THE HALOGEN/MAGNESIUM-EXCHANGE USING iPrMgCl·LiCl AND RELATED EXCHANGE REAGENTS

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Abstract – We have described the regio- and chemoselective preparation of various (hetero)aryl-Grignard reagents via halogen/magnesium-exchange along with applications of these organometallics in various reactions. The LiCl-mediated halogen/magnesium-exchange proceeds readily under mild conditions and offers the opportunity to convert not only organic iodosides, but less activated organic bromides, as well. Furthermore, this exchange tolerates a broad spectrum of sensitive functionalities such as triazenes, methyl esters, silylated cyanohydrins, alcohols and acrylates. Electron-rich aryl derivatives can be converted into the corresponding Mg-species by using more activated bis-alkylmagnesium compounds. Subsequent functionalization reactions such as cross-couplings, allylations, acylations, addition reactions to ketones, cyclization reactions, fluorinations, disulfenylations, aminations as well as sulfoxide/magnesium-exchange reactions have been performed, readily furnishing highly functionalized derivatives as well as biologically active heterocycles.

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1. INTRODUCTION
Since it was realized that, besides zinc and boron organometallics, Grignard reagents are compatible with a broad range of functional groups, the preparation of functionalized aryl and heteroaryl magnesium reagents has become an important synthetic methodology.1 Although, Grignard reagents can be readily prepared by the direct insertion of magnesium turnings into organic halides,2 the homogenous nature of
the halogen/magnesium-exchange reaction is a serious advantage, as it allows performing this exchange reaction under very mild conditions compared to the appropriate insertion reactions. To the best of our knowledge, the halogen/magnesium-exchange was first reported by Charles Prévost in 1931. It has found several applications for the preparation of organomagnesium reagents which had been difficult to prepare by the direct insertion, such as magnesium carbenoids. Also, Furukawa and Quéguiner applied this method to the preparation of heterocyclic organomagnesium reagents. Until 2004, the only limitation consisted in the slow rates of the I/Mg- and the Br/Mg-exchanges compared to the corresponding I/Li- and Br/Li-exchanges. This fact prevented the performance of this exchange with unsaturated bromides bearing esters, cyanides, ketones and related sensitive functionalities. The breakthrough experiment in this field was achieved by F. F. Kneisel discovering that halogen/metal-exchange reactions can be catalyzed by the addition of metal salts. Thus, the addition of 10% Li(acac) was found to dramatically accelerate the I/Zn-exchange reaction presumably by forming an ate intermediate of type 1. Hence, this exchange reaction was so mild that, in the case of an I/Zn-exchange, an aldehyde functional group was tolerated (Scheme 1).

![Scheme 1. Iodine/Zinc-Exchange Catalyzed by 10% Li(acac)](image)

This catalysis could be extended to the halogen/magnesium-exchange reaction using iPrMgCl-LiCl and thus, allowed to perform this exchange with moderately reactive aryl and heteroaryl bromides. In this review, we will cover the recent developments of the halogen/magnesium-exchange reaction using mainly iPrMgCl-LiCl and related reagents.

