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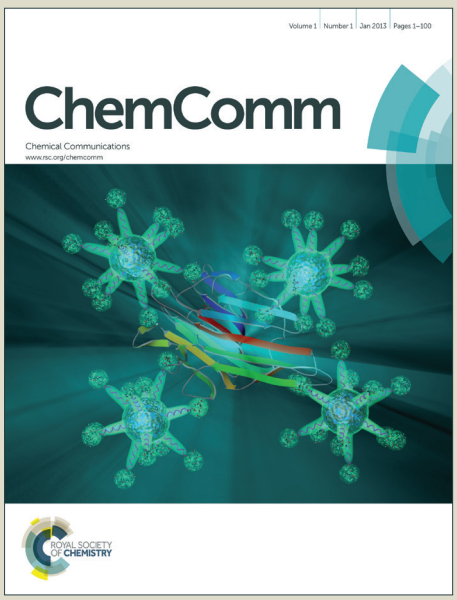

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Progress and developments in the turbo Grignard reagent *i*-PrMgCl·LiCl: a ten-year journey

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Over the past decade, the effectiveness of *i*-PrMgCl·LiCl has been constantly highlighted by a number of research groups. Its enhanced nucleophilicity brings prosperity to highly functionalized Grignard reagents, other useful bimetallic (alkali-metal) agents and nucleophilic alkylation products under mild reaction conditions. In this feature article, a comprehensive, systematical and in-depth overview of *i*-PrMgCl·LiCl is provided in a multidisciplinary idea. It involves the structural and kinetic perspectives of *i*-PrMgCl·LiCl as well as its unique reactivity and selectivity, with knowledge of the former helping to rationalize trends of the later.

1. Introduction

French Chemist François Auguste Victor Grignard[1a] discovered, in 1900, that the organomagnesium halides are produced by allowing metallic magnesium to react with an organic halide in a dry ether solvent, inspired by the Barbier reaction[1b]. These reagents, subsequently named Grignard reagents, are extremely valuable and indispensable synthetic tools for invention of new carbon-carbon and carbon-heteroatom bond-forming reactions.[2] Despite their wide application, three specific aspects increase difficulties on synthesis of Grignard reagents through the classical reaction of organohalides with metallic magnesium.[3] The first is that many organic halides just react very sluggishly with ordinary magnesium turnings, leading to poor yields and/or incomplete conversion. The second relates to likely formation of undesired byproducts and/or thermal decomposition of Grignard reagents. The third is that the incompatibility of some reducible electrophilic functional groups and the exothermic reaction are not easy to control during industrial processes. These three hurdles have led to the development of a range of methods designed for the preparation of Grignard reagents,[2d, 2e] such as transmetalation,[2d] hydromagnesation,[4] direct oxidative addition of Rieke's active magnesium to organic halides,[5] and the halogen[6] (or sulfoxide[7])-magnesium exchange reactions. Among them, the halogen (or sulfoxide)-magnesium exchange reactions have proved to be good choices to prepare novel functionalized magnesium Grignard reagents for considerable interest and synthetic utility. However, the corresponding exchange rates are very slow at lower temperatures, which limit their synthetic application.

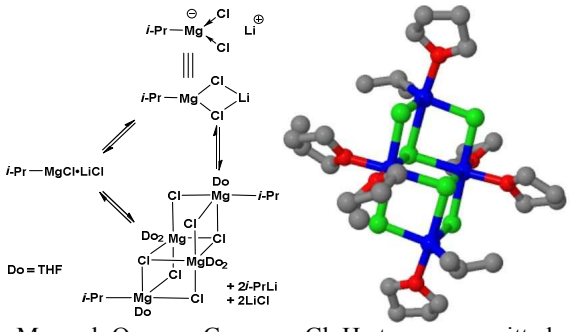
Since the pioneering studies on *i*-PrMgCl·LiCl published by Prof. Knochel in 2004,[8] the general and promising reagent (known as the turbo Grignard reagent) has been highly praised not only in considerably accelerating halogen (or sulfoxide)-magnesium exchange reactions, but also in a wide range of elegant application in laboratory syntheses and up-scaled industrial processes. Needless to mention, the past decade has witnessed not only the emergence in the limelight of the turbo Grignard reagent *i*-PrMgCl·LiCl, but also its remarkable progress and developments in preparative organic chemistry, for which was awarded the EROS (**E**ncyclopedia of **R**eagents for **O**rganic **S**ynthesis) Best Reagent Award 2011.

