis of these useful organometallics: the first method involves a direct metal insertion and uses organic halides of type **1** as substrates, whereas the second method is based on a C–H activation of aromatic (or heterocyclic structures such as **2**) (Scheme 1). Applications of these polyfunctional organometallics for carbon-carbon bond forming reactions will also be described.

2. Preparation of polyfunctional Zn- and Mg-organometallics

2.1. Insertion reactions to organic halides

Whereas the insertion of zinc dust to aryl iodides can be accomplished only by using highly reactive zinc powder (Rieke zinc) [5] or polar solvents, the reaction of commercial zinc dust with ethyl 4-iodobenzoate (**3**) in THF is very sluggish and provides the desired zinc reagent **4** in less than 5% after 24 h at 70 °C. However, in the presence of LiCl (0.3–2 equiv) a fast reaction takes place at 25 °C and leads to the desired zinc reagent **4** in ca. 98% yield. The role of LiCl is to solubilize the aryl zinc halide (ArZnX) produced on the zinc surface (Scheme 2) [6].

This reaction is very versatile and allows the synthesis of various aromatic and heterocyclic zinc reagents bearing sensitive functional groups like an ester, an aldehyde, or a ketone (Scheme 3).

This LiCl-activation of the zinc surface is quite general and a number of metals like Al, In, or Mg can be efficiently activated by addition of LiCl in THF. Thus, the treatment of the mixed carbonate **4** with Mg powder in the presence of LiCl provides the expected Grignard reagent **5** in 91% yield. The insertion reaction is complete at −20 °C within 1 h. Quenching with an aldehyde

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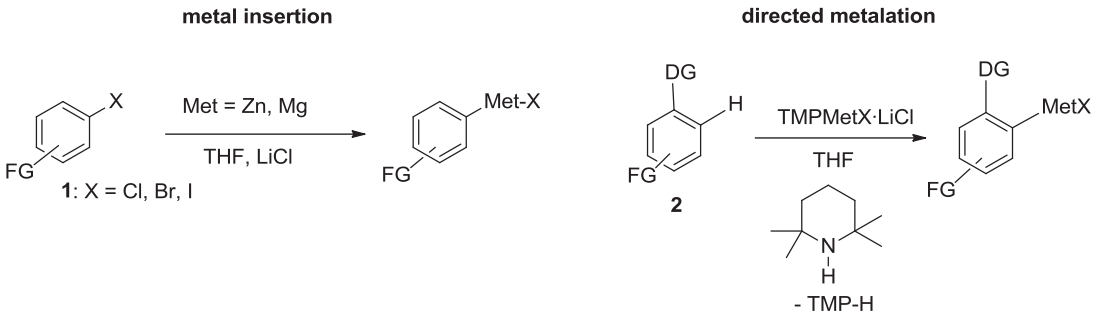
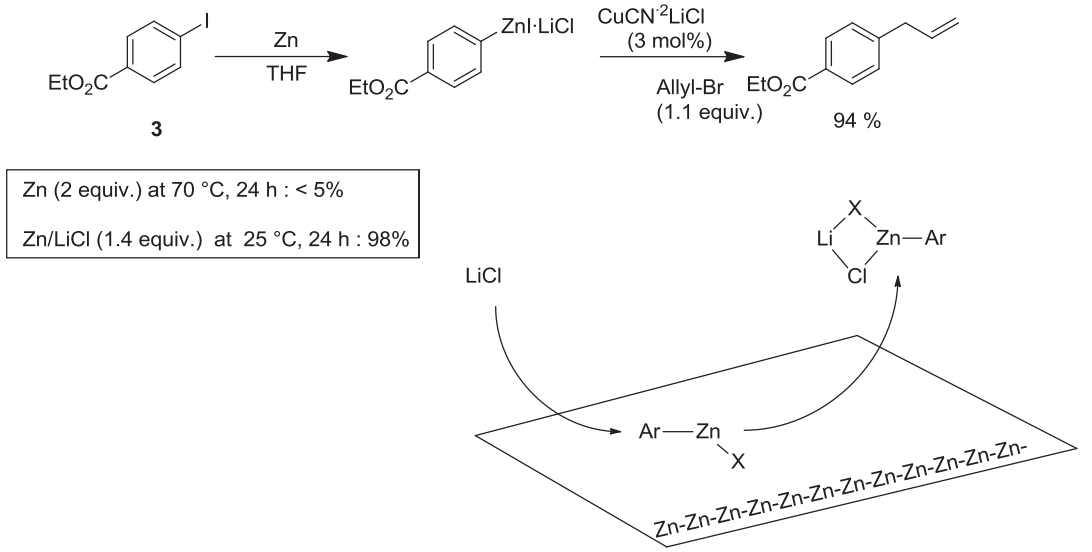


