HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 827 - 844. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 6th July, 2013, Accepted, 24th September, 2013, Published online, 1st October, 2013
DOI: 10.3987/REV-13-SR(S)4

THE HALOGEN/MAGNESIUM-EXCHANGE USING *i*PrMgCl·LiCl AND RELATED EXCHANGE REAGENTS

Nadja M. Barl, Veronika Werner, Christoph Sämann, and Paul Knochel*

Ludwig-Maximilians-University Munich, Butenandtstr. 5-13, 81377 Munich, Germany

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 iodides, 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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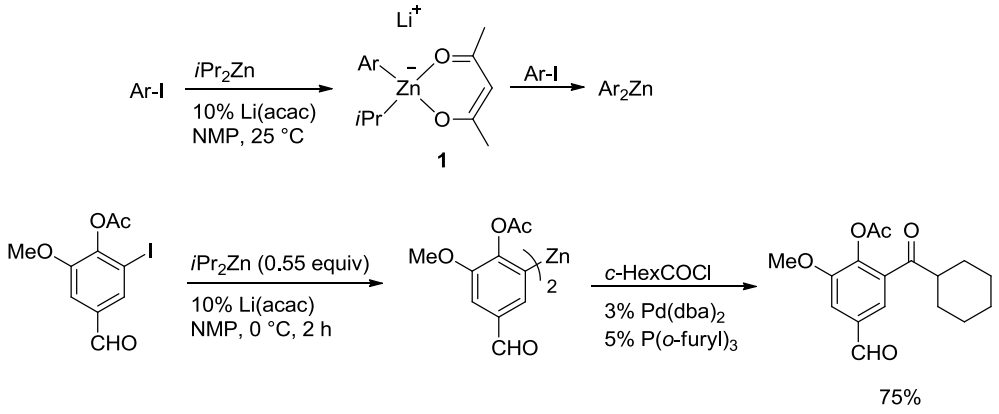
1. INTRODUCTION

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.[3] To the best of our knowledge, the halogen/magnesium-exchange was first reported by Charles Prévost in 1931.[4] 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.[5,6] Also, Furukawa and Quéguiner applied this method to the preparation of heterocyclic organomagnesium reagents.[6b,7] 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.[8] 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.[9] 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).



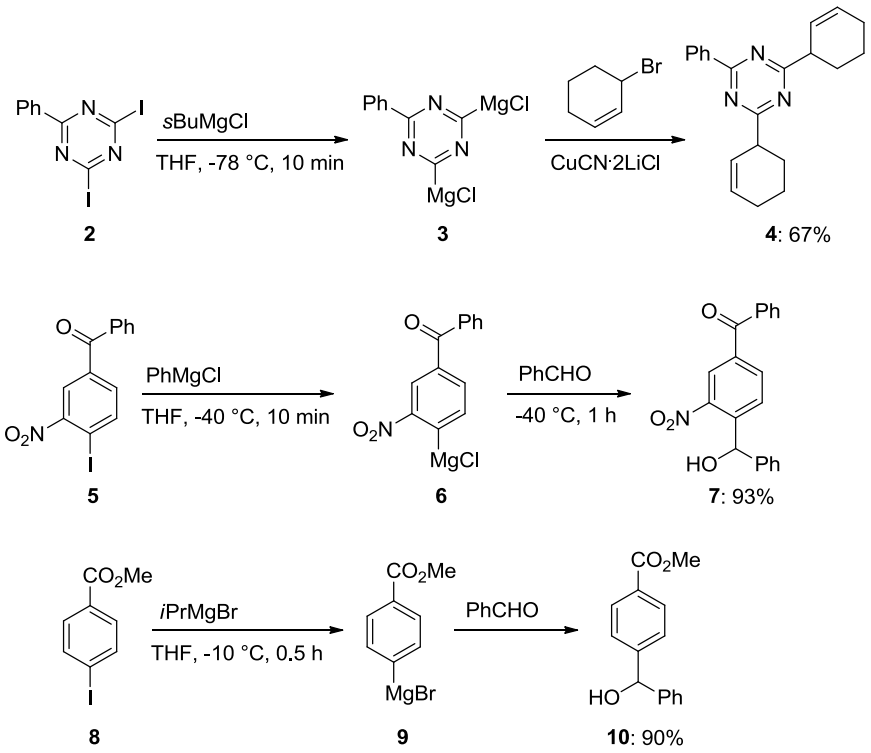
Scheme 1. Iodine/Zinc-Exchange Catalyzed by 10% Li(acac)

This catalysis could be extended to the halogen/magnesium-exchange reaction using *i*PrMgCl·LiCl and thus, allowed to perform this exchange with moderately reactive aryl and heteroaryl bromides.[10] In this review, we will cover the recent developments of the halogen/magnesium-exchange reaction using mainly *i*PrMgCl·LiCl and related reagents.