Recently, several review articles[9] and book chapters[2e, 10] have touched on some aspects of *i*-PrMgCl·LiCl. However, a comprehensive treatment that covers all substrate types, mechanistic studies, and synthetic application has yet to appear. This feature article refinedly summarizes current trends and developments in the use of the turbo Grignard reagent *i*-PrMgCl·LiCl as a versatile partner, presents its related structural and kinetic analysis, demonstrates its attempts in flow chemistry, and highlights its synthetic application to the complex organic molecules in the past decade. It should be emphasized, however, that some valuable approaches using (*i*-Pr)$_2$Mg·LiCl, (*s*-Bu)$_2$Mg·LiCl, *s*-BuMgCl·LiCl, and the potential of the synthetically important turbo Hauser bases for promoting further organic transformations have escaped our attention, for which we must express our sincere apologies.

2. Structural and kinetic information

In his initial study,[8] Prof. Knochel has speculated that the role of LiCl in the turbo Grignard was to activate the *i*-PrMgCl and increase the nucleophilic character of the isopropyl group, through the deaggregation of *i*-PrMgCl oligomers and further formation of a four-membered MgClLiCl ring structure. Indeed, crystallographic proof of the related turbo Hauser base (TMP)MgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) supported the existence of the four-membered MgClLiCl coordination mode.[11] However, in the corresponding studiesy aimed at finding crystallographic proof of the turbo Grignard reagent, Lerner and co-workers[12] were unable to obtain the proposed four-membered ring structure. Actually, they found that the connectivity of [*i*-PrMgCl(THF)]$_2$[MgCl$_2$(THF)$_2$]$_2$ as

single crystals obtained from a THF solution of *i*-PrMgCl·LiCl with addition of Et_2O was similar to the one in the crystals grown from plain RMgCl[13] (R = Me, *t*-Bu, Ph, Bn) solutions, namely dimeric Grignard-$MgCl_2$ adduct (Scheme 1). In a further attempt to drive the equilibrium of *i*-PrMgCl·LiCl to the four-membered MgClLiCl adduct, dioxane was added to the THF solution of *i*-PrMgCl·LiCl to precipitate $MgCl_2$ as its dioxane-bridged adduct. This procedure was thought to hamper the formation of the dimeric Grignard-$MgCl_2$ adduct, since $MgCl_2$ was removed from the equilibrium, leaving behind a higher local concentration of LiCl. Unfortunately, the incorporation of LiCl in the solid-state structure was still not observed from THF/dioxane by slow evaporation.

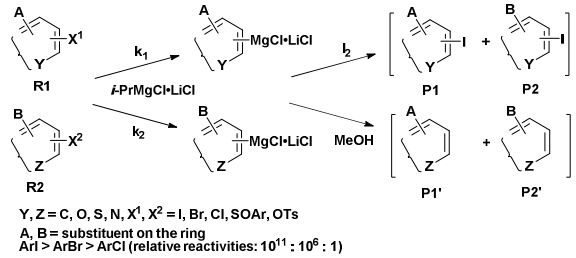


Blue: Mg, red: O, gray: C, green: Cl, H atoms are omitted.
Scheme 1 Structure of the turbo Grignard reagent.[12]

As a result, an awkward problem is raised, whether the structure aggregated by posited LiCl is really stable or just a transient species. As the authors suggested in their findings, if the steric requirements are met (small organic substituents such as the isopropyl group), the stronger Lewis acid $MgCl_2$ acts in a manner as proposed for the smaller LiCl. Notably, in comparison with the organolithium compounds,[14] a direct correlation between the solid-state structure and the reactivity in a solution is rather dubious.