2. THE CATALYZED HALOGEN/MAGNESIUM-EXCHANGE USING iPrMgCl-LiCl AND RELATED EXCHANGE REAGENTS

The high polarity of the carbon-lithium bond makes the I/Li-exchange reaction a very fast process. Similarly, the Br/Li-exchange is usually a fast reaction, as well, being mostly completed within few
minutes at -78 °C. However, the resulting aryl- or heteroaryl-lithium reagents do not tolerate many functional groups. The halogen/magnesium-exchange is much slower and strongly depends on the electron-density of the ring system. Thus, the more electron-deficient the aromatic or heterocyclic bromides and iodides are, the faster the exchange reaction proceeds. In practice, the I/Mg-exchange reaction can be well realized, if no sensitive functionality is present. As a consequence, the diiodotriazine 2 undergoes a double exchange reaction with sBuMgCl at -78 °C within 10 min and provides the bis-Grignard reagent 3 which is readily allylated in the presence of CuCN·2LiCl leading to the triazine 4 in 67% yield. Similarly, the very electron-poor aryl iodide 5 bearing a keto-group and a sensitive nitro-functionality smoothly reacts with PhMgCl in an I/Mg-exchange at -40 °C. The resulting Grignard reagent 6, although displaying a moderate nucleophilicity, undergoes the typical quenching reactions with electrophiles. Its addition to benzaldehyde furnishes the trisubstituted arene 7 in 93% yield. Interestingly, the performance of an I/Mg-exchange at -10 °C is compatible with the presence of a methyl ester as in substrate 8. It reacts smoothly with iPrMgBr in THF at -10 °C and furnishes the desired Grignard reagent 9 in high yield. This functionalized magnesium reagent is stable at 0 °C for several hours showing that the presence of a methyl ester substituent in the arylmagnesium reagent 9 considerably reduced its nucleophilicity. Furthermore, it stabilizes this Grignard reagent to such extend that the sensitive methyl ester does not undergo an addition reaction to this arylmagnesium species. Quenching the Grignard reagent 9 with benzaldehyde produces the alcohol 10 in 90% yield (Scheme 2).

Scheme 2. Preparation of Polyfunctional Grignard Reagents Starting from Aryl or Heteroaryl Iodides
Usually, aromatic and heterocyclic bromides are much more reluctant to undergo this exchange reaction, and an efficient Br/Mg-exchange can only be realized, if a good directing group is present in the organic halide.\textsuperscript{15} Thus, in a first step, the functionalized aryl bromide 11 chelates the Grignard exchange reagent \textit{i}PrMgBr. This chelation leads to an intramolecular Br/Mg-exchange at -30 °C and produces the chelate-stabilized Grignard reagent 12 in excellent yield. Copper(I)-catalyzed allylation of 12 with allyl bromide affords the benzonitrile 13 in 80% yield.\textsuperscript{16} Also, such a chelate-effect helps in directing the exchange reaction. Hence, the dibromoimidazole 14 undergoes a fully regioselective exchange reaction, and only the appropriate bromide which may lead to the formation of a 5-membered ring chelate is exchanged to give the Grignard reagent 15. Quenching of 15 with ethyl cyanoformate produces the trisubstituted imidazole 16 in 48% yield.\textsuperscript{17} However, harsh conditions are required to perform a Br/Mg-exchange on the aryl ether 17. The presence of an additional bromine substituent is not sufficient to activate 17 towards an exchange at low temperatures and finally, the reaction has to be conducted at 40 °C. Nevertheless, after the addition of 10% of CuI, a smooth ring closure occurs furnishing the heterocyclic ring system 18 in 78% yield (Scheme 3).\textsuperscript{18}

![Scheme 3. Preparation of Functionalized Grignard Reagents Using a Br/Mg-Exchange](image)

This last example shows that catalyzing the Br/Mg-exchange would be highly desirable. Although Li(acac) cannot be used, since Grignard reagents react with the acetylacetonate moiety, the use of another lithium salt such as lithium chloride proves to give satisfactory results. Thus, using \textit{i}PrMgCl·LiCl\textsuperscript{10} as exchange reagent a fast exchange reaction can be performed with numerous functionalized aryl and heteroaryl bromides. The role of lithium chloride may be explained by postulating that it favors the
formation of the ate-species 19, which displays a higher nucleophilicity in the Br/Mg-exchange reaction. It should be noticed that the resulting Grignard reagent 20 is also complexed by LiCl and hence, displays a reactivity superior to standard Grignard reagents.10,19

\[
\text{Ar-Br + } i\text{PrMgCl\cdot LiCl} \xrightarrow{\text{fast}} \text{ArMgCl\cdot LiCl + } i\text{PrBr}
\]

\[
\text{ArMgCl\cdot LiCl} + i\text{PrMgCl\cdot LiCl}
\]

