Functionalized magnesium organometallics as versatile intermediates for the synthesis of polyfunctional heterocycles

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In the last few years, we have demonstrated that the halogen/magnesium-exchange reaction is a unique method for preparing a variety of new functionalized aryl, alkenyl, heteroaryl magnesium compounds which has considerably extended the range of functionalized Grignard reagents available for synthetic purposes. A variety of functional groups such as an ester, nitrile, iodide, imine and even sensitive groups like nitro, hydroxyl and boronic ester can be tolerated in these organomagnesium compounds. We wish to describe the application of this halogen/magnesium-exchange reaction for the preparation of a broad range of five- and six-membered functionalized heteroaryl magnesium compounds and their reactions with various electrophiles providing a new entry to a range of polyfunctional heterocycles such as thiophene, furan, pyrrole, imidazole, thiazole, antipyrine, pyridine, quinoline and uracil derivatives.

1. Introduction

The synthesis of polyfunctionalized heterocyclic compounds is of considerable importance in many research areas: natural product synthesis,[1] drug design,[2] molecular recognition[3] and preparation of new materials with defined properties.[4] Although directed metalation[5] or selective Br/Li-exchange[6] have provided very selective methods for the preparation of a wide range of lithiated heterocycles, the high polarity of the carbon–lithium bond precludes the presence of sensitive functional groups such as ester or cyano groups in these lithium organometallics due to their too high reactivity. Besides, these reactions often require low temperatures not easy to realize on an industrial scale. On the other hand, the more covalent character of the carbon–magnesium bond

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tolerates the presence of more functional groups. The synthesis of these polyfunctional reagents is however a problem, since the insertion of magnesium metal into aryl or heteroaryl iodides bearing electron-withdrawing groups is inhibited or hampered by the presence of these functionalities.[7] Recently, we have shown that the halogen/magnesium-exchange reaction is a unique method for the preparation of a variety of new functionalized aryl, alkenyl and heteroaryl magnesium compounds which has considerably extended the range of functionalized Grignard reagents available for synthetic purposes.[8] The halogen/metal-exchange proceeds under mild conditions so that various sensitive functional groups such as an ester, nitrile or an amide function are tolerated during the organomagnesium reagent formation. These functionalized organometallics have an excellent reactivity towards many electrophiles and they readily undergo transmetalation to provide a wide variety of organometallic reagents which has considerably enhanced the scope of these reagents for performing cross-coupling reactions. The halogen/magnesium-exchange is an attractive method for the generation of positionally stable functionalized heteroarylmagnesium compounds. Thus, it is possible to metalate the ring positions of heteroaromatic systems, which are sometimes not accessible by direct metalation. In the present review, we wish to report applications of halogen/magnesium-exchange for the synthesis of a wide range of functionalized heteroaryl and arylmagnesium compounds and their further reactions providing an entry to numerous polyfunctional five- and six-membered heterocycles that are otherwise difficult to prepare.

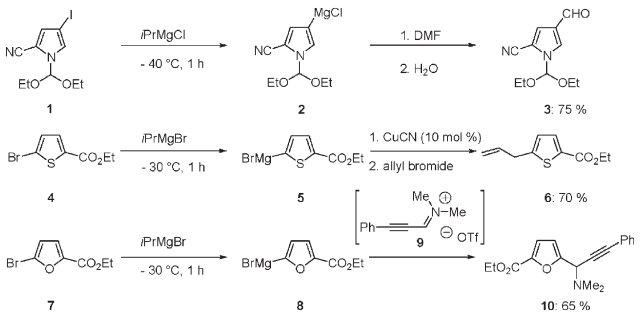
2. Synthesis of polyfunctional heterocycles using functionalized heteroaryl magnesium compounds

A variety of functionalized heteroarylmagnesium compounds bearing electron-withdrawing groups can be readily prepared by using an I/Mg- or Br/Mg-exchange between −30 °C and −20 °C within a few hours.[8] The electronic nature of the heterocycle influences the halogen/magnesium-exchange rate: electron-poor heterocycles react faster and electron-withdrawing substituents strongly accelerate the exchange rate.

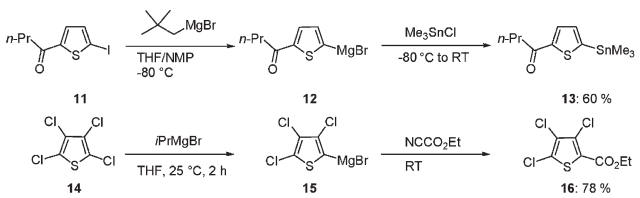
2.1 Five-membered heterocycles

Thus, the protected iodopyrrole **1** undergoes an I/Mg-exchange at −40 °C within 1 h leading to a 3-magnesiated pyrrole **2** which reacts with DMF to furnish the 3-formylpyrrole **3** in 75% yield (Scheme 1).[9] Similarly the bromothiophene **4** and the furan **7** bearing an electron-withdrawing ester function undergo an exchange, giving the magnesiated species **5** and **8**. Reaction of **5** with allyl bromide in the presence of a copper(I)-catalyst affords the 2-allylated thiophene **6** in 70% yield,[10,11] whereas the furylmagnesium compound **8** adds to the immonium salt **9** (generated from the corresponding alkynyl aminal in the presence of Tf_2O) and provides the furan **10** bearing a propargylic amine functionality (Scheme 1).[12]

By tuning the reaction conditions, the preparation of a ketone containing a heteroarylmagnesium species such as **12** can also be achieved (Scheme 2).[13] To avoid side reactions, a



Scheme 1 Preparation of five-membered heteroarylmagnesium compounds using halogen/Mg-exchange.

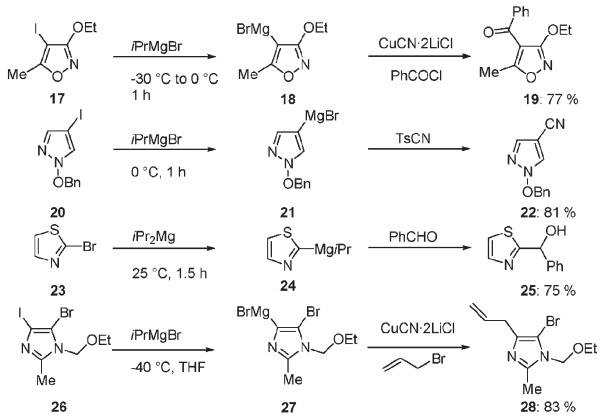


Scheme 2 Preparation of five-membered functionalized organomagnesium compounds by halogen/Mg-exchange.