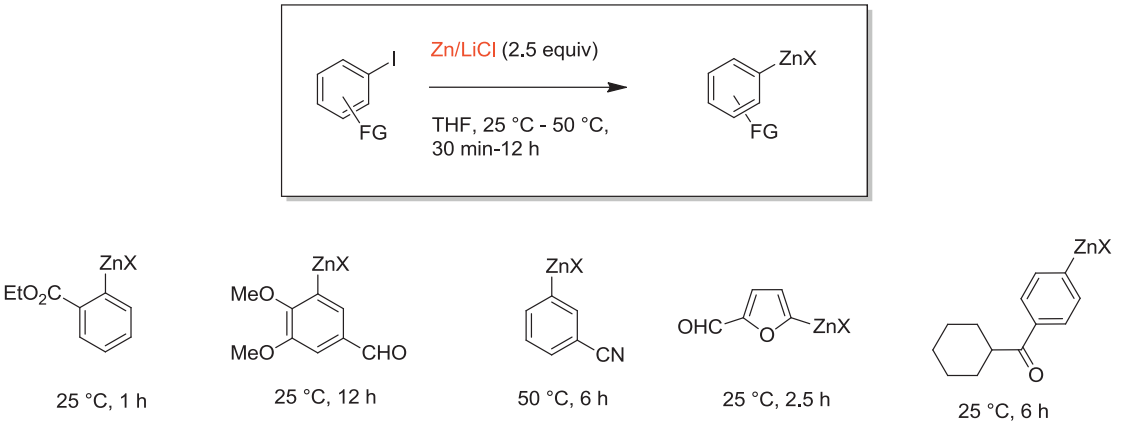
Scheme 1. Polyfunctional organometallics in organic synthesis.



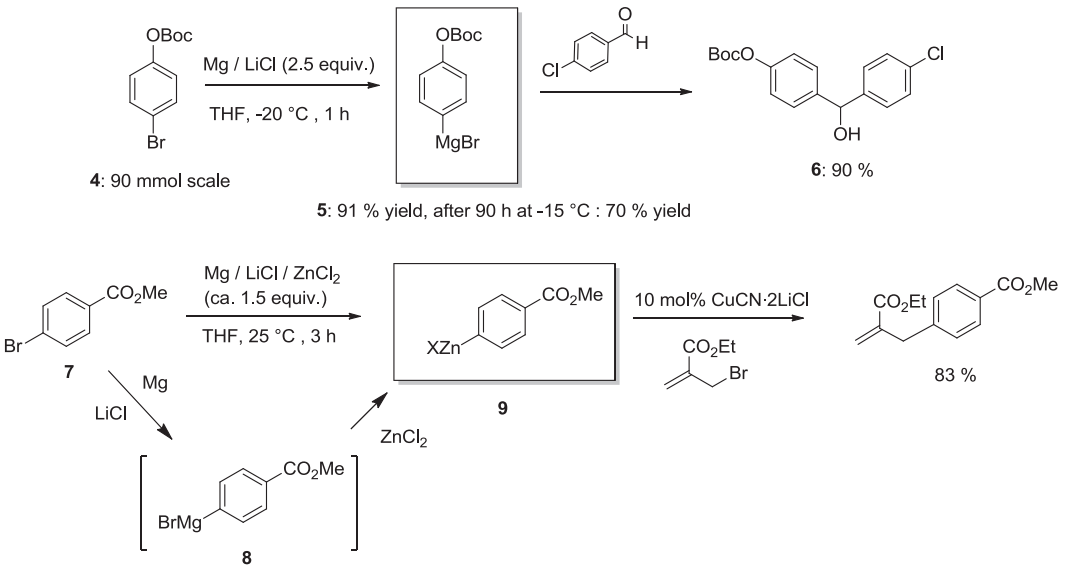
Scheme 2. LiCl-mediated preparation of functionalized organozinc reagents.

provides the expected alcohol **6** in 90% yield [7]. In the presence of more sensitive functional groups such as a methyl ester (**7**), the Mg-insertion is performed in the presence of $ZnCl_2$, so that the intermediate Mg-reagent (**8**) is converted *in situ* into the corresponding zinc reagent (**9**). Copper-catalyzed allylation affords the diester **10** in 83% yield (Scheme 4).

Benzylic chlorides are excellent substrates for preparing the corresponding Zn-reagent, either by a direct reaction with Zn dust in the presence of LiCl or by using Mg-powder in the presence of $ZnCl_2$ and LiCl-. This second method allows an expeditive synthesis of the zinc reagent **11** (45 min us. 24 h using only Zn and LiCl) [8]. The presence of $MgCl_2$ generated during the formation of a



Scheme 3. General Preparation of Functionalized Organozinc Reagents.



Scheme 4. Chemoselective preparation of functionalized arylmagnesium reagents.