Scheme 4. \(i\text{PrMgCl\cdot LiCl}\) Undergoes a Fast Br/Mg-Exchange Reaction

Because of its high propensity to undergo the Br/Mg-exchange reaction, lower reaction temperatures can be chosen, resulting in excellent regioselectivities. Thus, the tribromobenzene 21 undergoes a fully selective Br/Mg-exchange leading to the Grignard reagent 22. Quenching of 22 with pivalaldehyde provides the alcohol 23 in 89% yield (Scheme 5).10 Interestingly, the introduction of a nitrogen atom in the ring, leading to the corresponding pyridine 24, changes the regioselectivity of the Br/Mg-exchange and a selective exchange reaction occurs at position 3.20 This regioselectivity switch may be explained by recognizing that 3-magnesiated pyridines possess the highest thermodynamic stability due to a type of anomeric effect (interaction of the \(\sigma\)(C-Mg) bond with the \(\sigma^*\)(C-N) bond). This exchange reaction can also be utilized to prepare other organometallic reagents like, for example, organocopper species. Thus, the reaction of 3,5-dibromopyridine (27) with \(i\text{PrMgCl\cdot LiCl}\) followed by CuCN·2LiCl produces the copper reagent 28 which undergoes a smooth iron(III)-catalyzed cross-coupling with aryl iodide 29 to furnish the polyfunctional pyridine 30 in 57% yield (Scheme 5).21

Scheme 5. Regio- and Chemoselective Preparation of Aryl- and Pyridylmagnesium Reagents
Also, the Br/Mg-exchange provides a convenient access to various arylmagnesium species such as 31. A solvent change from THF to a 4:1 mixture of dichloromethane and perfluorodecalin allows an electrophilic fluorination using (PhSO₂)₂NF (NFSI), which leads to the pyridine 32 in 65% yield. The regioselectivity of the Br/Mg-exchange can be directed by the position of the substituents. As a consequence, the presence of an aryl-substituent in position 2 of the pyridine ring 33 enhances the reactivity of the adjacent bromine on C3 towards a Br/Mg-exchange. After transmetalation of the corresponding magnesium reagent 34 with ZnCl₂ and subsequent Negishi cross-coupling, the expected 2,3-diarylated pyridine 35 is obtained in 88% yield (Scheme 6).²³

Interestingly, the presence of sterically hindered substituents in the neighbor position disfavors the exchange reaction due to steric effects, and the Br/Mg-exchange proceeds at the opposite site.²³

Scheme 6. Selective Exchanges on 3,5-Dibromopyridines

Scheme 7. Regioselective Br/Mg-Exchange Reaction
Thus, the treatment of the 2-trimethylsilylpyridine 36 with the sterically hindered arylmagnesium reagent 37 provides only the Grignard reagent 38. After Negishi cross-coupling, the expected arylated pyridine 39 is obtained in 60% yield.23 Similarly, the dibromothiophene 40 undergoes a fully selective exchange with the same exchange reagent (37), providing the magnesiated thiophene 41 with complete regioselectivity (Scheme 7).23

The I/Mg-exchange with iPrMgCl-LiCl or iPrMgCl is also used to prepare various boronic reagents24, using either a two-step procedure or a non-cryogenic preparation of arylboronic esters through an I/Mg-exchange with in situ quench.25 Thus, the diiodoquinoline 42 is converted to the corresponding Grignard reagent 43 with iPrMgCl. Treatment with the dioxaborolane 44 gives the boronic ester 45 in 81% yield.24 A very practical in situ procedure was then developed by Chavant, avoiding the use of cryogenic conditions. Hence, the treatment of a mixture of the iodobenzoate 8 with the dioxaborolane 46 followed by the addition of iPrMgCl-LiCl at 0 °C provides the expected boronic ester 47 in 77% yield (Scheme 8).25