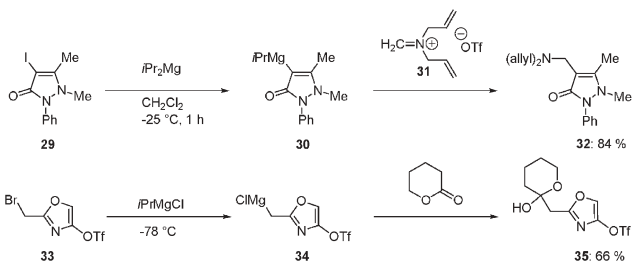
sterically hindered but still reactive Grignard reagent such as neopentylmagnesium bromide (NpMgBr) together with *N*-methylpyrrolidinone (NMP) as polar cosolvent, are the reaction conditions of choice. The Grignard reagent **12** reacts with chlorotrimethylstannane to give 2-thienylstannane **13** in 60% yield. Similarly the presence of several electron-withdrawing groups such as in tetrachlorothiophene **14** allows the performance of a Cl/Mg-exchange leading to the desired organomagnesium compound **15** which reacts with typical electrophiles such as ethyl cyanoformate yielding the trichlorothiophene-2-carboxylate (**16**) in 78% yield (Scheme 2).[11]

Functionalized Grignard reagents derived from 1,2- and 1,3-azoles can also be prepared either by I/Mg- or Br/Mg-exchanges (Scheme 3). Thus, 4-iodo-3-ethoxy-5-methylisoxazole (**17**) is efficiently converted into the Grignard reagent **18** which reacts smoothly with benzoyl chloride in the presence of a Cu(I)-catalyst affording the highly functionalized 4-benzoylisoxazole **19** in 77% yield.[14] Similarly, the positionally stable 4-magnesiated pyrazole **21** is readily generated from the 4-iodopyrazole **20** at 0 °C and could be converted to 4-cyanopyrazole **22** in 81% yield by reaction with tosyl cyanide (Scheme 3).[15] The unfunctionalized 2-bromothiazole (**23**) undergoes a Br/Mg-exchange at room temperature to give 2-magnesiated thiazole **24** which on addition of benzaldehyde gives the carbinol **25** in 75% yield.[11] A selective I/Mg-exchange of 5-bromo-4-iodoimidazole **26** similarly provides the 4-magnesiated imidazole **27** which on allylation affords the tetrasubstituted imidazole **28** in 83% yield (Scheme 3).[11,16]

Antipyrine derivatives have analgesic properties which makes their preparation of pharmaceutical interest. A smooth exchange occurs with 4-iodo-3-pyrazolin-5-one **29** leading to 4-magnesiated antipyrine **30** which has been trapped by the immonium salt **31**,[17] resulting in the



Scheme 3 Preparation of heteroarylmagnesium compounds from azoles.



Scheme 4 Preparation of functionalized magnesium species from antipyrine and oxazole by halogen/Mg-exchange.

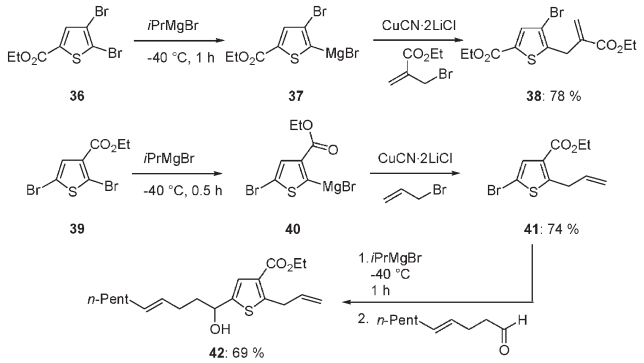
formation of 4-aminomethylated antipyrine **32** in 84% yield (Scheme 4).[11,16]

A sensitive heterocyclic 'benzylic' magnesium species **34** is readily generated by a Br/Mg-exchange from bromomethylisoxazole **33** at −78 °C in the presence of δ-valerolactone in order to minimize self condensation products leading to the hemiketal **35** in 66% yield (Scheme 4).[18] The reaction has been used to prepare an advanced intermediate in the total synthesis of (+)-phorboxazole.[18]

2.2 Selective halogen/magnesium-exchange in polyhalogenated five-membered heterocycles

Polyhalogenated heterocycles usually undergo a single regio- and chemo-selective halogen/magnesium-exchange, since after the first magnesiation, the electron density of the heterocycle increases to such an extent that the subsequent second exchange is very slow. This very general behaviour leads to highly chemoselective I/Mg- or Br/Mg-exchange reactions.[8,10,11]

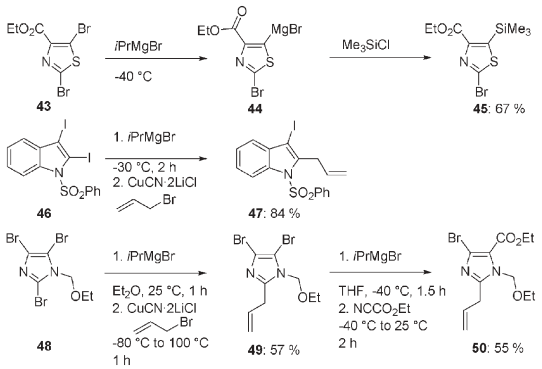
The presence of chelating groups in polyhalogenated heterocycles also influences the regioselectivity of I/Mg- and Br/Mg-exchange reactions.[10,11] Thus, an unsymmetrically substituted 2,3-dibromothiophene such as **36** undergoes regioselective exchange only at the 2-position yielding after allylation the highly functionalized thiophene **38** in 78% yield (Scheme 5).[11] On the other hand, the 2,5-dibromothiophene-3-carboxylate **39** undergoes a selective Br/Mg-exchange at the 2-position owing to the chelating effect of ethoxycarbonyl group leaving the bromine at C-5 unaffected.



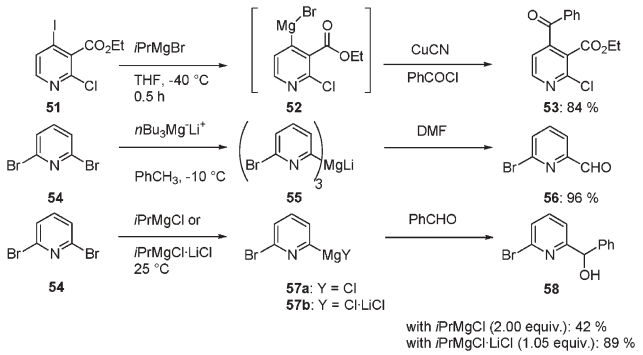
Scheme 5 Selective halogen/Mg-exchange in polyhalogenated five-membered heterocycles.