2. THE CATALYZED HALOGEN/MAGNESIUM-EXCHANGE USING *i*PrMgCl·LiCl AND RELATED EXCHANGE REAGENTS

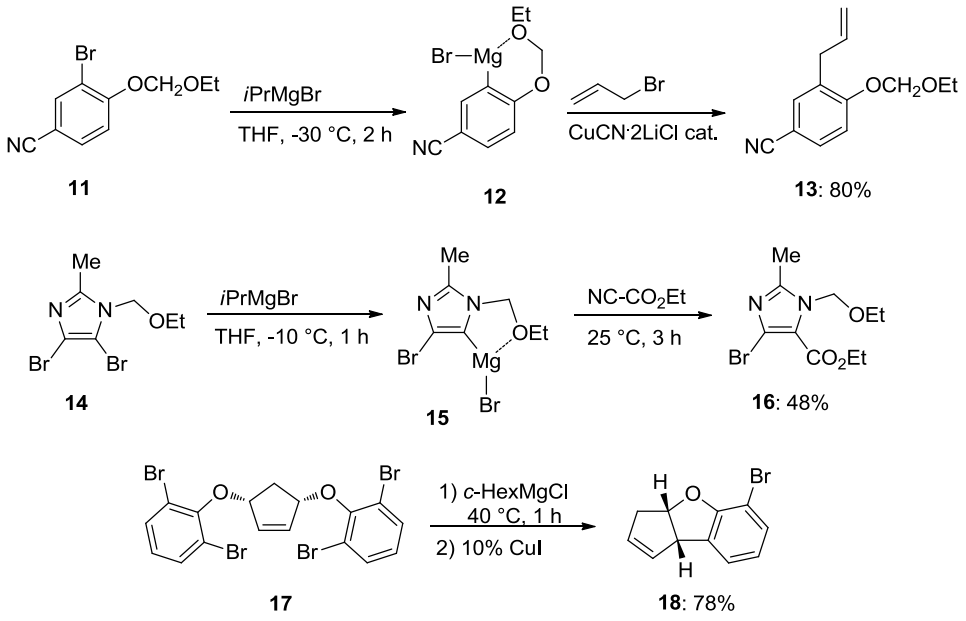
The high polarity of the carbon-lithium bond makes the I/Li-exchange reaction a very fast process.[11] Similarly, the Br/Li-exchange is usually a fast reaction, as well, being mostly completed within few

minutes at -78 °C.[8] 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.[12] 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 *s*BuMgCl 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.[13] 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.[14] 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 *i*PrMgBr 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

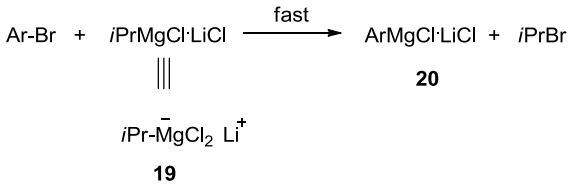
Usually, aromatic and heterocyclic bromides are much more reluctant to undergo this exchange reaction, and an efficient Br/Mg-exchange can only be realized, if a good directing group is present in the organic halide.[15] Thus, in a first step, the functionalized aryl bromide **11** chelates the Grignard exchange reagent *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.[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.[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).[18]



Scheme 3. Preparation of Functionalized Grignard Reagents Using a Br/Mg-Exchange

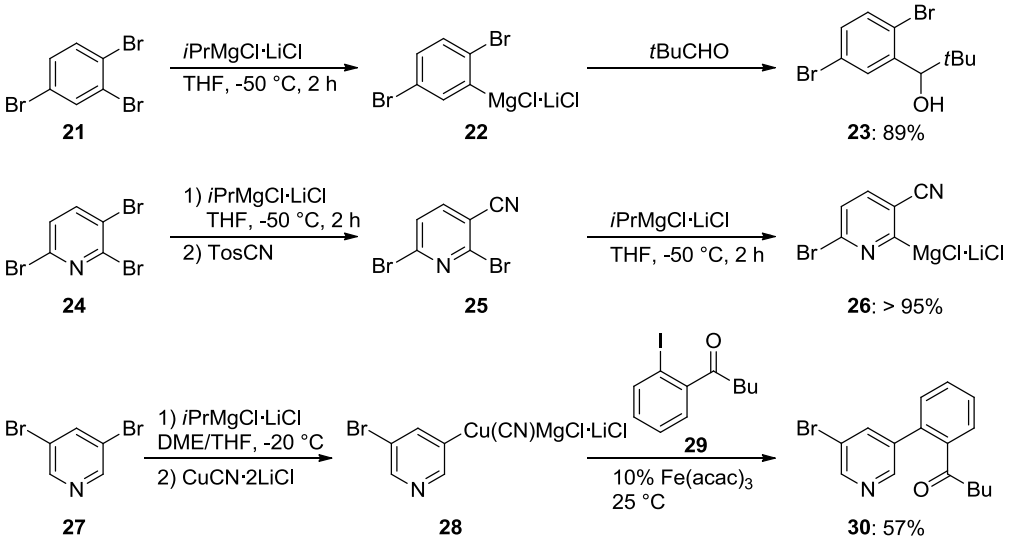
This last example shows that catalyzing the Br/Mg-exchange would be highly desirable. Although Li(acac) cannot be used, since Grignard reagents react with the acetylacetonate moiety, the use of another lithium salt such as lithium chloride proves to give satisfactory results. Thus, using *i*PrMgCl·LiCl[10] 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]