Although the structural information of the turbo Grignard reagent has not been fully elucidated until now, the minimization of the undesired side reactions and the acceleration of highly desirable process in the halogen (or sulfoxide)-magnesium exchange reactions are equally well resolved with addition of lithium chloride. In 2006, Murso and co-workers[15] studied the relationship between percent conversion and reaction time in the halogen-magnesium exchange reactions of unactivated electron-poor bromobenzene. The result of their experiments revealed that the highly desirable acceleration of the efficient halogen-magnesium exchange process was dependent not only on the presence and amount of dissolved lithium chloride but also on the nature of the organic fragment attached to the magnesium center of the Grignard reagent. In addition, the undesired competitive reaction, which was the elimination of HBr from the alkyl bromide accompanied by evolution of gaseous side products, was also monitored through inline IR and gas flow measurements, respectively. Speculating from the data of both measurements, the higher LiCl content led to slower elimination of HBr and less consumption of Grignard reagents, therefore giving higher conversions.

At a more fundamental level, Knochel and Mayr performed the kinetic studies of the halogen (or sulfoxide)-magnesium exchange reactions using *i*-PrMgCl·LiCl with a series of substituted bromobenzenes,[16a, 16b] heteroaryl bromides,[16c] and other aromatic halides.[16d] For this purpose, competition experiments were performed by adding less than one equivalent of *i*-PrMgCl·LiCl in THF at 0 °C to an excess of two diverse substituted aromatic halides (Scheme 2). The ratio of the resulting arylmagnesium chlorides was then derived from the gas-chromatographically determined product ratio obtained after quenching with iodine or methanol.

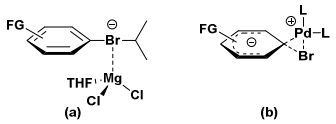


Scheme 2 Determination of relative halogen-magnesium exchange rates.[16]

The relative reactivities of **R1** and **R2** towards *i*-PrMgCl·LiCl could be expressed by the competition constant κ, which was calculated by eqn. (1).[17] From the experimental data, it is clear that electron-withdrawing substituents dramatically accelerated the halogen (or sulfoxide)-magnesium exchange reactions. Unlike in classical electrophilic and nucleophilic aromatic substitutions,[18] where the activating and deactivating effects of *ortho*- and *para*-substituents were much greater than the corresponding *meta*- effects, the substituent effects decreased with increasing distance from the reaction center, agreeing with a predominant influence on inductive effects and formation of a hypervalent halogen complex[19] (Scheme 3a). Moreover, from the reaction constants ρ = 5.38 (for the *meta*-substituted compounds), and ρ = 2.65 (for the *para*-substituted compounds), it also could be derived that the exchange reactions were predominantly accelerated by inductively withdrawing substituents. Because the σ_m values exclusively reflected inductive effects, the resulting ρ values were larger than that derived from σ_p, which included inductive effects and mesomeric effects. To convert the relative rate constants into absolute rate constants, the authors determined the second-order rate constants of the bromine-magnesium exchange reactions of 4-bromobenzonitrile (2.97×10^{-3} M^{-1} s^{-1}) and 1-bromo-3-chlorobenzene (8.37×10^{-4} M^{-1} s^{-1}) with *i*-PrMgCl·LiCl at 0 °C, which were helpful to calculate the exchange reaction times needed for conversion.

$$\kappa = \frac{k_1}{k_2} = \frac{\log([\mathbf{R1}]_0/[\mathbf{R1}]_t)}{\log([\mathbf{R2}]_0/[\mathbf{R2}]_t)} = \frac{\log(1+[\mathbf{P1}]_t/[\mathbf{R1}]_t)}{\log(1+[\mathbf{P2}]_t/[\mathbf{R2}]_t)} \quad (1)$$