Copper(I)-catalyzed allylation of **40** with allyl bromide gives 2-allylated thiophene **41** (74%), which undergoes a second Br/Mg-exchange followed by the reaction of the 5-magnesiated species with a long chain aldehyde furnishing the polyfunctionalized thiophene **42** in 69% yield (Scheme 5).[11]

Regio- and chemo-selective chelation controlled Br/Mg- and I/Mg-exchange has also been observed in polyhalogenated thiazole and indole derivatives such as **43** and **46** (Scheme 6).[11] Subsequent treatment of the chelated magnesium species (*e.g.* **44**) with either Me_3SiCl or with allyl bromide provides the functionalized thiazole and the indole derivatives **45** and **47** in high yields. A regioselective double Br/Mg-exchange has also been achieved with the tribromoimidazole **48** (Scheme 6).[11] First, the bromine at the 2-position undergoes exchange in diethyl ether due to chelation affording after allylation the 2-allyl-4,5-dibromoimidazole **49** in 57% yield. As expected, the second exchange is also regioselective leading after reaction with ethyl cyanoformate the tetrasubstituted polyfunctionalized imidazole **50** in 55% yield.[11] The overall sequence shows the synthetic potential of these regioselective sequential halogen/magnesium-exchange reactions for the preparation of functionalized heterocycles. The selective I/Mg-exchange has been used to convert 4,5-diiodoimidazole to 4-iodoimidazole by treatment with EtMgI followed by protonation.[19]



Scheme 6 Selective halogen/Mg-exchange in polyhalogenated five-membered heterocycles.



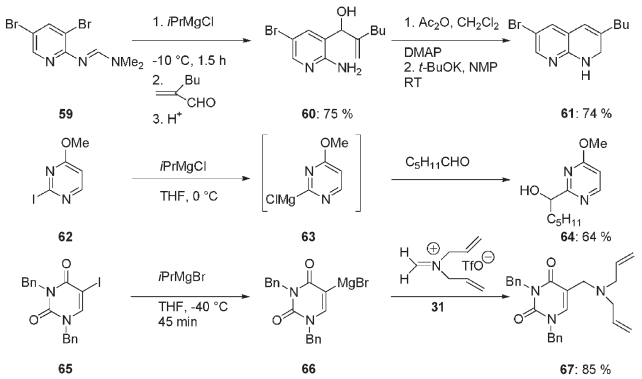
Scheme 7 Preparation of functionalized pyridylmagnesium compounds by halogen/Mg-exchange.

2.3 Functionalized six-membered heteroaryl Grignard reagents: pyridine, quinoline, diazines

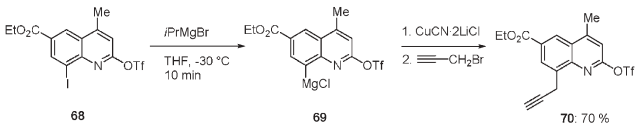
Functionalized pyridines such as **51** bearing electron poor functionalities like a chlorine and an ester group undergo a smooth I/Mg-exchange within a few minutes at −40 °C to give the corresponding chloromagnesiated pyridine **52** (stabilized by chelation) which on reaction with benzoyl chloride in the presence of CuCN provides the trisubstituted functionalized pyridine **53** in 84% yield (Scheme 7).[11,20] Quéguiner has studied the regioselectivity of the Br/Mg-exchange for various isomeric dibromopyridines to generate monomagnesiated bromopyridines which on subsequent treatment with various electrophiles afford regiospecifically substituted functionalized pyridines in good yields.[21,22] The use of the magnesiated species Bu_3MgLi proves to be advantageous for performing a selective Br/Mg-exchange in 2,6-dibromopyridine (**54**) on a large scale, leading to the ate complex **55**,[23] which reacts with DMF furnishing the aldehyde **56** in 96% yield (Scheme 7).[24] The mixed organometallic *i*PrMgCl·LiCl allows one to perform the Br/Mg-exchange under exceedingly mild conditions. Thus, the reaction of 2,6-dibromopyridine (**54**) with *i*PrMgCl (2.0 equiv.) affords the alcohol **58** in 42% yield,[22] whereas by using *i*PrMgCl·LiCl (1.05 equiv.), the carbinol **58** is obtained in 89% yield (Scheme 7).[25]

The presence of an amidine group *ortho* to bromine strongly accelerates the selective Br/Mg-exchange of the dibromopyridine **59** due to a chelation effect leading to the selective functionalization at the 3-position by reaction with 2-butylacrolein to give the carbinol **60** (75%), which could be transformed into dihydro-1,8-naphthyridine **61** in 74% yield in two steps *via* intramolecular cyclization (Scheme 8).[26] Quéguiner has developed reaction conditions which allow the preparation of various magnesiated diazines *via* an exchange on halogenated pyrimidines, pyridazine and pyrazine derivatives.[27] Thus, 2-iodo-4-methoxypyrimidine (**62**) undergoes an I/Mg-exchange at 0 °C leading to the 2-magnesiated pyrimidine **63** which reacts with various electrophiles such as hexanal furnishing the 2-functionalized pyrimidine **64** in 64% yield (Scheme 8).[11,27]

The preparation of functionalized uracils is of interest owing to the potential biological properties of this important class of heterocycles. The reaction of the *N*-protected 5-iodouracil **65** with *i*PrMgBr leads to the formation of the corresponding



Scheme 8 Preparation of functionalized magnesium compounds from pyridine and pyrimidine derivatives.



Scheme 9 Preparation of functionalized quinolinylmagnesium compound by halogen/Mg-exchange.

magnesium compound **66**, which can be trapped by the immonium salt **31** leading the 5-aminomethyluracil **67** in 85% yield (Scheme 8).[11,28]

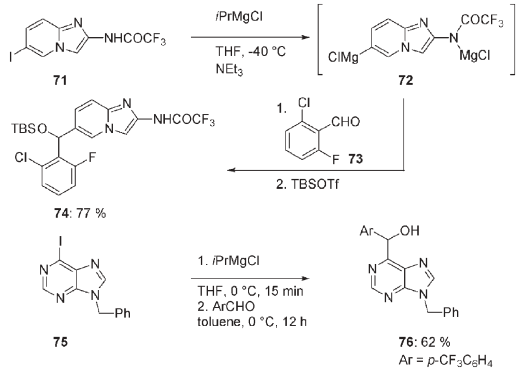
A highly functionalized 8-quinolinyl Grignard reagent such as **69** can be readily generated *via* an I/Mg-exchange on the tetrasubstituted 8-iodoquinoline **68** (Scheme 9).[29] The magnesiated species **69** is subjected to transmetalation with either copper(I) or zinc(II) salts followed by cross-coupling with various unsaturated halides affording a series of 8-functionalized quinolines such as **70** (Scheme 9).[29]