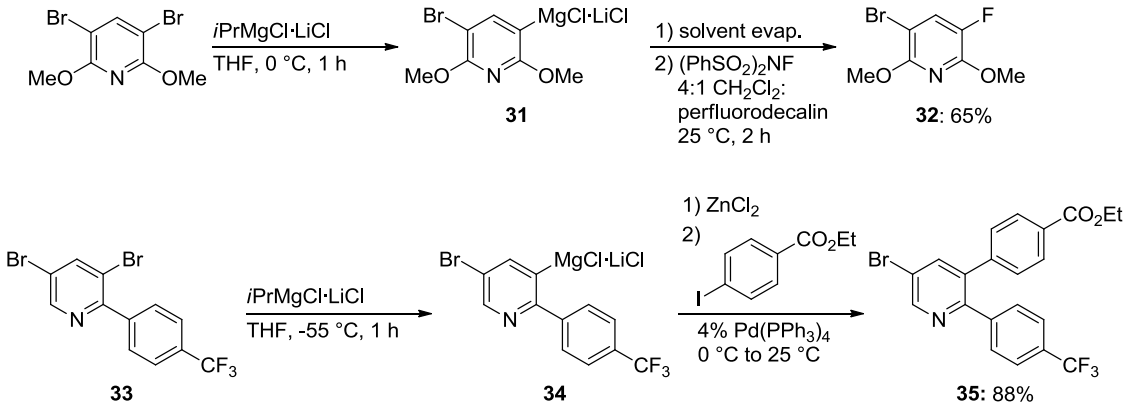
Scheme 4. *i*PrMgCl·LiCl Undergoes a Fast Br/Mg-Exchange Reaction

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 σ(C-Mg) bond with the σ*(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-dibrompyridine (**27**) with *i*PrMgCl·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]



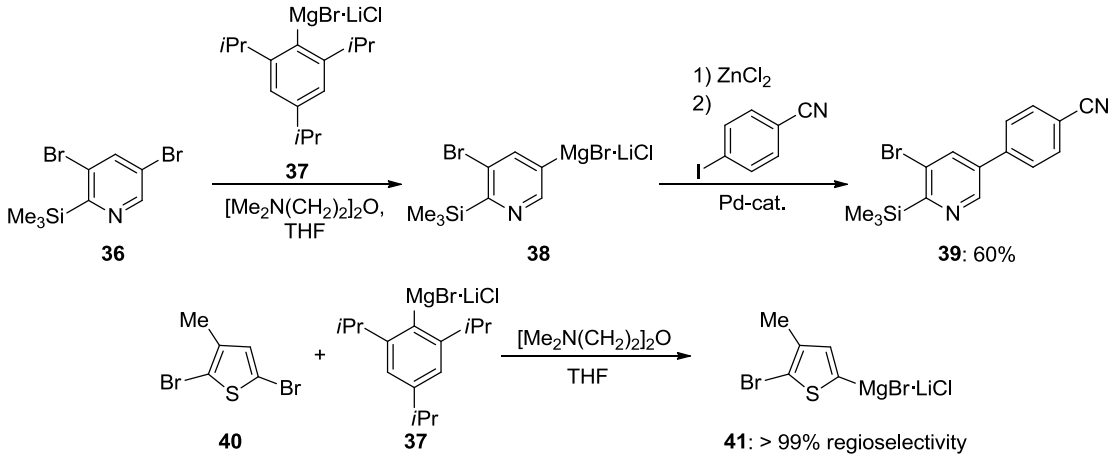
Scheme 5. Regio- and Chemoselective Preparation of Aryl- and Pyridylmagnesium Reagents

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 $(PhSO_2)_2NF$ (NFSI), which leads to the pyridine **32** in 65% yield.[22] 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 $ZnCl_2$ and subsequent Negishi cross-coupling, the expected 2,3-diarylated pyridine **35** is obtained in 88% yield (Scheme 6).[23]



Scheme 6. Selective Exchanges on 3,5-Dibromopyridines

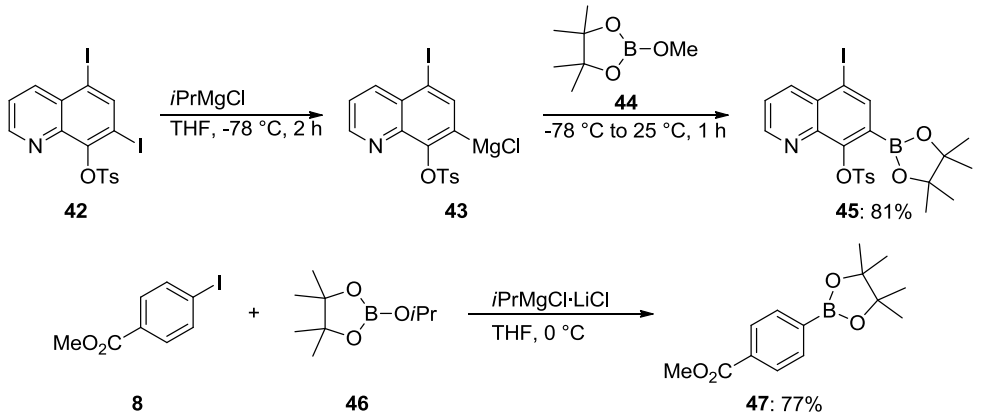
Interestingly, the presence of sterically hindered substituents in the neighbor position disfavors the exchange reaction due to steric effects, and the Br/Mg-exchange proceeds at the opposite site.[23]