In contrast to substituted bromobenzene derivatives, most heteroaryl bromides underwent the bromine-magnesium exchange reactions considerably faster than bromobenzene. In the series of the five-membered heteroarenes (furan, pyrrole and thiophene), the 2-bromo derivatives were much more reactive than the 3-substituted isomers, and 3-bromo-*N*-methylpyrrole was even slightly less reactive than bromobenzene. In the pyridine series, 2-bromopyridines was substantially less reactive compared with 3- and 4-bromopyridines possibly due to repulsion between lone pairs. An analogous evaluation of the reaction of 3-bromobenzo[*b*]thiophene with *i*-PrMgCl (without LiCl) in THF gave a second-order rate constant of 1.78×10^{-4} M^{-1} s^{-1}, which showed that the reaction with *i*-PrMgCl (without LiCl) was approximately 19 times slower than that with *i*-PrMgCl·LiCl. Among the investigated heteroaryl bromides, 3,4-dibromofuran, 2-bromothiophene, 3,5-dibromopyridine, and 2-bromothiazole were so reactive that the 19 times less active *i*-PrMgCl (without LiCl) appeared to be more appropriate for the bromine-magnesium exchange reactions.



Scheme 3 (a) Transition state of the bromide-magnesium exchange with *i*-PrMgCl·LiCl. (b) Transition state of the oxidative addition of PdL_2.[19]

In 2012, the same authors further explored the leaving-group dependence on the relative reactivities and absolute rate constants of halogen (or sulfoxide)-magnesium exchange reactions. Analogously, the increase of exchange rates was in the order ArCl < ArBr < ArI in the ratio of $1:10^6:10^{11}$. Preliminary experiments showed that the *p*-tolylsulfinyl group was exchanged slightly faster than iodide, while tosylate was exchanged at least 10^4 times more slowly than bromide. With the detailed kinetic data in hand, one might predict and control the regioselectivities of halogen (or sulfoxide)-magnesium exchange reactions of polyfunctional compounds.

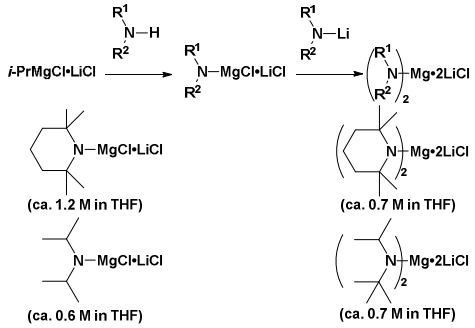
Using the similar competition experiments, the same research team[17e] has evaluated the relative reaction rates of palladium-catalyzed Negishi cross-coupling reactions between bromobenzenes carrying various substituents and the arylzinc iodide-lithium chloride complexes ArZnI·LiCl. On the one hand, the oxidative addition was strongly accelerated by electron-withdrawing groups, and meanwhile the accelerating effects of various substituents increased in the order *ortho* < *meta* < *para*, opposite the reactivity order in bromine-magnesium exchange reactions with *i*-PrMgCl·LiCl. From the good linear Hammett correlation for *meta*- and *para*-substituted bromobenzenes ($\rho = 2.5$), it was concluded that the oxidative addition to the reactive Pd^0 species proceeded over a three-centered transition state (Scheme 3b), resembling that of nucleophilic aromatic substitutions. On the other hand, electron-donating groups on the *para*-substituted arylzinc iodides could accelerate the transmetalation step. A Hammett analysis indicated that the substituent effects on the transmetalation were relatively small ($\rho = -0.98$ for the reaction with 4-$NCC_6H_4PdL_n$) and declined with decreasing electrophilicity of the arylpalladium intermediates.

3. Preparation of functionalized organomagnesium reagents

A wide range of polyfunctionalized organomagnesium reagents can be prepared through the metalation of the C–H or C–X/LG (LG = leaving group, X = Cl, Br, I) bonds through reactions with the turbo Grignard reagent in a stoichiometric way, which allows for unprecedented selective conversions to reactive intermediates within a molecule containing sensitive functionalities under mild reaction conditions. Further, the reactivity, stability and selectivity of organomagnesium reagents can be effectively tuned after the transmetallation with other metallic salts, which dramatically broaden their scope and generality. In this section, the preparation of organomagnesium reagents using *i*-PrMgCl·LiCl and the scope of their application will be described as follows.