2.4 Functionalized Grignard reagents from biologically important fused heterocycles

Imidazo[1,2-*a*]pyridines are a pharmaceutically useful class of heterocycles. Preparation of a range of 6-functionalized 2-aminoimidazo[1,2-*a*]pyridines of type **74** has been realized by a chemoselective I/Mg-exchange on the heterocyclic iodide **71** to give the magnesiated species **72**, which on quenching with various electrophiles like *o*-halogenated aldehyde **73** affords the 6-functionalized imidazopyridine **74** in 77% yield (Scheme 10).[30] Similarly, the 9-benzyl-4-iodopurine (**75**) undergoes an I/Mg-exchange in toluene in nearly quantitative yield.[31] Such a purine derived Grignard reagent reacts selectively with aromatic aldehydes yielding the carbinol **76** in 62% yield (Scheme 10).[31] The I/Mg-exchange has also been extended to triacetyl ribonucleoside to give the carbinol adduct but only in moderate yield.[31]

3. Preparation of heterocycles with reactive functional groups *via* functionalized heteroaryl organomagnesium compounds

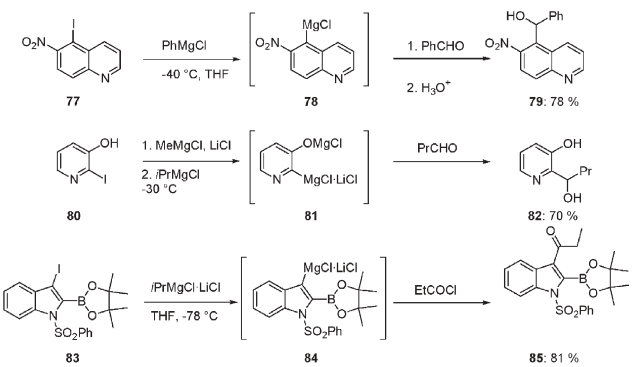
Heteroarylmagnesium reagents bearing a reactive nitro group in the *ortho* position such as **78** have been recently prepared by



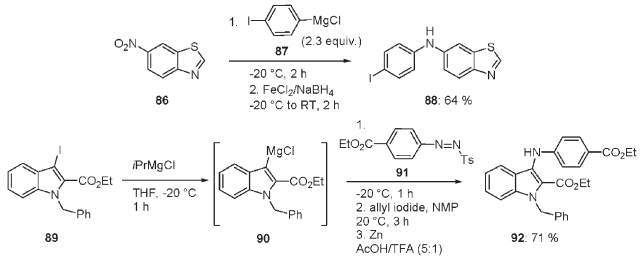
Scheme 10 Preparation of functionalized organomagnesium species from biologically important fused heterocycles.

an I/Mg-exchange on the corresponding *o*-nitroiodoquinoline **77** with PhMgCl.[32] These nitro-substituted magnesiated heterocycles display excellent stability below −40 °C and do not undergo electron transfer reactions. The reaction of the *o*-nitromagnesiated species **78** with benzaldehyde furnishes the nitro-substituted carbinol **79** in 78% yield (Scheme 11).[32] Similarly, the hydroxyl function of heterocyclic iodides such as **80** can be *in situ* protected with MeMgCl in the presence of LiCl producing magnesium phenolates which undergo a rapid I/Mg-exchange with *i*PrMgCl giving the corresponding dimagnesiated species **81** which reacts with standard electrophiles such as butyraldehyde yielding the corresponding 3-hydroxy-2-pyridylcarbinol **82** in 70% yield (Scheme 11).[33] Heteroaryl magnesiated species bearing a boronic ester functionality can be prepared by an I/Mg-exchange.[34] Thus, the treatment of 3-iodo-2-indolyl boronic ester **83** with *i*PrMgCl·LiCl at −78 °C furnishes the corresponding 3-magnesiated boronic ester **84** which can be acylated with propionyl chloride providing the corresponding 3-propionyl-2-indolyl boronic ester **85** in 81% yield (Scheme 11).[34] These polyfunctional boronic esters can be further elaborated to more complex heterocycles *via* a Suzuki cross-coupling reaction to give potential building blocks for the synthesis of pharmaceuticals, agrochemicals and new materials.

Arylamino functionalities are commonly found in pharmaceuticals and materials with interesting electronic properties.



Scheme 11 Preparation of heterocycles with reactive functional groups *via* functionalized heteroaryl organomagnesium compounds.

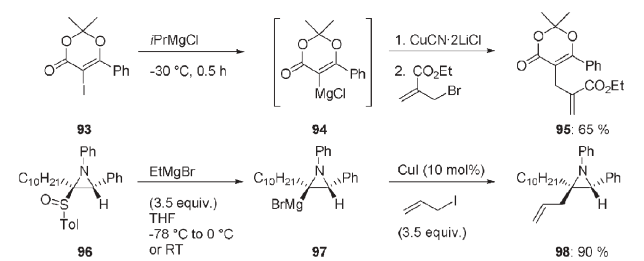


Scheme 12 Synthesis of heterocycles with functionalized arylamino functionalities.

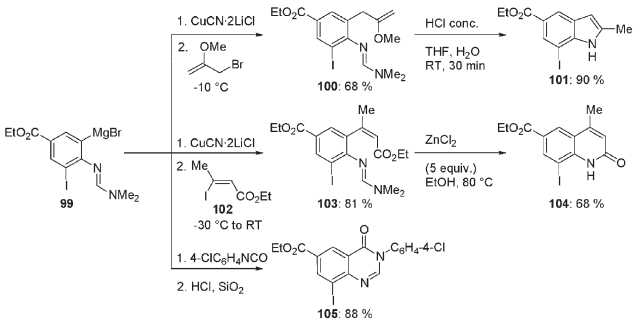
A functionalized arylamino group can be introduced into nitro-substituted heteroaryl compounds such as 6-nitrobenzothiazole (**86**) by reacting it with a functionalized arylmagnesium species like **87** followed by a reductive work-up procedure furnishing the desired 6-(arylamino)benzothiazole **88** in 64% yield (Scheme 12).[35] Alternatively, an arylamino functionality can be introduced by the reaction of a functionalized heteroaryl reagent such as 3-indolylmagnesium species **90** with highly electrophilic arylazo tosylamide such as **91**. Subsequent *in situ* allylation of the addition product followed by reductive cleavage with Zn/AcOH/TFA furnishes the functionalized 3-(arylamino)indole **92** in 71% yield (Scheme 12).[36]

4. Preparation of unsaturated and aliphatic heterocyclic magnesium compounds

5-Magnesiated 1,3-dioxin-4-one species such as **94** are obtained *via* an I/Mg-exchange from the corresponding 5-iodo-1,3-dioxin derivative **93**, although the organomagnesium species **94** bearing an oxygen at the β-position might have a tendency to undergo elimination (Scheme 13).[37] The magnesiated 1,3-dioxin **94** reacts with various electrophiles such as ethyl (bromomethyl)acrylate to give the 5-allylated 1,3-dioxin **95** in 65% yield (Scheme 13).[37a] Sato has recently shown that non-stabilized magnesiated aziridines such as **97** can be generated from the sulfinylaziridine **96** *via* sulfoxide/Mg-exchange with excess of EtMgBr.[38] The aziridinylmagnesium species **97** undergoes a substitution reaction with allyl iodide in the presence of CuI affording the trisubstituted aziridine **98** in 90% yield with high retention of configuration (Scheme 13).[38a]



Scheme 13 Preparation of unsaturated and aliphatic heterocyclic magnesium compounds.