Scheme 7. Regioselective Br/Mg-Exchange Reaction

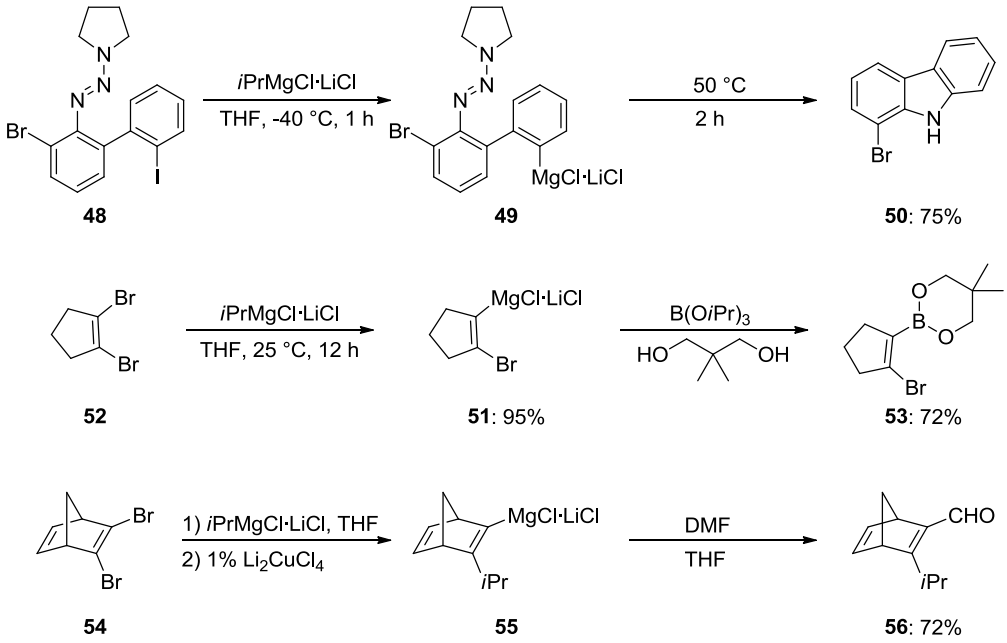
Thus, the treatment of the 2-trimethylsilylpyridine **36** with the sterically hindered arylmagnesium reagent **37** provides only the Grignard reagent **38**. After Negishi cross-coupling, the expected arylated pyridine **39** is obtained in 60% yield.[23] Similarly, the dibromothiophene **40** undergoes 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 *i*PrMgCl·LiCl or *i*PrMgCl is also used to prepare various boronic reagents,[24] 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 *i*PrMgCl. 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 *i*PrMgCl·LiCl at 0 °C provides the expected boronic ester **47** in 77% yield (Scheme 8).[25]



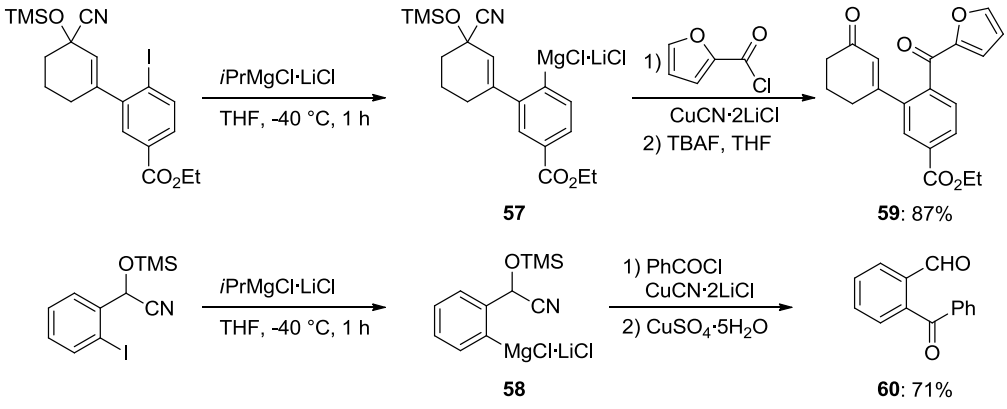
Scheme 8. Preparation of Boronic Esters *via* an I/Mg-Exchange Using *i*PrMgCl·LiCl

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% Li_2CuCl_4, 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