3.1 Preparation of magnesium amides

The directed metalation using amide bases or alkyl organometallics is recognized as one of the most useful and practical methodologies, whereas a more or less activated carbon-hydrogen bond is directly transformed into the corresponding functionalized organometallic species in a regio- and stereoselective manner. However, traditional strong organic bases such as alkylithiums and lithium amides may cause competing side reactions (e. g., Chichibabin reactions) and require the relatively low temperatures (mostly -78 °C) for the deprotonations. Besides, the disadvantages of these metalations mediated by common magnesium amide bases (termed Hauser bases)[20] are the limited solubility as well as the requirement for a large excess of magnesium bases (2-7 equiv.) to achieve high conversions.



Scheme 4 Typical preparation of the mixed Mg/Li amides.[20, 21]

In 2006, Knochel and co-workers succeeded in the development of the mixed lithium and magnesium amide bases $R^1R^2NMgCl·LiCl$ by reacting *i*-PrMgCl·LiCl with the corresponding secondary amines in THF (Scheme 4),[21a] which displayed a better solubility than Hauser bases R^1R^2NMgCl and a higher reactivity for the magnesiation of functionalized aromatic and heteroaromatic compounds.[21] The authors believed that oligomeric aggregates were broken up in the presence of TMPMgCl·LiCl, which was in a similar manner to *i*-PrMgCl·LiCl. The main advantages of $R^1R^2NMgCl·LiCl$ compared to R^1R^2NLi or R^1R^2NMgCl were the long term stability of this reagent at 25 °C, the better compatibility with sensitive functional groups even in non-cryogenic conditions and the greater stability of the metalated products.

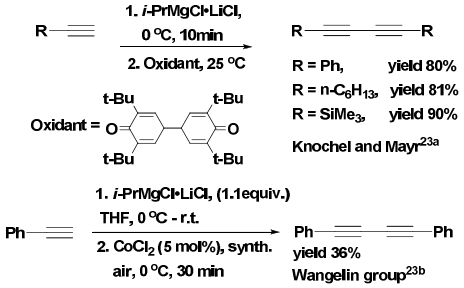
However, some moderately activated arenes and heteroarenes still resisted to undergo the directed magnesiation in the presence of $R^1R^2NMgCl·LiCl$. This gap was bridged by the development of more kinetically active bis-amide bases, such as $(TMP)_2Mg·2LiCl$ by the reaction of TMPMgCl·LiCl with lithium 2,2,6,6-tetramethylpiperamide for 30 min at 0 °C,[21b, 21c] which showed an improved reactivity and excellent functional group tolerance. The only drawback was the weak stability of $(TMP)_2Mg·2LiCl$ that it was only stable for a maximum of 24 h at 25 °C, which limited its practical utility.[21d]

In short, the sterically hindered Knochel Hauser Bases $R^1R^2NMgCl·LiCl$ and $(R^1R^2N)_2Mg·2LiCl$ have been found to be effective in a plethora of the alkali-metal-mediated metalation (AMMM) processes,[22] and readers can find their further application details in recent reviews.[9, 10, 21e] The primary advantage of these reagents was lack of an obligatory carbon-halogen bond. Thus a more or less activated carbon-hydrogen bond could be directly converted into the corresponding metal species.