Scheme 14 Preparation of functionalized heterocycles *via* heterocyclization of amidine protected functionalized arylmagnesium compounds.

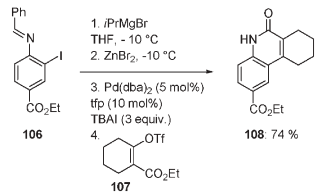
5. Heterocycle synthesis *via* heterocyclization of functionalized aryl Grignard reagents

5.1 Heterocycle synthesis *via* cyclization of amine protected functionalized arylmagnesium compounds

Use of formamidine as a protecting group allows the efficient generation of highly functionalized aminated arylmagnesium compounds which are useful scaffolds for the synthesis of polyfunctionalized indole, quinoline and quinazoline derivatives (Scheme 14).[39] Thus, the allylation of the magnesiated species **99**, obtained from the corresponding diiodoamidine, *via* an I/Mg-exchange with 2-methoxyallyl bromide affords 2-allylated amidine **100**, which undergoes a facile acid induced intramolecular cyclization after deprotection, to the functionalized 7-iodoindole **101** in 90% yield (Scheme 14). Alternatively, the transmetalation of the monomagnesiated species **99** by treatment with CuCN·2LiCl followed by an addition–elimination reaction with (*Z*)-2-iodo-2-enoate **102** gives the unsaturated ester **103** (81%), which is subjected to deprotection and intramolecular cyclization in the presence of $ZnCl_2$ furnishing the trisubstituted 2-quinolone **104** in 68% yield (Scheme 14).[29] This quinolone is further functionalized at the 8-position by converting it to the corresponding 2-triflate **68** with triflic anhydride/pyridine followed by successive I/Mg-exchange and treatment with various electrophiles (Scheme 9).[29]

Several of the diversely functionalized 2-magnesiated amidines such as **99** can be transformed into biologically active quinazolinones of type **105** by treatment with a range of aryl isocyanates followed by acid work-up and treatment with silica gel (Scheme 14).[39] The same sequence could also be used for the synthesis of several quinazolinones on solid phase using Wang resin.[39]

The imine protected iodoaniline **106** can also be converted into the tetrahydrophenanthridone derivative **108** by transmetalation of the corresponding magnesiated imine. Cross-coupling with cyclohexene triflate **107** with *in situ* intramolecular cyclization of the deprotected imine derivative leads to the heterocycle **108** (Scheme 15).[39] The phenanthridone derivative **108** can be further functionalized by its conversion to a triflate (Tf_2O/pyridine) followed by Negishi coupling with arylzinc reagents.[39]



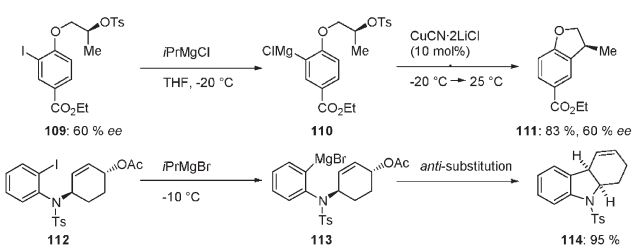
Scheme 15 Preparation of functionalized heterocycles *via* heterocyclization of imine protected functionalized arylmagnesium compounds.

5.2 Functionalized heterocycles *via* cyclization of *ortho* functionalized arylmagnesium compounds

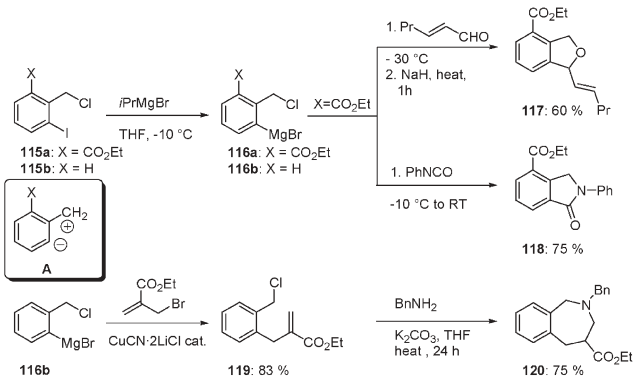
Complementary heterocyclization can also be achieved with *ortho*-functionalized arylmagnesium species that bear a more remote leaving group such as a tosylate, a halide or an acetate (Scheme 16).[40a] Thus, the arylmagnesium species **110** derived from the iodotosylate **109** undergoes a facile stereospecific ring closure in the presence of CuCN·2LiCl with complete inversion of configuration to give the benzofuran **111** (83%) without eroding the original 60% *ee* of the starting material **109** (Scheme 16). An *anti* S_N2'-substitution is also observed with organomagnesium species **113** from the iodoacetate **112** providing *cis*-tetrahydrocarbazole **114** in nearly quantitative yield. Interestingly, the organomagnesium species **113** undergoes ring closure in the absence of a copper catalyst (Scheme 16).[40a]

Functionalized organomagnesium reagents such as **116a–b** prepared by the selective I/Mg-exchange of the 2-chloromethyliodobenzenes **115** are synthetic equivalents of zwitterionic synthon **A** and are well suited for heterocycle synthesis through cyclization reactions (Scheme 17).[41] Thus, the reaction of the arylmagnesiated species **116a** with cinnamaldehyde or with phenyl isocyanate affords respectively the corresponding isobenzofuran **117** and the *N*-phenylphthalimidone derivative **118** in 60% and 75% yield (Scheme 17).[41] Similarly, the functionalized arylmagnesium species **116b** could be converted to the benzazepine derivative **120** in 75% yield *via* an allylation with ethyl 2-(bromomethyl)acrylate in the presence of CuCN·2LiCl and subsequent intramolecular heterocyclization of the allylated product **119** in the presence of benzylamine (Scheme 17).[41]

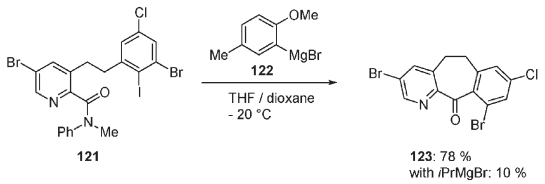
Wu has reported an efficient regio- and chemoselective cyclization of the polyfunctional amide **121** to the tricyclic heterocyclic ketone **123** which is a key intermediate in the synthesis of the potent farnesyl protein transferase inhibitor Sch 66336 (Scheme 18).[42] The best yield of the cyclic ketone



Scheme 16 Synthesis of heterocycles *via* intramolecular heterocyclization of functionalized organomagnesium compounds.