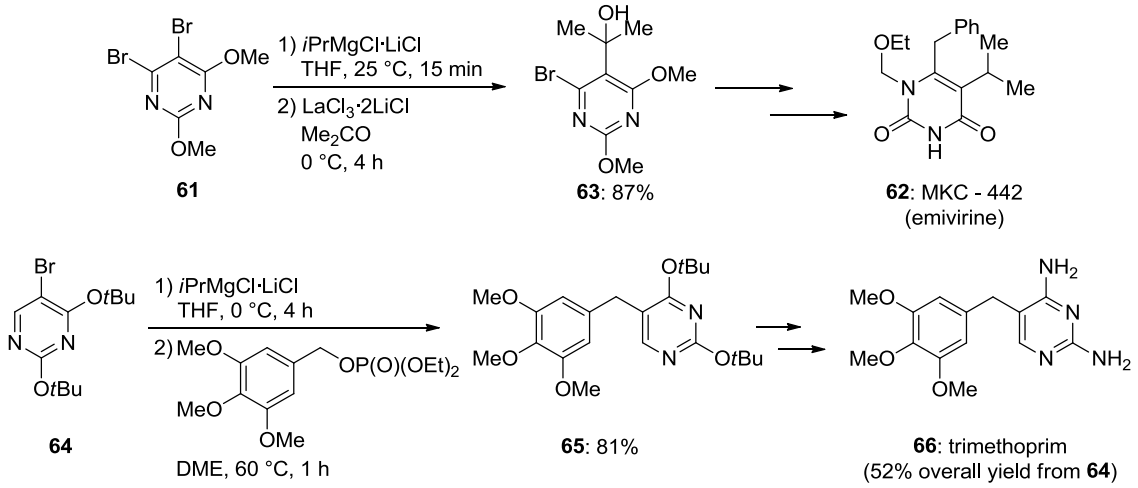
Due to the mild conditions used to perform the I/Mg-exchange with *i*PrMgCl·LiCl, magnesiated unsaturated silylated cyanohydrins, which serve as synthetic ketone or aldehyde equivalents of aromatic and heterocyclic magnesium derivatives such as **57** and **58**, can readily be prepared. After quenching with electrophiles such as acid chlorides, highly functionalized aromatics bearing carbonyl groups like **59** and **60** are obtained (Scheme 10).[28]



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

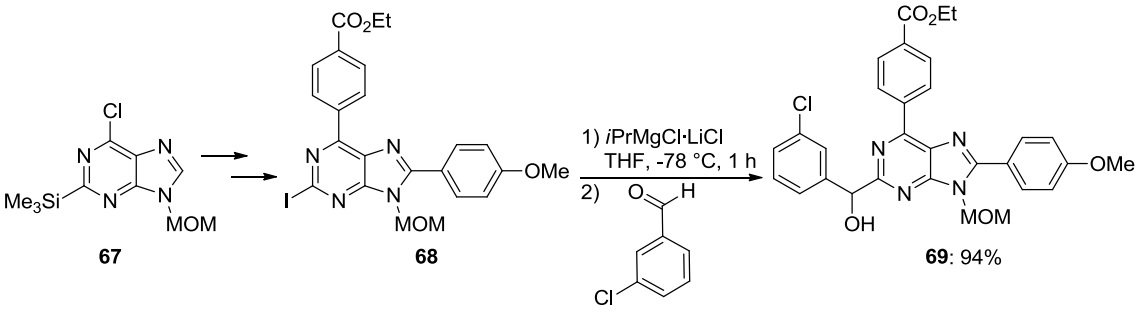
Highly substituted pyridines are prepared by using *i*PrMgCl·LiCl.[29] Similarly, the functionalization of uracil derivatives such as **61** allows the preparation of the reverse transcriptase inhibitor emivirine **62** in a

short sequence.[30] Thus, the treatment of **61** with *i*PrMgCl·LiCl leads to a selective Br/Mg-exchange. A $LaCl_3 \cdot 2LiCl$[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 *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).[32]



Scheme 11. Synthesis of Biologically Active Heterocycles Using *i*PrMgCl·LiCl

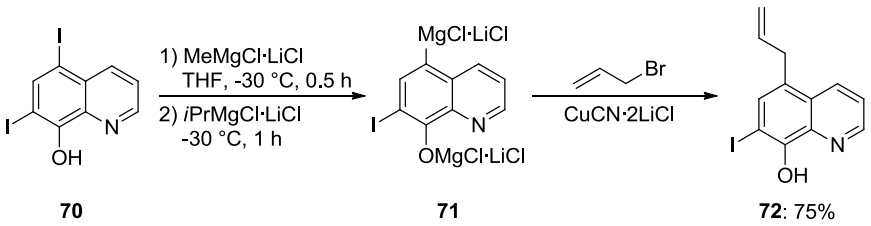
The functionalization of all positions of the purine scaffold is also achieved starting with the heterocyclic building block **67**. In a few steps, this purine derivative is converted to the iodide **68**. Treatment of the iodide **68** with *i*PrMgCl in THF (-78 °C, 1 h) produces an intermediate Grignard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



Scheme 12. Functionalization of the Purine Skeleton at C2 Using *i*PrMgCl·LiCl

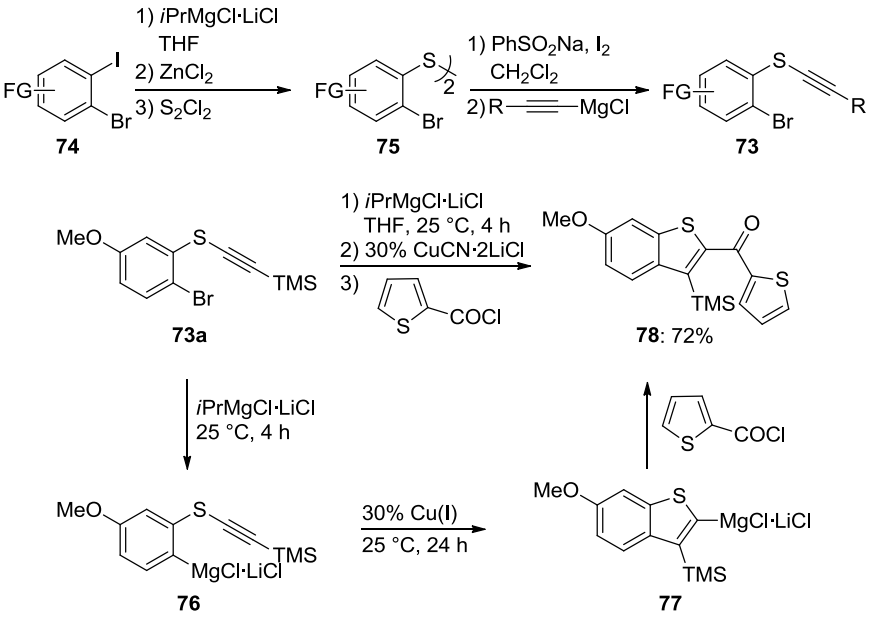
Interestingly, the use of *i*PrMgCl·LiCl leads to various side reactions, and the best yield for this exchange reaction is obtained with the less reactive exchange reagent *i*PrMgCl. The presence of a hydroxy