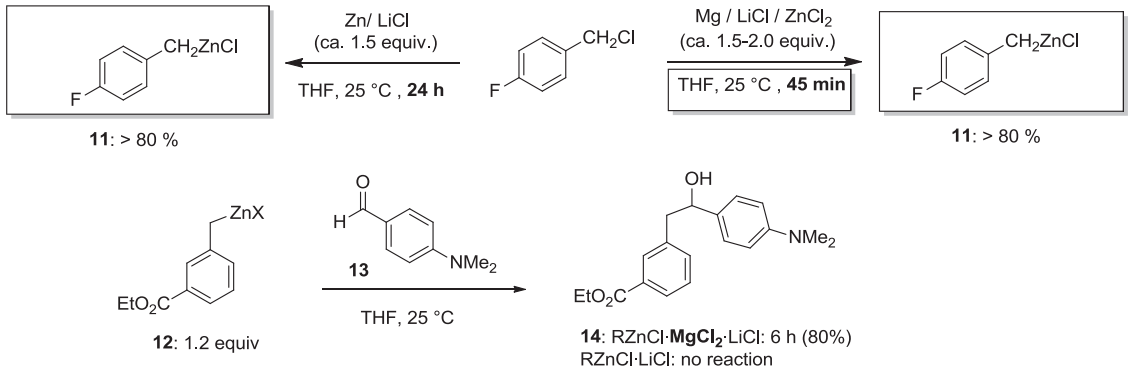
benzylic zinc reagent using $Mg/ZnCl_2/LiCl$ has an additional beneficial effect. It enhances greatly the reactivity of the zinc species. Thus, whereas the zinc compound **12** does not react with the aldehyde **13** in the absence of $MgCl_2$, in its presence a fast reaction occurs producing the alcohol **14** in 80% isolated yield [9] (Scheme 5).

The presence of $MgCl_2$ facilitates the addition CO_2 to the zinc reagent, a reaction which otherwise proceeds only in polar solvents [10]. This allowed us to prepare ibuprofen (**15**) in 89% yield in a one-pot procedure starting from the benzylic chloride (**16**) [11]. The rate acceleration due to $MgCl_2$ is best explained by assuming that the usual transition state **A** for the addition of a zinc organometallic to a carbonyl compound is now rather of the type **B** where the carbonyl group is coordinated to $MgCl_2$ which is a much stronger Lewis-acid than R'ZnCl (Scheme 6) [9].

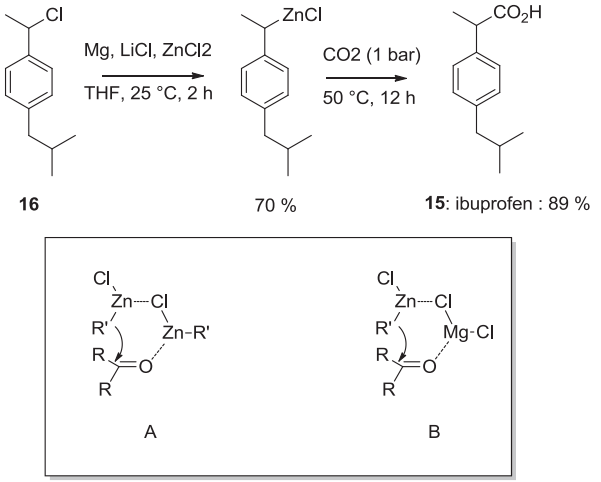
2.2. Directed deprotonation using LiCl-solubilized TMP-bases

The use of sterically hindered 2,2,6,6-tetramethylpiperidyl (TMP)-metal amides solubilized by LiCl allows the direct magnesiation or zincation of a range of polyfunctional aromatics and heterocycles. Thus, TMPMgCl·LiCl (**17**) which is readily prepared by the reacting of 2,2,6,6-tetramethylpiperidine with *i*PrMgCl·LiCl has a monomeric structure in solution as shown by García-Álvarez et al. [11]. It has excellent solubility in THF (1.2 M) and deprotonates positions in heterocycles otherwise difficult to metalate. Thus, the furan (**18**) reacts readily at −78 °C with TMPMgCl·LiCl (**17**) producing the magnesium reagent **19** which after transmetalation with $ZnCl_2$ undergoes a smooth cross-coupling with an aryl iodide providing the cross-coupling product **20** in 79% yield (Scheme 7) [12].

The corresponding zinc base TMPZnCl·LiCl (**21**) is prepared in a similar way starting from TMP-H using BuLi and a subsequent transmetalation with $ZnCl_2$. The base (**21**) has also an excellent solubility in THF (ca. 1.3 M) and shows a unique chemoselectivity in deprotonation reactions. Thus, the heterocycles **22** and **23** which bear respectively an aldehyde and an nitro group are readily zincated at 25 °C with TMPZnCl·LiCl (**21**) within a few minutes (Scheme 8) [13].



Scheme 5. New preparation of benzylic zinc reagents using Mg as reducing agent.