Scheme 17 Synthesis of heterocycles *via* heterocyclization of *o*-functionalized arylmagnesium compounds.



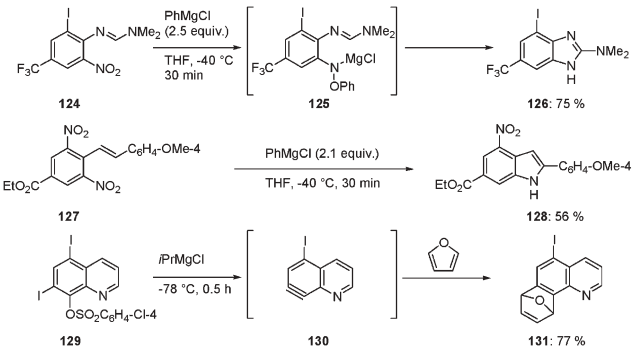
Scheme 18 Synthesis of the key precursor for Sch 66336 by cyclization of *o*-functionalized arylmagnesium compounds.

123 (78%) is obtained when 2-methoxy-5-methylphenylmagnesium bromide (**122**) is used to effect the I/Mg-exchange on the sterically crowded substrate **121**. Alkyl- or aryl-lithiums were not found suitable for this exchange reaction. Also *i*PrMgBr and other sterically crowded Grignard reagents give the cyclic ketone **123** in lower yields (Scheme 18).[42]

5.3 Heterocycles *via* cyclizations of functionalized magnesium nitrenoids and benzyne intermediates

A number of highly functionalized benzimidazole and indole derivatives can be prepared in high yields on treatment of sterically crowded *o*-nitro substituted amidines or *ortho*-nitro substituted stilbenes with phenylmagnesium chloride (2 equiv.) (Scheme 19).[43] Thus, *o*-nitroamidine **124** on treatment with PhMgCl at −40 °C affords within 0.5 h, the corresponding disubstituted 2-(dimethylamino)benzimidazole **126** in 75% yield (Scheme 19). Similarly, the reaction of 2,6-dinitrostilbene **127** with PhMgCl under similar conditions furnishes the highly functionalized 2-arylindole **128** in 56% yield.[43] The formation of these heterocycles is best explained through the involvement of functionalized magnesium nitrenoids of type **125** generated by the attack of PhMgCl on oxygen of a nitroso intermediate formed during the reaction. An intramolecular C–H insertion of the nitrene furnishes these polyfunctionalized heterocycles. The mild reaction conditions and the faster rate of cyclization assures broad functional group compatibility in these substrates such as CN, CO_2Et, CF_3, Br, Cl and OMe.[43]

Highly functionalized bridged benzo-fused oxabicycles can be synthesized by cycloaddition of furan with functionalized benzynes obtained by readily tunable elimination of the 2-magnesiated arylsulfonates obtained by an I/Mg-exchange on the functionalized *o*-iodoarylsulfonates (Scheme 19).[44a]

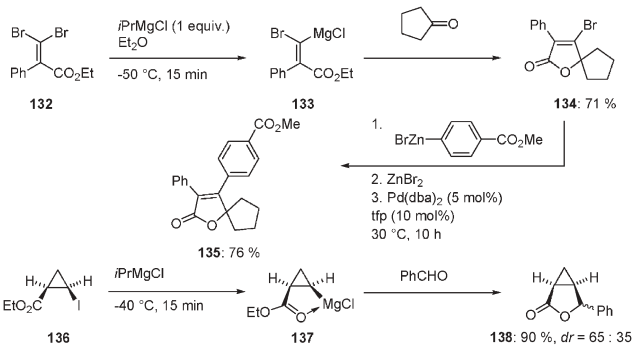


Scheme 19 Synthesis of functionalized heterocycles *via* cyclization of functionalized nitrenoids and benzyne intermediates.

Thus, the iodoquinolinyl sulfonate **129** is readily converted into the corresponding magnesiated species which on elimination gives the functionalized benzyne intermediate of type **130** (Scheme 19). This intermediate **130** undergoes an *in situ* cycloaddition with furan to provide the quinoline fused oxabicycle **131** in 77% yield.[44a] A variety of functionalities such as iodine, ester, nitrile, trifluoromethyl and the sensitive groups like keto and nitro are tolerated in these aryne intermediates for the first time.[44]

6. Synthesis of oxygen heterocycles *via* cyclization of functionalized alkenyl, cyclopropyl and aliphatic organomagnesium compounds and the related carbenoids

The I/Mg-exchange method has also been used to generate functionalized alkenylmagnesium compounds from the corresponding β-iodoenoates with high stereoselectivity.[45] These alkenylmagnesium reagents add to various aldehydes and ketones followed by *in situ* lactonization, furnishing the corresponding unsaturated lactones in high yields.[45] Of particular interest is the generation of the functionalized alkenylmagnesium carbenoids of type **133** from the corresponding dibromoenoates like **132** through a highly stereospecific I/Mg-exchange (Scheme 20).[46] These functionalized alkenylmagnesium carbenoids also react with various acyclic and cyclic aldehydes and ketones in a highly stereoselective manner with retention of configuration providing polyfunctional unsaturated spirolactones such as **134** in 71% yield



Scheme 20 Synthesis of functionalized γ-lactones *via* cyclization of functionalized alkenyl- and cyclopropylmagnesium compounds.

(Scheme 20).[46] The spirobromolactone **134** can be further functionalized *via* Negishi coupling with an arylzinc reagent to give the cross-coupled lactone **135** in 76% yield (Scheme 20).[46]

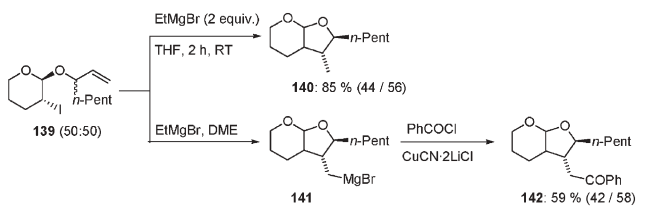
Using an I/Mg-exchange, it has also been possible to prepare functionalized cyclopropylmagnesium chloride and the corresponding carbenoid species in a highly stereoselective manner (Scheme 20).[47] Thus, the readily available 2-iodocyclopropane carboxylate **136** undergoes a facile I/Mg-exchange to give *cis*-cyclopropylmagnesium chloride **137** which shows excellent stability due to the chelating and inductive effect of the ester group. Compound **137** undergoes spontaneous addition and lactonization with benzaldehyde to give the cyclopropyl fused lactone **138** as a separable mixture of two diastereoisomers (Scheme 20).[47]