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 *i*PrMgCl·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**.

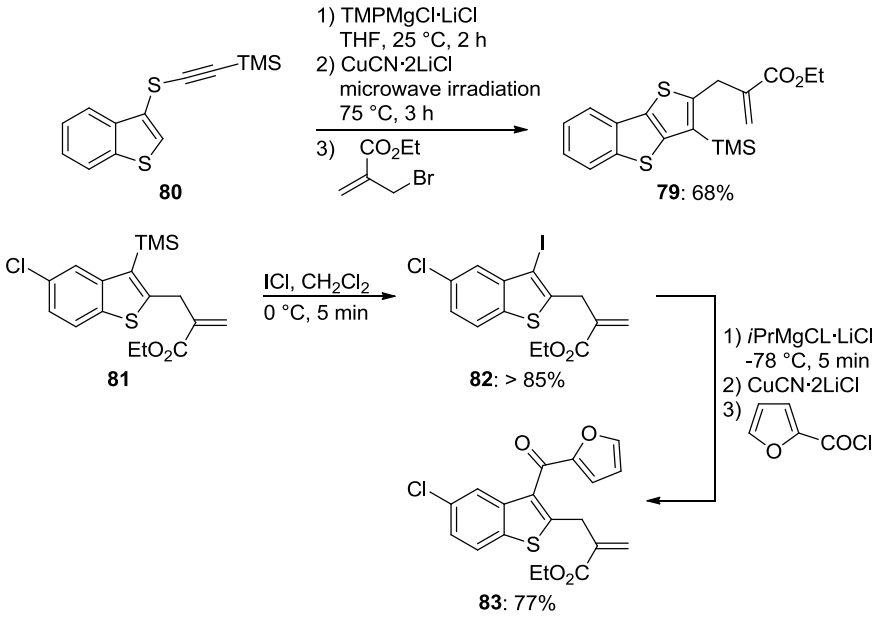


Scheme 14. Synthesis of Benzo[*b*]thiophenes

Thus, the I/Mg-exchange performed on **74** with *i*PrMgCl·LiCl provides, after transmetallation with $ZnCl_2$, an organozinc reagent which readily reacts with S_2Cl_2[36] to furnish the diaryl disulfide **75** in excellent yield. Renewed addition of *i*PrMgCl·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]

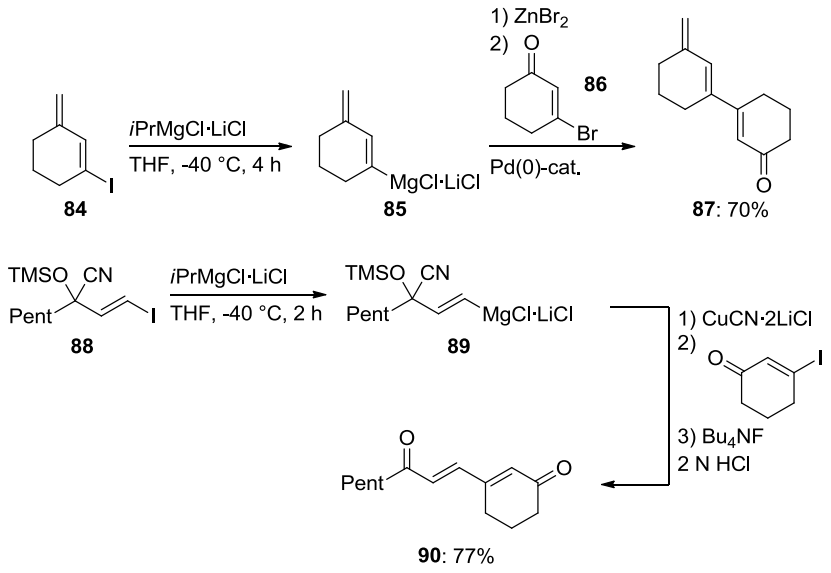
This method can be extended to the preparation of benzo[*b*]thieno[3,2-*d*]thiophenes such as **79**. Thus, the treatment of the benzo[*b*]thiophene **80** with TMPMgCl·LiCl[37,38] (TMP = 2,2,6,6-tetramethylpiperidyl) followed by the addition of CuCN·2LiCl and microwave irradiation at 75 °C for 3 h furnishes, 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 *i*PrMgCl·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