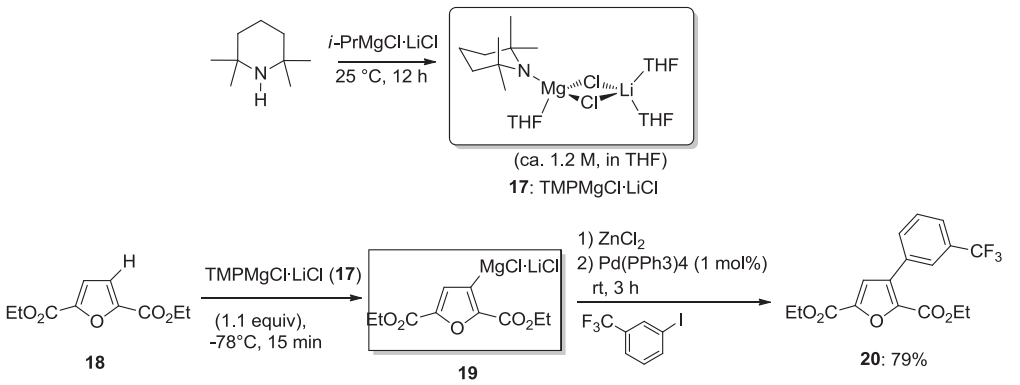


Scheme 6. MgX_2-addition of organic reagents to carbonyl derivatives.

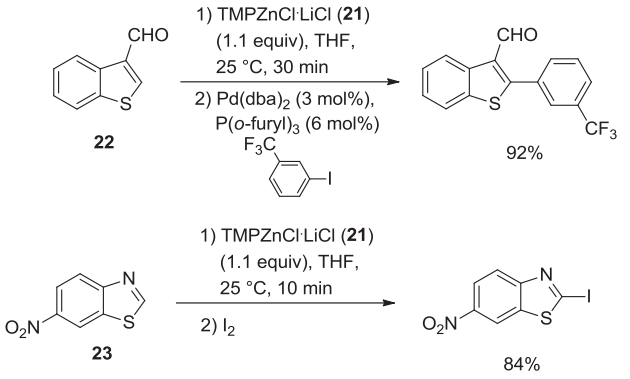
Also, a sensitive heterocycles such as the purine (**24**) are zincated at 25 °C with TMPZnCl·LiCl (**21**) leading to a selective zincation at the imidazole ring of the purine skeleton. Very sensitive substrates like the furan (**25**) which bears both a nitro group and an ester function is smoothly zincated with TMPZnCl·LiCl (**21**) at the α-position to the methyl ester group. After allylation with 3-bromocyclohexene the expected furan **26** is obtained in 76% yield (Scheme 9) [13].

Remarkably, TMPZnCl·LiCl is also able to zincate functionalized olefins such as the trifluoromethyl ketone derivative **27** or nitro olefins of type **28**. The resulting zinc reagents **29** and **30** can either be acylated or allylated providing polyfunctional compounds like **31** and **32** (Scheme 10) [14].

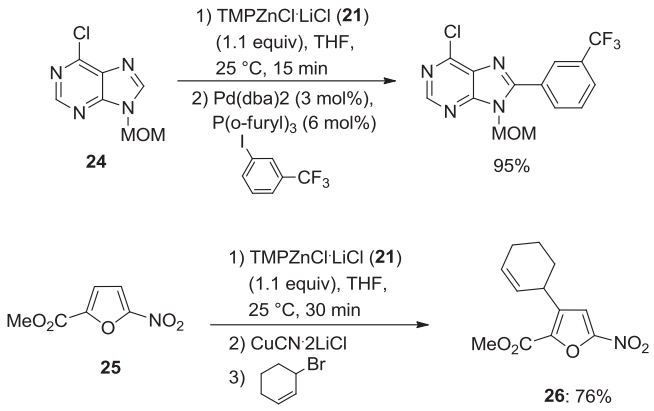
The metalation of pyridines is an important synthetic challenge and Kessar et al. have shown that $BF_3{\cdot}OEt_2$ enables a low temperature lithiation of pyridines with TMPLi [15]. We could show that LiCl-solubilized TMP-bases such as TMPMgCl·LiCl (**17**) or TMPZnCl·LiCl (**21**) are compatible with $BF_3{\cdot}OEt_2$ at temperature below −20 °C. Thus, 3-fluoropyridine (**33**) can be readily metalated in position 4 by the reaction with $BF_3{\cdot}OEt_2$ followed by the addition of TMPMgCl·LiCl (**17**) [16]. After a Pd-catalyzed cross-coupling with an aryl iodide the desired 4-substituted pyridine (**34**) is obtained in 74% yield. In contrast with the absence of $BF_3{\cdot}OEt_2$, a selective magnesiation occurs in position 2 providing the 2-arylated pyridine **35** [16]. A similar behaviour is observed for a number of pyridines bearing an electron-withdrawing substituent in position 3. Thus, 3-cyanopyridine (**36**) can be substituted with complete regioselectivity either in position 2 in the