Oshima has shown that a variety of β-iodoacetals like **139** undergo intramolecular radical type cyclization on treatment with EtMgBr in THF to give a fused tetrahydrofuran derivative such as **140** in 85% yield (Scheme 21).[48] Interestingly, the use of DME as solvent instead of THF dramatically changes the reaction course affording a cyclic organomagnesium compound like **141** which can be coupled with various electrophiles like benzoyl chloride to give the functionalized bicyclic furan derivative **142** in 59% yield (Scheme 21).[48]

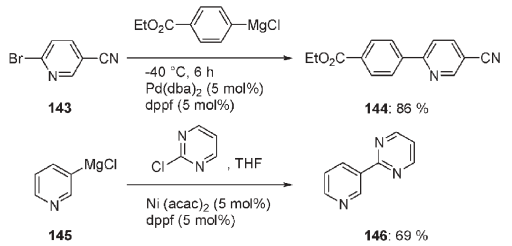
7. Heterocycle synthesis *via* cross-coupling of functionalized aryl and heteroaryl magnesium compounds

The availability of functionalized organomagnesium compounds has considerably enhanced the scope of these reagents for performing cross-coupling reactions which are frequently used in the synthesis of polyfunctional heterocycles. Thus, 4-carboethoxyphenylmagnesium chloride directly undergoes a cross-coupling reaction with substituted 2-halopyridines like **143** in the presence of a Pd(0)-catalyst and dppf to give the functionalized pyridine **144** in 86% yield (Scheme 22).[49,50] These remarkably fast cross-coupling reactions do not proceed in the absence of the palladium catalyst and are therefore not direct addition–elimination reactions. These reactions proceed rather through an organopalladate of the type $[MgX]^+[ArPdL_2]^-$ which undergoes a fast addition–elimination reaction with 2-halopyridines.[49,50]

Alternatively, the heterocycle magnesium species such as 3-pyridylmagnesium chloride **145** has been subjected to a cross-coupling reaction with various chloroazines like 2-chloropyrimidine affording the corresponding 3-(2-pyrimidyl)pyridine (**146**) in 69% yield (Scheme 22).[51] A Ni(0)-catalyst is found to be more efficient than palladium catalysis for this coupling reaction with haloazines.[51]



Scheme 21 Synthesis of functionalized oxygen heterocycles *via* cyclization of functionalized alkylmagnesium compounds.



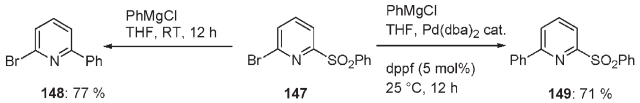
Scheme 22 Synthesis of heterocycles *via* cross-coupling of functionalized organomagnesium compounds.

Quéguiner has reported an interesting chemoselectivity in the cross-coupling reaction of bromosulfone **147** (Scheme 23).[50] Thus, PhMgCl reacts with the disubstituted pyridine **147** by direct substitution of the phenylsulfonyl group leading to 2-bromo-6-phenylpyridine (**148**) in 77% yield. On the other hand, the use of a palladium catalyst allows the preparation of functionalized 2-phenylpyridine-6-sulfone **149** in 71% yield (Scheme 23).[50]

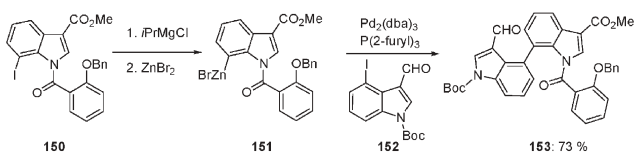
The highly functionalized 4,7-bisindole **153**, a precursor for the synthesis of diazonamide A, a highly potent anticancer agent, has been prepared starting from the polyfunctionalized zinc reagent **151** obtained from the iodide **150** through an I/Mg-exchange (Scheme 24).[52] The organozinc reagent reacts readily with the indolylaldehyde **152** in the presence of a palladium catalyst under mild conditions to furnish the bisindole compound **153** in 73% yield (Scheme 24).[52]

The low cost and toxicity of iron(III)-salts has allowed these complexes to be used with success in several coupling reactions,[53] especially with aliphatic Grignard reagents leading to a large variety of polysubstituted heterocycles which has been recently reviewed by Fürstner.[54] Heterocyclic ketones such as **155** bearing several functionalities can be prepared in high yields by acylation of a 4-carboethoxyphenylmagnesium compound with more reactive acyl cyanides like **154** (Scheme 25).[55] The yields of the ketones are found to be lower in the absence of iron catalyst or with the corresponding acyl chlorides.[56]

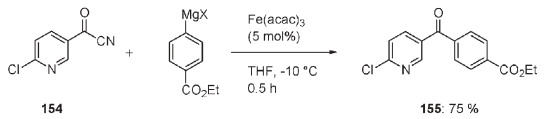
Cahiez has recently developed a novel, highly chemoselective homocoupling of functionalized aryl- and heteroaryl



Scheme 23 Example of chemoselective palladium-catalyzed cross-coupling of 2-phenylsulfonyl pyridines.



Scheme 24 Synthesis of diazonamide A precursor by palladium-catalyzed cross-coupling with a functionalized organozinc reagent.



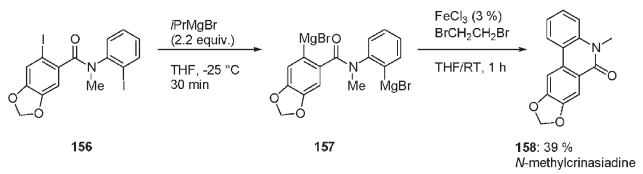
Scheme 25 Synthesis of heteroaryl ketones by iron(III)-catalyzed acylation of functionalized organomagnesium compounds with acyl cyanides.