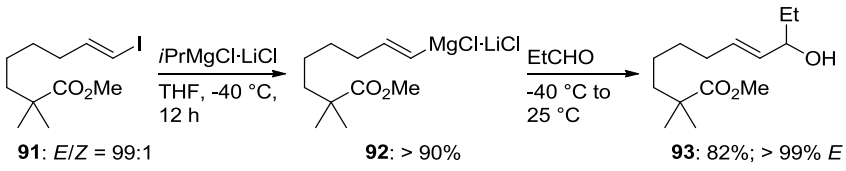
Although, the batch preparation of Grignard reagents via I/Mg-exchange is satisfactory in many cases, a continuous preparation of arylmagnesium reagents using flow-techniques has been reported.[39] A further extension can be achieved in the preparation of functionalized alkenylmagnesium derivatives.[40] Thus, the treatment of the sensitive dienyl iodide **84** with *i*PrMgCl·LiCl furnishes the corresponding magnesium reagent **85**. Transmetalation with $ZnBr_2$ and palladium-catalyzed cross-coupling with the cyclohexenyl

bromide **86** provides the trienic compound **87** in 70% yield.[40] 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-diketenone **90** is obtained in 77% yield (Scheme 16).[41]



Scheme 16. Preparation of Functionalized Alkenylmagnesium Reagents

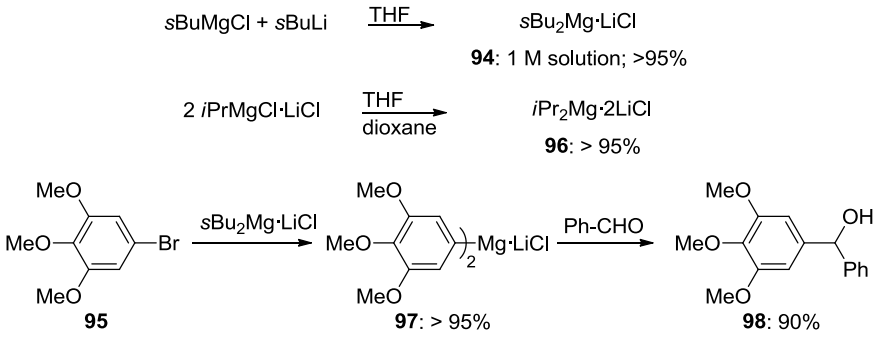
Compared to other exchange reagents, the main advantages using *i*PrMgCl·LiCl consist in the mild conditions for performing the exchange as well as in the high functional group tolerance. This is well-illustrated in the case of the iodoalkenyl derivative **91** which undergoes a stereoselective I/Mg-exchange 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. [41]



Scheme 17. Stereoselective Preparation of an Alkenylmagnesium Reagent Bearing an Ester Functionality

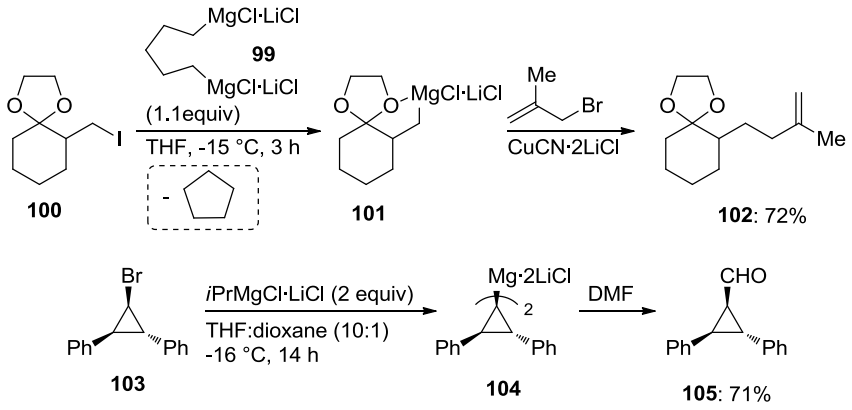
In cases where the electron-density of the aromatic ring is too high, the use of *bis*-secondary alkylmagnesium reagents such as *s*Bu_2Mg·LiCl (**94**) proves to be advantageous. Thus, the treatment of the aryl bromide (**95**) with *s*Bu_2Mg·LiCl leads to a complete exchange in THF at 25 °C within 2 h. Interestingly, the treatment of *i*PrMgCl·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]



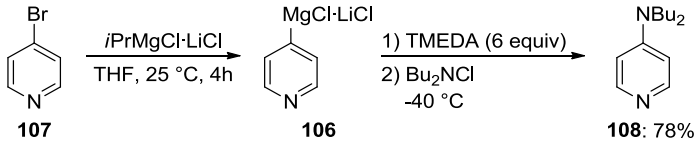
Scheme 18. Use of $R_2Mg \cdot n$LiCl as Exchange Reagent for Electron-Rich Aromatics

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 R_2Mg (R = *i*Pr or *s*Bu) 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 *i*PrMgCl·LiCl in a THF:dioxane mixture (in situ generation of $iPr_2Mg \cdot 2$LiCl (**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]