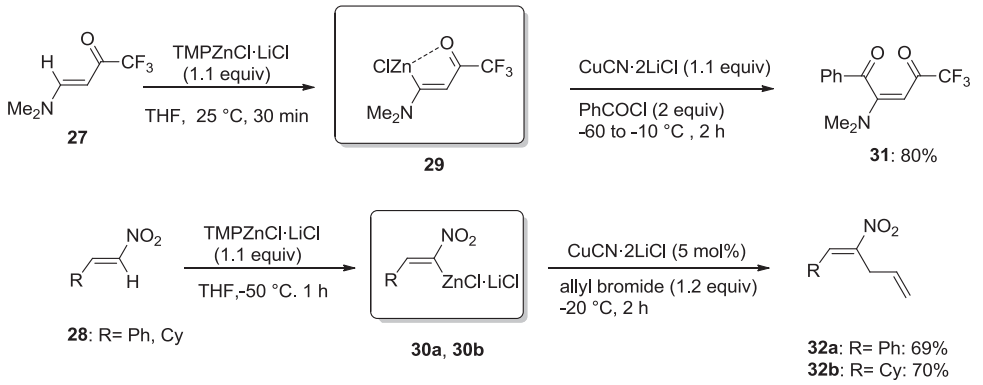
Scheme 7. Synthesis of magnesiated furans and pyrroles.



Scheme 8. TMPZnCl·LiCl: a chemoselective base for the directed zincation of sensitive aromatics and heteroaromatics.



Scheme 9. Zincations in the presence of ester, nitro groups and aldehydes.

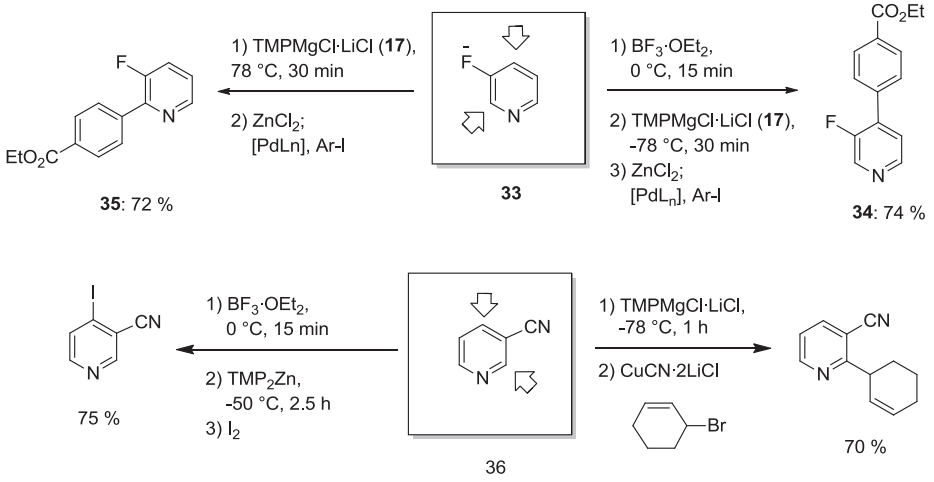


Scheme 10. Zincation of electron-poor Olefins.

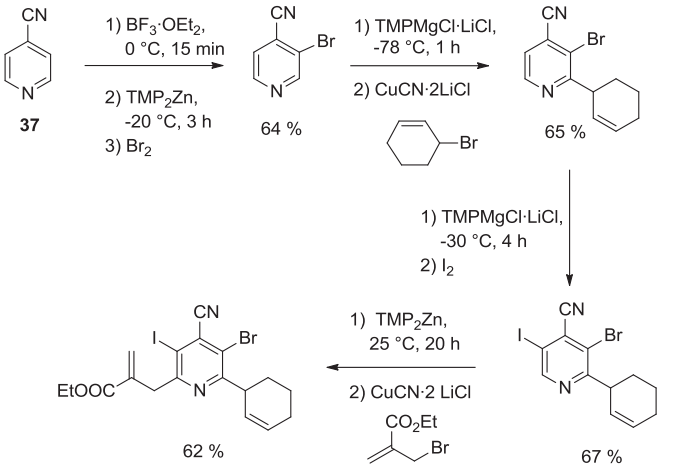
absence of $BF_3{\cdot}OEt_2$ or in position 4 in the presence of $BF_3{\cdot}OEt_2$ (Scheme 11) [16].

A full functionalization of the pyridine scaffold was performed using LiCl-solubilized TMP-bases of Zn and Mg. Thus, 4-cyanopyridine (**37**) is successively functionalized in position 3, then position 2, then position 5 and finally in position 6. This demonstrates the versatility of the TMP-bases and although all functionalizations of a given pyridine cannot be achieved in each case, a significant progress has been made with these new TMP-bases in combination with $BF_3{\cdot}OEt_2$ (Scheme 12) [17].

Organozincs were used for the synthesis of new types of heterocycles or for improving current heterocycle syntheses. Thus, the Fisher-indole synthesis requires strong acidic



Scheme 11. BF_3-triggered selective metalations.



Scheme 12. Preparation of fully substituted pyridines.