Sensitive functionalities such as a triazene unit and an adjacent bromo group are readily tolerated in such exchange reactions. Thus, the aryltriazene 48 is smoothly converted to the corresponding Grignard compound 49, which by heating to 50 °C, undergoes a ring closure to furnish the carbazole 50 in 75% isolated yield.26 Also, a cyclic Grignard reagent 51 bearing a β-leaving group (e.g. bromide) can be prepared starting from 1,2-dibromocyclopentene 52. After borylation with triisopropylborate, the corresponding boronic ester 53 is obtained in 72% yield.27 Interestingly, the dibromonorbornadiene 54 is converted to the isopropyl-substituted Grignard reagent 55 by a cross-coupling reaction in the presence of 1% Li2CuCl4, introducing the isopropyl substituent in β-position. After quenching with DMF, the corresponding aldehyde 56 is furnished in 72% yield (Scheme 9).27
Scheme 9. Preparation of Grignard Reagents Bearing a Triazene or a β-Leaving Group

Due to the mild conditions used to perform the I/Mg-exchange with iPrMgCl-LiCl, magnesiated unsaturated silylated cyanohydrins, which serve as synthetic ketone or aldehyde equivalents of aromatic and heterocyclic magnesium derivatives such as 57 and 58, can readily be prepared. After quenching with electrophiles such as acid chlorides, highly functionalized aromatics bearing carbonyl groups like 59 and 60 are obtained (Scheme 10).

Scheme 10. Preparation of Grignard Reagents Bearing Silylated Cyanohydrins Serving as Ketone or Aldehyde Equivalents

Highly substituted pyridines are prepared by using iPrMgCl-LiCl. Similarly, the functionalization of uracil derivatives such as 61 allows the preparation of the reverse transcriptase inhibitor emivirine 62 in a
short sequence.\textsuperscript{30} Thus, the treatment of 61 with \textit{i}PrMgCl·LiCl leads to a selective Br/Mg-exchange. A LaCl\textsubscript{3}·2LiCl\textsuperscript{31}-catalyzed addition of acetone produces the tertiary alcohol 63 in 87% yield, which is converted to emivirine 62 in 5 steps. Similarly, the bromouracil 64 undergoes a clean Br/Mg-exchange with \textit{i}PrMgCl·LiCl. After a Cu(I)-catalyzed cross-coupling with a benzylic phosphate, the uracil derivative 65 is obtained in 81% yield. This uracil is converted in two steps to the antibiotic trimethoprim 66 in 52% overall yield starting from 64 (Scheme 11).\textsuperscript{32}

\begin{center}
\textbf{Scheme 11. Synthesis of Biologically Active Heterocycles Using \textit{i}PrMgCl·LiCl}
\end{center}

The functionalization of all positions of the purine scaffold is also achieved starting with the heterocyclic building block 67. In a few steps, this purine derivative is converted to the iodide 68. Treatment of the iodide 68 with \textit{i}PrMgCl in THF (-78 °C, 1 h) produces an intermediate Grignard reagent which reacts with a benzaldehyde derivative furnishing the alcohol 69 in 94% yield (Scheme 12).\textsuperscript{33}

\begin{center}
\textbf{Scheme 12. Functionalization of the Purine Skeleton at C2 Using \textit{i}PrMgCl·LiCl}
\end{center}

Interestingly, the use of \textit{i}PrMgCl·LiCl leads to various side reactions, and the best yield for this exchange reaction is obtained with the less reactive exchange reagent \textit{i}PrMgCl. The presence of a hydroxy
substituent in aromatic and heterocyclic systems does not hamper the performance of an I/Mg-exchange. In this context, the treatment of the diiodoquinoline 70 with MeMgCl-LiCl followed by the addition of iPrMgCl-LiCl at -30 °C produces the dianion intermediate 71, which can be allylated in the presence of CuCN-2LiCl to provide the expected allylation product 72. Notice that the regioselectivity of the I/Mg-exchange is reversed compared to the reaction of the corresponding tosylate 42 (Scheme 8 and Scheme 13).24,34

Scheme 13. Magnesiation of a Heterocyclic Ring Bearing a Hydroxyl Group

Because of the high chemoselectivity of the Br/Mg-exchange, this method has been used to prepare various benzo[b]thiophenes.35 The required precursors 73 are smoothly prepared from readily available 2-bromo-1-iodoarenes of type 74.