Grignard reagents using iron-catalysis for the synthesis of functionalized biaryl and biheteroaryl compounds.[57] Its intramolecular homocoupling version has been applied for the total synthesis of the alkaloid, *N*-methylcrinasiadine (**158**) (Scheme 26). Thus, highly functionalized bis-arylmagnesium compound **157** obtained from the diiodo compound **156** *via* I/Mg-exchange affords *N*-methylcrinasiadine (**158**) in 39% overall yield on treatment with 3% $FeCl_3$ in the presence of 1,2-dibromoethane at room temperature (Scheme 26).[57]

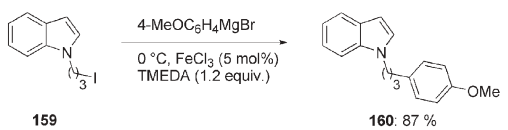
Nakamura has reported an efficient iron catalyzed cross-coupling of functionalized aryl Grignard reagents with alkyl halides.[58] Use of TMEDA as additive was found to be most important to suppress side reactions of the alkyl iodide such as elimination and reduction. Under these conditions, sensitive heterocycles like 1-(triiodomethyl)-1,2-dihydro-indole (**159**) underwent efficient coupling with 4-methoxyphenylmagnesium bromide in the presence of an iron catalyst to afford 1-(triarylmethyl)-1,2-dihydroindole (**160**) in 87% yield (Scheme 27).[58]

This iron-catalyzed cross-coupling reaction has been realized with aryl halides/sulfonates and alkylmagnesium reagents, however, the cross-coupling between two aryl moieties remained problematic owing to extensive homocoupling reactions of the arylmagnesium species. On the other hand, it is observed that the iron-catalyzed cross-coupling reaction between functionalized aryl- or heteroaryl-copper reagents derived from the corresponding organomagnesium reagents proceeds readily with functionalized aryl iodides.[59]

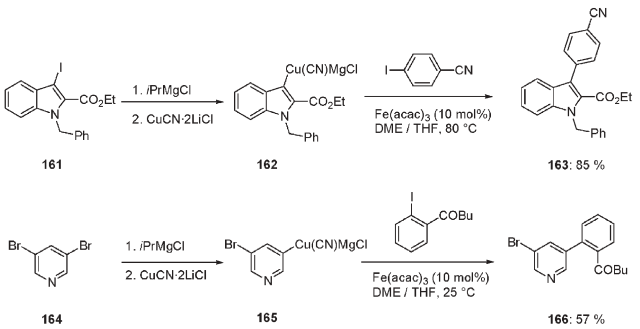
Thus, the 3-indolylcopper reagent **162** derived from 2-carboethoxy-3-iodoindole **161** by I/Mg-exchange followed by treatment with CuCN·2LiCl, reacts with 4-cyanoiodobenzene in the presence of $Fe(acac)_3$ as catalyst to give 3-(4-cyanophenyl)-2-carboethoxyindole **163** in 85% yield



Scheme 26 Synthesis of *N*-methylcrinasiadine by intramolecular iron(III)-catalyzed cross-coupling of functionalized arylmagnesium compounds.



Scheme 27 Functionalization of heterocycles by iron(III)-catalyzed cross-coupling of arylmagnesium compounds.



Scheme 28 Synthesis of heterocycles *via* iron(III)-catalyzed cross-coupling of functionalized organocopper compounds.

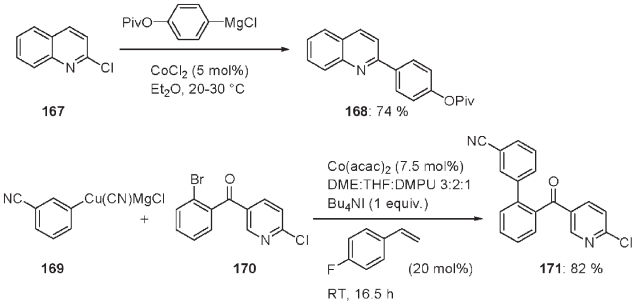
(Scheme 28).[59] Similarly, the 3-pyridylcopper reagent **165** prepared from the corresponding 3,5-dibromopyridine (**164**) yields the corresponding highly functionalized 3-bromo-5-(2-pivaloylphenyl)pyridine (**166**) in 57% yield on coupling with 2-pivaloyliodobenzene in the presence of $Fe(acac)_3$ (10 mol%) (Scheme 28).[59] The new procedure not only represents an economic way (approximately three times cheaper than Pd-catalyzed reactions) to perform aryl–aryl or heteroaryl cross-couplings, but the synergetic effect between copper and iron also opens up new synthetic possibilities for the future.

8. Synthesis of polyfunctional heterocycles *via* cobalt(II)-catalyzed cross-coupling reaction

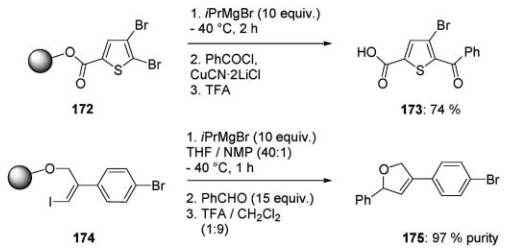
Finally, 2-chloroazines such as 2-chloroquinoline (**167**) undergo efficient cross-coupling with arylmagnesium compounds in the presence of cobalt(II) chloride (5 mol%) at room temperature, yielding the corresponding arylated heterocycles such as 2-arylquinoline **168** in 74% yield (Scheme 29).[60] Similarly, the functionalized heterocyclic ketone **171** is prepared in 82% yield by coupling of functionalized arylcopper reagent **169** and *o*-bromoketone **170** in the presence of $Co(acac)_2$ as a catalyst, Bu_4NI and 4-fluorostyrene as additives (Scheme 29).[61]

9. Synthesis of polyfunctional heterocycles *via* functionalized organomagnesium compounds on solid phase

Using heterocyclic bromo compounds attached to resin, several of the functionalized heterocyclic Grignard reagents



Scheme 29 Synthesis of heterocycles *via* cobalt(II)-catalyzed cross-coupling of organomagnesium and organocopper compounds.



Scheme 30 Synthesis of polyfunctional heterocycles on solid phase *via* functionalized organomagnesium compounds.

can be generated on resin and reacted with various electrophiles.[8b,11,39] Thus, a number of bromothiophenes and furans have been attached to Wang resin leading to a substrate like **172** (Scheme 30).[62] Treatment of **172** with excess of *i*PrMgBr (10 equiv.) at low temperature followed by reaction with various electrophiles like benzoyl chloride affords after cleavage from resin (TFA), a range of functionalized thiophenes like **173** (Scheme 30).[8b,11] Similarly, treatment of the resin attached (*Z*)-alkenyl iodide **174** with an excess of *i*PrMgBr followed by addition of benzaldehyde furnishes after cleavage from resin the 2,5-dehydrofuran **175** in 97% purity (Scheme 30).[62]

Conclusions

We have described in this review the applications of the halogen/magnesium-exchange reaction for the generation of a variety of functionalized five- and six-membered heteroarylmagnesium compounds and their subsequent reactions with several electrophilic substrates to provide a range of regiospecifically functionalized heterocycles. A variety of polyfunctional heterocycles bearing even sensitive functional groups like nitro, keto, hydroxyl and boronic acid ester can be synthesized by this route. Also, many of the functionalized aryl- and heteroaryl-magnesium compounds can be subjected to heterocyclization or cross-coupling reactions providing new scaffolds for heterocycle synthesis. In view of the growing importance of heterocyclic compounds in various fields like drug discovery, chemical genetics, materials science and molecular recognition *etc.*, we believe that functionalized organomagnesium compounds will play a key role in diversity oriented synthesis of these important classes of compounds.

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