3.2 Preparation of sp hybridized organomagnesium reagents

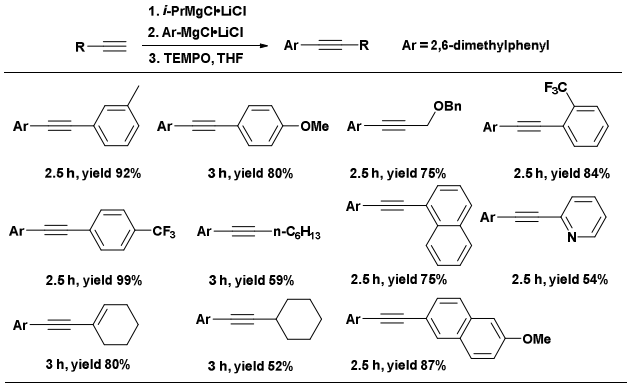
Acetylenic Grignard reagents as the type of RC≡CMgCl·LiCl were prepared, not from an acetylenic halide, but by an acid-base reaction in which the turbo Grignard reagent *i*-PrMgCl·LiCl abstracted a proton from a terminal alkyne. Knochel and Mayr research team[23a] and Jacobi von

Wangelin group[23b] reported successively the oxidative homocoupling of alkynylmagnesium compounds, which were easily available by deprotonation of the corresponding acetylenes with *i*-PrMgCl·LiCl, using the 3,3',5,5'-tetra-*tert*-butyldiphenoquinone or catalytic $CoCl_2$ and 1 bar synthetic air as the terminal oxidant (Scheme 5). The extension of their own work to aryl and alkenyl magnesium chloride-lithium chloride complexes have already been investigated, and the reaction proceeded effectively to afford the corresponding biaryls and dienes in good yields.



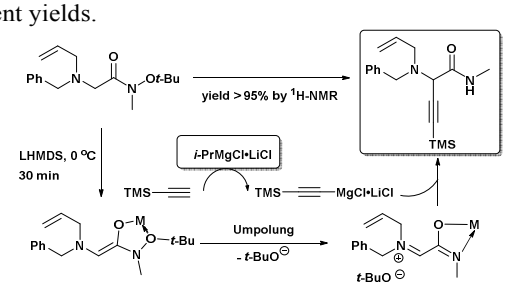
Scheme 5 Homocoupling of sp hybridized Grignard reagents.[23a, 23b]

Similarly, Studer and co-workers[23c] demonstrated the oxidative cross-coupling reactions between aryl and alkynyl magnesium chloride-lithium chloride complexes by using 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an environmentally benign and commercially available organic oxidant (Scheme 6). It was pointed out that the undesired oxidative homocoupling of aryl Grignard reagents occurred far faster as compared to the analogous reactions with alkynyl Grignard reagents. Consequently, a big excess of *ortho*-substituted aryl Grignard reagents was necessary to obtain good yields of the final heterocoupling products.



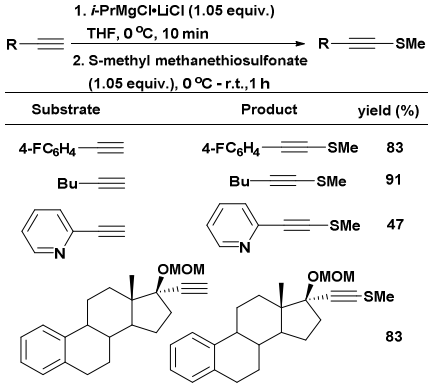
Scheme 6 Heterocoupling between alkynyl and aryl Grignard reagents.[23c]

Acetylenic Grignard reagents obtained *via* deprotonation of terminal alkynes with *i*-PrMgCl·LiCl might be considered to be synthetically equivalent to a carbanion, which could react with various other electrophiles. Somfai and co-workers[24] disclosed that the α alkynylation of 2-(*N*-allyl-*N*-benzylamino)-*N*-*tert*-butoxy-*N*-ethylacetamide with trimethylsilylethynyl magnesium chloride-lithium chloride complex could afford the expected α-substituted amino amide in a quantitative yield, and the proposed mechanism was depicted in Scheme 7. The Weinreb amide was deprotonated to generate enolate, which was converted into the iminium ion through the subsequent elimination of *t*-BuO$^-$. As a result, the dipole of the α carbon center was reversed (umpolung) from the nucleophilic character to the electrophilic one. Analogously, the use of 5-Br-(3-pyridinyl)Mg·LiCl and *i*-PrMgCl·LiCl also afforded the corresponding α-substituted glycine derivatives in good to excellent yields.