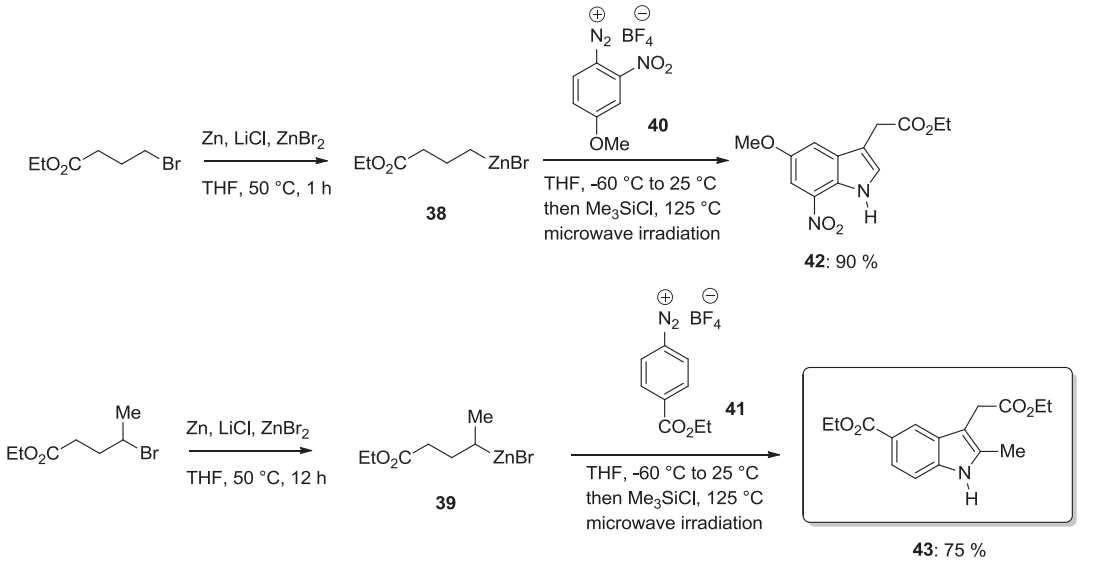
conditions, uses non-commercial aryl hydrazines as substrates and provides often a mixture of regioisomeric indoles. These problems can be solved by performing a zinc mediated Fischer-indole synthesis. This one-pot procedure requires readily available aryldiazonium salts and tolerate a range of functional groups. Thus, various zinc reagents such as **38** and **39** add under mild conditions to the aryldiazonium salts **40** and **41** providing after a [3,3]-sigmatropic shift at 125 °C (microwave irradiation) the indoles **42** and **43** in 75–90% yields (Scheme 13) [18].

Secondary cycloalkylzinc reagents can be used as well. These reagents produce annulated indoles such as **44** and **45** in 81–88% yields. This method has also be applied to the synthesis of biologically active indoles such as iprindole **46** which is prepared in a efficient procedure starting from cyclohexylzinc bromide which is obtained by the direct zinc insertion to cyclohexyl bromide using Zn dust and LiCl in THF (50 °C, 1 h); Scheme 14 [18].

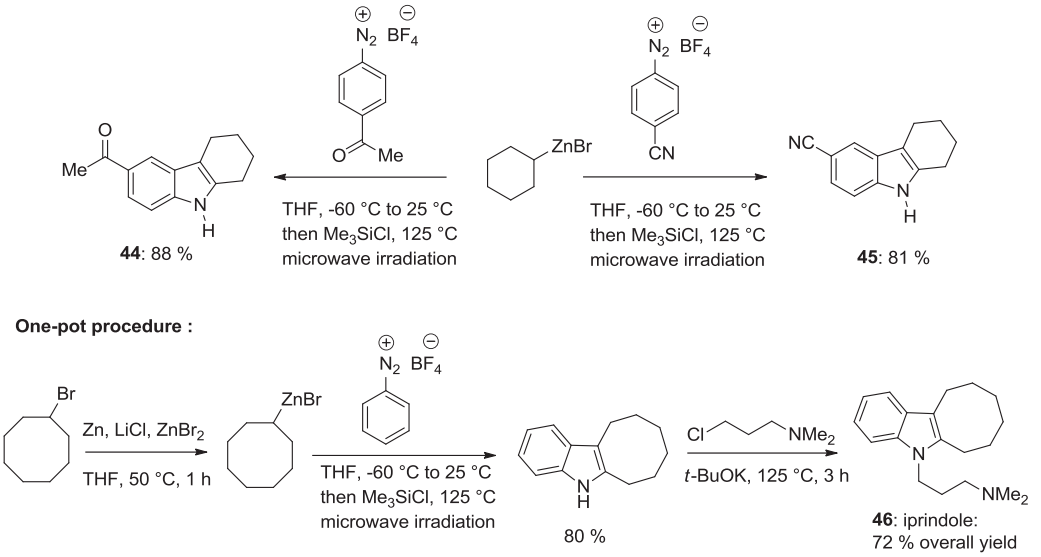
2.3. Diastereoselective cross-couplings

The preparation of diastereomerically pure compounds by using cross-coupling reactions is an important synthetic method. Starting from menthyl iodide (**47**), we have found that the resulting diastereomeric zinc reagent react in a stereoconvergent way with an arylpalladium(II)-halide providing only one Pd(II)-intermediate bearing all the substituents in a equatorial position (**48**). After reductive elimination, arylated menthyl derivatives of type **49** are obtained with high diastereoselectivity (Scheme 15) [19].