Scheme 14. Synthesis of Benzo[b]thiophenes

Thus, the I/Mg-exchange performed on 74 with iPrMgCl-LiCl provides, after transmetallation with ZnCl2, an organozinc reagent which readily reacts with S2Cl236 to furnish the diaryl disulfide 75 in excellent yield. Renewed addition of iPrMgCl-LiCl, this time at 25 °C, leads to a full Br/Mg-exchange within 4 h,
providing the Grignard reagent 76. Its treatment with 30% CuCN·2LiCl leads to an intramolecular carbocupration reaction furnishing, after 24 h, the cyclized magnesium reagent 77. Subsequent Cu-catalyzed acylation produces the 2,3-disubstituted benzo[b]thiophene 78 in 72% overall yield (Scheme 14).35

This method can be extended to the preparation of benzo[b]thieno[3,2-d]thiophenes such as 79. Thus, the treatment of the benzo[b] thiophene 80 with TMPMgCl·LiCl37,38 (TMP = 2,2,6,6-tetramethylpiperidyl) followed by the addition of CuCN·2LiCl and microwave irradiation at 75 °C for 3 h furnishes, after the addition of ethyl (2-bromomethyl)acrylate, the thienothiophene derivative 79 in 68% overall yield.35 The trimethylsilyl substituent at position 3 of these benzothiophene rings can be smoothly converted to an iodide by a short reaction of 81 with ICl producing the 3-iodobenzothiophene 82 which undergoes a fast I/Mg-exchange using iPrMgCl·LiCl at -78 °C. This exchange is compatible with the ethyl acrylate functionality present in 81. After a copper-catalyzed acylation, the 2,3-disubstituted benzothiophene 83 is obtained in 77% yield (Scheme 15).35

![Scheme 15: Transformation of Benzo[b]thiophenes](image)

Although, the batch preparation of Grignard reagents via I/Mg-exchange is satisfactory in many cases, a continuous preparation of arylmagnesium reagents using flow-techniques has been reported.39 A further extension can be achieved in the preparation of functionalized alkenylmagnesium derivatives.40 Thus, the treatment of the sensitive dienyl iodide 84 with iPrMgCl·LiCl furnishes the corresponding magnesium reagent 85. Transmetalation with ZnBr2 and palladium-catalyzed cross-coupling with the cyclohexenyl
bromide 86 provides the trienic compound 87 in 70% yield. Also, the functionalized alkenyl iodide 88 undergoes a stereoselective I/Mg-exchange at -40 °C within 2 h leading to the E-Grignard reagent 89. After a copper-catalyzed addition-elimination reaction and deprotection of the silylated cyanohydrin functionality, the 1,4-diketone 90 is obtained in 77% yield (Scheme 16).

![Scheme 16. Preparation of Functionalized Alkenylmagnesium Reagents](image)

Compared to other exchange reagents, the main advantages using iPrMgCl·LiCl consist in the mild conditions for performing the exchange as well as in the high functional group tolerance. This is well-illustrated in the case of the iodoalkenyl derivative 91 which undergoes a stereoselective I/Mg-exchange proceeding at -40 °C and therefore, tolerating the methyl ester group present in the intermediate Grignard reagent 92. After the addition of propionaldehyde, the expected E-allylic alcohol 93 is obtained in 82% yield; Scheme 17.