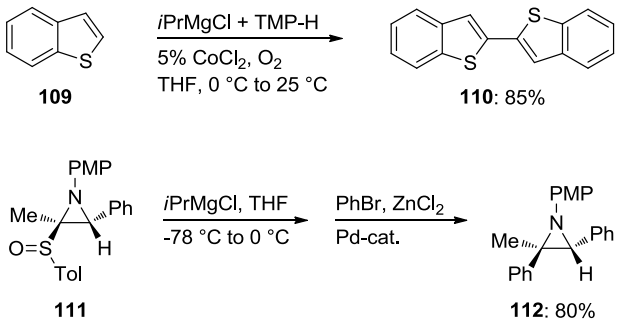
Scheme 19. Halogen/Magnesium-Exchanges at C(sp3)-Centers

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.[46] Thus, the pyridylmagnesium derivative **106** is formed from the corresponding bromide **107** by adding *i*PrMgCl·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).[46]



Scheme 20. Amination of Grignard Reagents Activated by TMEDA

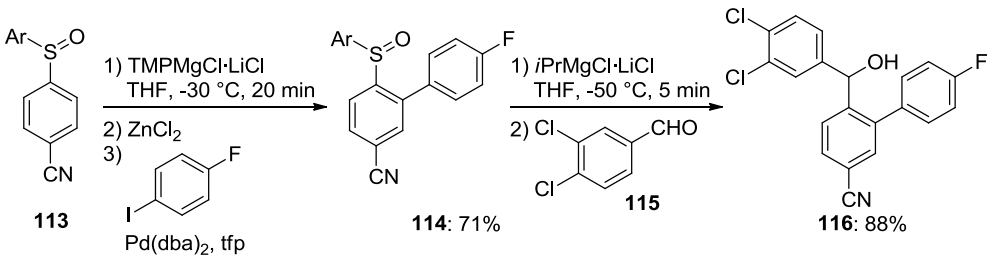
Oxidative couplings have been performed by using *i*PrMgCl in the presence of TMP-H (2,2,6,6-tetramethylpiperidine) using 5% $CoCl_2$ as catalyst and oxygen (1 atm) as oxidant. Benzothiophene **109** smoothly dimerizes under these conditions leading to the dimer **110** in 85% yield.[47] Interestingly, *i*PrMgCl·LiCl can also be successfully used to generate aziridinylmagnesium derivatives[48] using a sulfoxide/magnesium exchange.[49] Thus, the treatment of the sulfoxide **111** with *i*PrMgCl (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).[48]



Scheme 21. Further Magnesiation Reactions Initiated by *i*PrMgCl

This sulfoxide exchange can be applied to functionalize aromatics in a 1,2-fashion.[50] 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 $ZnCl_2$ and Pd-catalyzed cross-coupling with 4-fluoro-1-iodobenzene, the biphenyl sulfoxide **114** is obtained in 71% yield. Addition of *i*PrMgCl·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

(Scheme 22).[51]



Scheme 22. Functionalization of Aromatics in a 1,2-Fashion *via* Sulfoxide/Magnesium-Exchange

3. CONCLUSION

In conclusion, we have shown that the use of *i*PrMgCl·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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Nadja Barl was born in Munich (Germany) in 1986. She completed her undergraduate studies at the Ludwig-Maximilians-Universität in Munich (2005–2011). In 2010 she joined Prof. Knochel for her master thesis and worked on the synthesis and the full-functionalization of the pteridine scaffold. She started her PhD in the same group in 2011. Her work is focused on the synthesis and full-functionalization of azaindoles *via* directed selective metalation, metal/halogen- and sulfoxide/magnesium-exchange. Furthermore, her research is concentrated on the preparation and the reactions of heterobenzylic zinc reagents.

Veronika Werner was born in Munich (Germany) in 1985. After undergraduate studies at the Ludwig-Maximilians-Universität in Munich (2005–2011), she joined Prof. Knochel in 2010 for her master thesis and worked on the synthesis of heterocycle-based *bis*-boronic acids as building blocks for organic materials. She started her PhD in the same group in 2011. Her work is concentrated on the regioselective functionalization of (hetero)arenes *via* direct metalation, as well as the preparation and reaction of organoboron and organomagnesium reagents.

Christoph Sämann was born in Hardheim/Odenwald (Germany) in 1986. He completed his undergraduate studies at the Ruprecht-Karls-Universität in Heidelberg (2005–2010) with the diploma thesis in the group of Prof. Gade working on iridium complexes for oxidation catalysis. In 2010 he started his PhD in the group of Prof. Knochel at the Ludwig-Maximilians-Universität in Munich. His work is focused on the selective synthesis of (hetero)aromatic organometallic reagents through selective metalation, metal/halogen-exchange, -insertion or transmetalation reactions and their subsequent functionalization. Furthermore, he is working on adamantylzinc reagents and on the full functionalization of the imidazole scaffold.

Paul Knochel was born in 1955 in Strasbourg (France). He completed his undergraduate studies at the University of Strasbourg and his PhD at the ETH Zurich with Prof. D. Seebach (1982). He spent 4 years in the group of Prof. J.-F. Normant (Paris) and 1 year with Prof. M. F. Semmelhack (Princeton) as a postdoctoral researcher. After professorships at the University of Michigan (Ann Arbor) and the Philipps-Universität (Marburg), he moved to the Ludwig-Maximilians-Universität (Munich) in 1999. His research interests include the development of new synthetic methods with organometallic reagents, new asymmetric catalysts, and natural product synthesis.