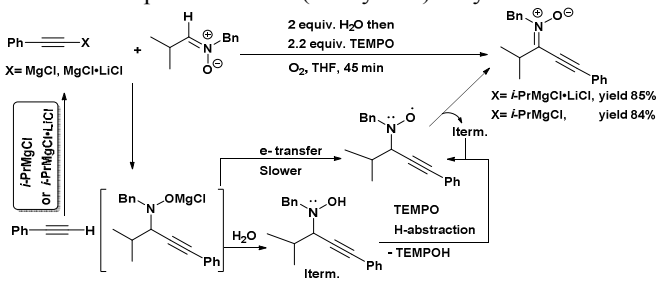


Scheme 7 α-alkynylation of the Weinreb amide.[24]

In the course of an investigation of the cross-coupling reactions between organozinc reagents and unsaturated thioethers,[25] Knochel and co-workers prepared the (methylthio)acetylenes through the deprotonation of the corresponding terminal alkynes with *i*-PrMgCl·LiCl and subsequent *in situ* trapping of the thus obtained alkynyl Grignard reagents with S-methyl methanethiosulfonate in moderate to good yields (Scheme 8).



Scheme 8 Preparation of the (methylthio)acetylenes.[25]



Scheme 9 Oxidative cross-coupling of nitrones with alkynyl Grignard reagents.[26]

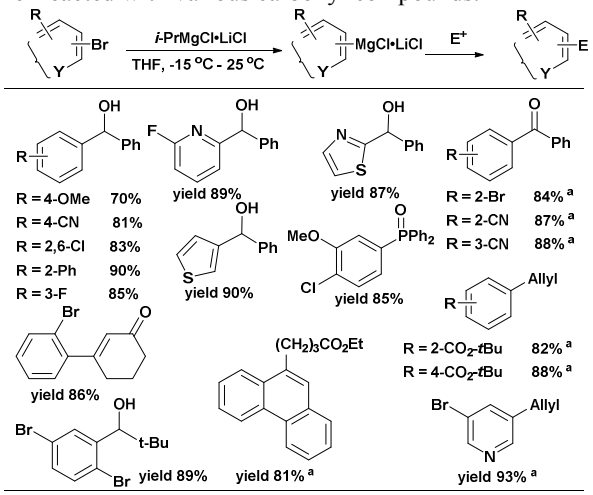
In 2011, Studer and co-workers [26] described that a series of α-alkynylated nitrones were efficiently and conveniently synthesized *via* an one-pot consecutive nucleophilic addition of alkynyl Grignard reagents to aliphatic nitrones, followed by TEMPO/O_2 catalyzed oxidation (Scheme 9). In this study, the authors found that the addition of water was beneficial, and this result could be rationalized considering that the formation of nitroxide with hydroxylamine by H-transfer was faster than direct electron-transfer from the metallized hydroxylamine. The resulting nitroxide contained an α-proton could undergo a subsequent disproportionation reaction to give the alkynylated nitrone product and hydroxylamine intermediate. Further

experiments demonstrated that the preparation of phenylethynyl Grignard reagents *via* different ways of the corresponding phenylacetylene with either *i*-PrMgCl·LiCl or *i*-PrMgCl was equally effective.