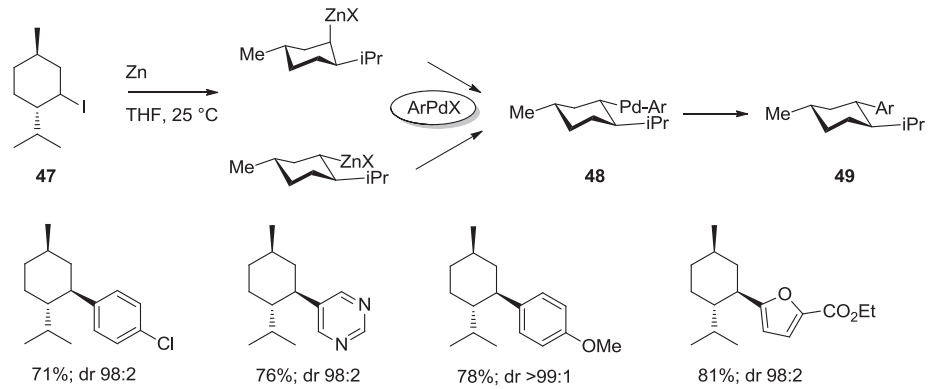
Remarkably, this diastereoselective cross-coupling can be extended to synthesis bearing a substituent in position 2, 3 or 4. Thus, cyclohexylzinc reagent such as **50**–**52** undergo highly diastereoselective cross-couplings with methyl 4-iodobenzoate leading to the arylated cyclohexane derivatives **53**–**55** in 72–82% yields and dr > 95:5; Scheme 16 [19].



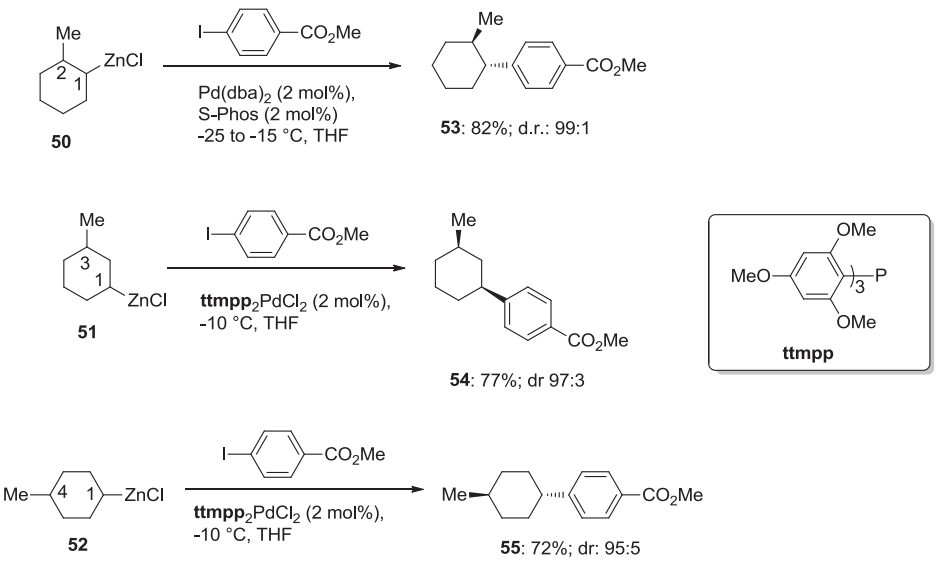
Scheme 13. Zinc-mediated Fischer indole synthesis.



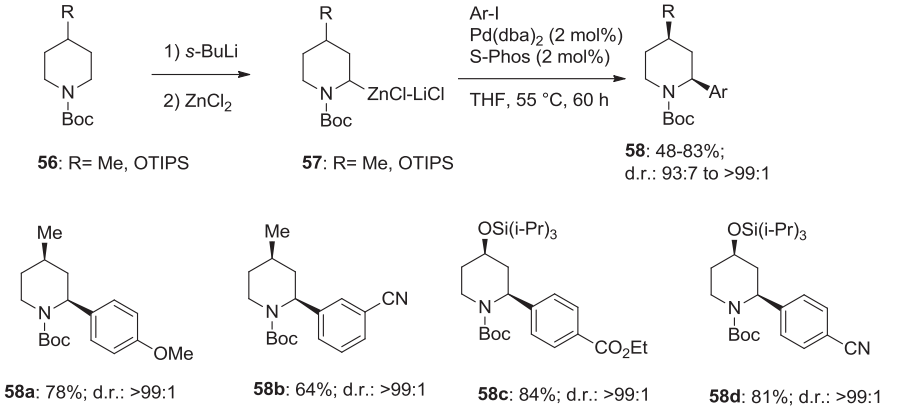
Scheme 14. Synthesis of iprindole.