![Scheme 17. Stereoselective Preparation of an Alkenylmagnesium Reagent Bearing an Ester Functionality](image)

In cases where the electron-density of the aromatic ring is too high, the use of bis-secondary alkylmagnesium reagents such as sBu₂Mg·LiCl (94) proves to be advantageous. Thus, the treatment of the aryl bromide (95) with sBu₂Mg·LiCl leads to a complete exchange in THF at 25 °C within 2 h. Interestingly, the treatment of iPrMgCl·LiCl with dioxane generates in situ the bis-alkylmagnesium
derivative 96. Both reagents 94 and 96 are synthetically very useful. The resulting diarylmagnesium derivative 97 readily adds to benzaldehyde and produces the expected alcohol 98 in 90% yield (Scheme 18).42

The presence of LiCl in 94 and 96 was found to be essential for the enhanced activity of dialkylmagnesium species. In the absence of LiCl, only a moderate activity of R₂Mg (R = iPr or sBu) for performing Br/Mg-exchanges was observed. It was shown that the use of related bis-Grignard reagents such as 99 allowed the performance of I/Mg-exchanges at primary centers. The driving force of this reaction is the formation of cyclopentane during the exchange reaction. Thus, the addition of 99 (1.1 equiv) to the iodoketal 100 produces the Grignard reagent 101 which is readily allylated furnishing 102 in 72% yield.43 The performance of a Br/Mg-exchange at cyclopropanic systems is readily achieved with iPrMgCl·LiCl in a THF:dioxane mixture (in situ generation of iPr₂Mg·2LiCl (96)). Thus, the cyclopropyl bromide 103, containing a pseudo-asymmetric center on the carbon atom bearing the bromide,44 undergoes a complete Br/Mg-exchange to furnish the Grignard reagent 104. This magnesium species leads, after quenching with DMF, to the aldehyde 105 in 71% yield (Scheme 19).45
As mentioned before, the presence of LiCl in THF-solutions of Grignard reagents enhances their reactivity. A further reactivity enhancement can be achieved by chelating additives such as N,N,N′,N′-tetramethylethylenediamine (TMEDA) which reduce the degree of aggregation of the Grignard species as shown by Nakamura. Thus, the pyridylmagnesium derivative 106 is formed from the corresponding bromide 107 by adding iPrMgCl·LiCl. In the presence of TMEDA (6 equiv), this Grignard reagent reacts with chloramines to produce the corresponding amine 108 in 78% yield (Scheme 20).

Oxidative couplings have been performed by using iPrMgCl in the presence of TMP-H (2,2,6,6-tetramethylpiperidine) using 5% CoCl₂ as catalyst and oxygen (1 atm) as oxidant. Benzothiophene 109 smoothly dimerizes under these conditions leading to the dimer 110 in 85% yield. Interestingly, iPrMgCl·LiCl can also be successfully used to generate aziridinylmagnesium derivatives using a sulfoxide/magnesium exchange. Thus, the treatment of the sulfoxide 111 with iPrMgCl (without LiCl) produces an intermediate magnesium reagent which undergoes a smooth Pd-catalyzed cross-coupling leading to the expected arylated aziridine 112 in 80% yield (Scheme 21).

This sulfoxide exchange can be applied to functionalize aromatics in a 1,2-fashion. Thus, the treatment of an anisyl aryl sulfoxide such as 113 with TMPMgCl·LiCl (-30 °C, 20 min) leads to an ortho-magnesiation of the sulfoxide. After transmetalation using ZnCl₂ and Pd-catalyzed cross-coupling with 4-fluoro-1-iodobenzene, the biphenyl sulfoxide 114 is obtained in 71% yield. Addition of iPrMgCl·LiCl to 114 at -50 °C leads to a very fast sulfoxide/magnesium-exchange. This newly produced magnesium reagent adds smoothly to the benzaldehyde 115 providing the alcohol 116 in 88% yield.
3. CONCLUSION

In conclusion, we have shown that the use of iPrMgCl·LiCl considerably extends the scope of the halogen/magnesium-exchange reactions. These exchanges occur at significantly lower temperatures and therefore tolerate a broader range of functional groups. Especially the applications in the synthesis of new heterocyclic ring systems on various polyfunctional heterocyclic scaffolds have been shown to be interesting.

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