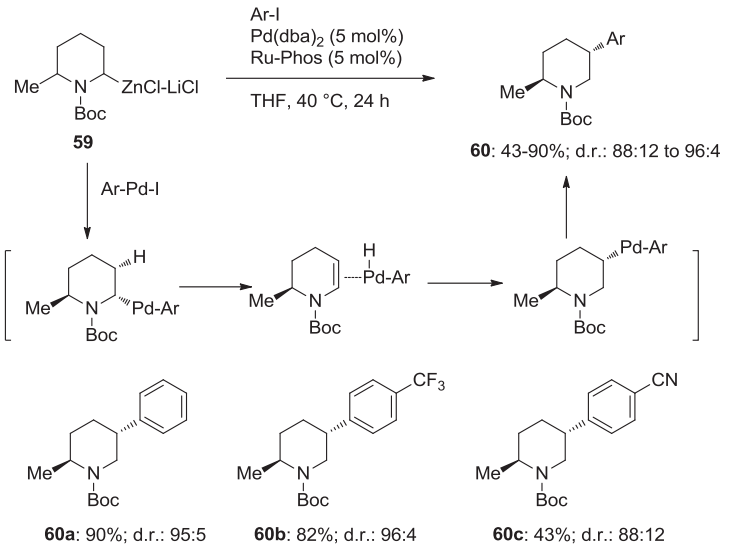
Scheme 15. Diastereoselective Negishi cross-couplings.



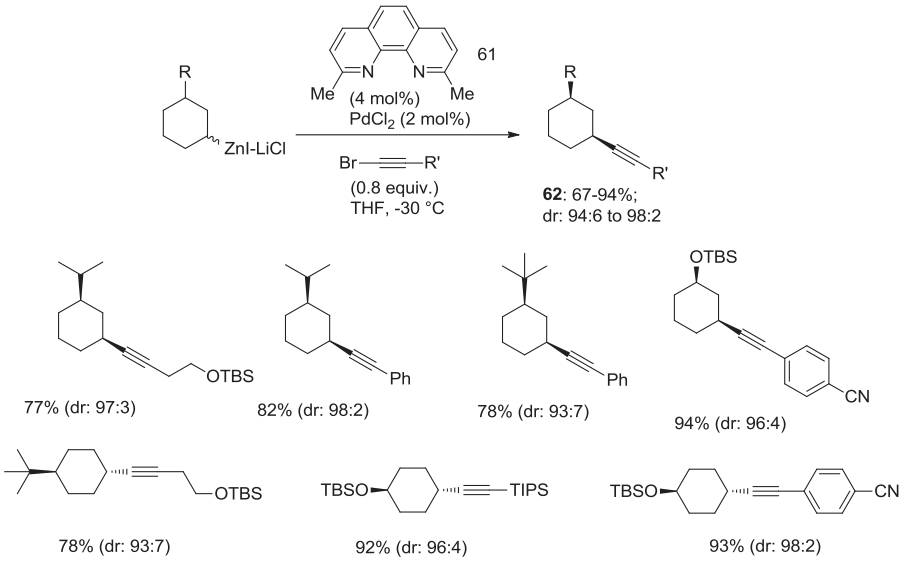
Scheme 16. Diastereoselective cross-coupling reactions.



Scheme 17. Diastereoselective cross-coupling reactions with piperidylzinc reagents.



Scheme 18. Rearrangements in diastereoselective cross-coupling reactions.



Scheme 19. Diastereoselective Csp-Csp^3 cross-coupling reactions.

It was also possible to extend these cross-coupling to the arylation of Boc-protected piperidines of type **56**. Their metalation with *s*-BuLi and transmetalation with $ZnCl_2$ provides the zinc reagents **57** which after reaction with an aryl iodide (Ar-I) are furnishing the 2,4-disubstituted piperidines **58a–d** in diastereoselectivities > 99:1; Scheme 17 [20].

By using 2,6-disubstituted zincated piperidines of type **59**, a Pd-catalyzed rearrangement takes place *via* an elimination and readdition of ArPd-H leading to 2,5-disubstituted piperidines of type **60**. Thus, the arylated piperidines **60a–c** are obtained with diastereoselectivities better than 88:12 (Scheme 18) [20].

The preparation of alkynylcyclohexane derivatives in a diastereoselective fashion can also be realized *via* a Pd-catalyzed cross-coupling. Interestingly, although most Pd-catalyses require a phosphine ligand, it was possible to perform Csp^3-Csp cross-coupling of cyclohexylzinc reagents with alkynyl bromides using neocuproine (**61**) as a ligand. The cross-coupling furnish the alkynylated products of type **62** in good yields and high diastereoselectivities (up to 98:2); Scheme 19 [21].

3. Conclusion

In conclusion, we have reported in this review article, a new range of general synthetic methods allowing the preparation of polyfunctional organometallics of magnesium and zinc. The low toxicity of these metals, excellent availability and exceptional chemoselectivity make these reagents very versatile tools for organic synthesis.

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