3.3 Preparation of sp^2 hybridized organomagnesium reagents

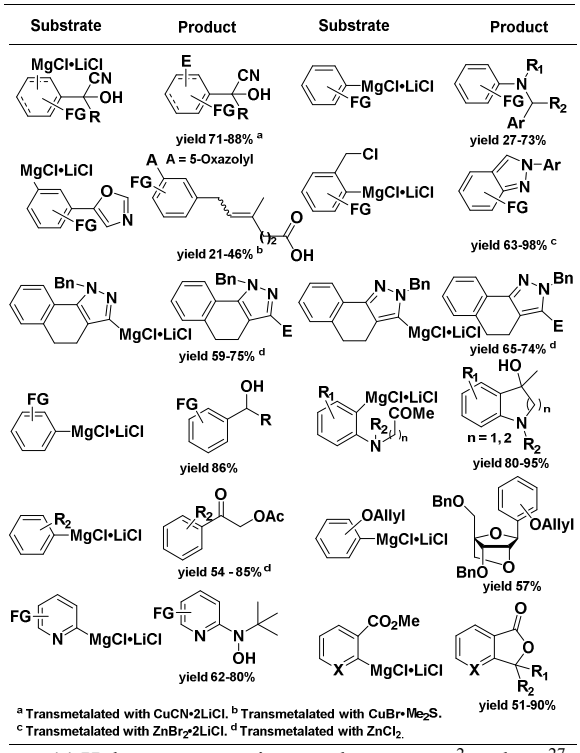
The deprotonation *via* *i*-PrMgCl·LiCl is not the only way to generate another more useful organomagnesium reagents. The turbo Grignard reagent can also remove halogen atoms (known as halogen–magnesium exchange) or other leaving groups (e. g., sulfoxide-magnesium exchange) from organic substances. By complexing *i*-PrMgCl with one equivalent of LiCl, Krasovskiy and Knochel[8] observed for the first time that the rate of the halogen-magnesium exchange was remarkably increased and the reactivity and solubility of the resulting Grignard reagents were enhanced. The reactivity-boost of the turbo Grignard reagent was a tremendous improvement because it allowed even electron-rich (hetero)aryl bromides to be used in halogen-magnesium exchange reactions compared to the usually more expensive and less stable iodides (Scheme 10).

Several research groups have applied this reaction sequence for the convenient and expedient preparation of highly functionalized aryl or heteroaryl compounds, such as unsaturated silylated cyanohydrins,[27a] tertiary aryl amines,[27b, 27c] mycophenolic acid derivatives,[27d] indazoles,[27e, 27f] secondary benzylic alcohols,[27g, 27h, 27i] 4-hydroxytetrahydroquinolines,[27j] α-hydroxyacetophenones,[27k] hydroxyphenyl nucleobase derivatives,[27l] substituted 2-pyridylhydroxylamines[27m] and 3-aryl- and alkylphthalides[27n] (Scheme 11). Even iodoporphyrins also underwent the iodine-magnesium exchange with *i*-PrMgCl·LiCl without decomposition of the porphyrin core and further reacted with various carbonyl compounds.[27o]



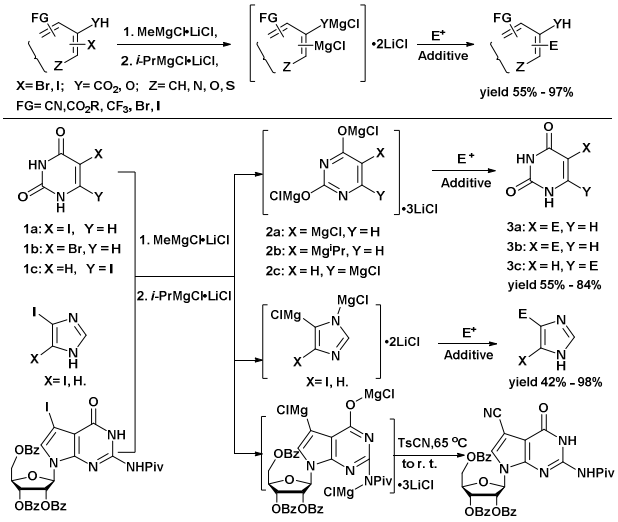
Scheme 10 The pioneering studies of sp^2 hybridized Grignard reagents by Knochel and Krasovskiy.[8]

Inspired by the pioneering work of Prof. Knochel, a variety of efforts have been made in the preparation of sp^2 hybridized organomagnesium reagents by using *i*-PrMgCl·LiCl. Moreover, the reactivity and selectivity of the resulting organomagnesium reagents can be further tuned after the *in situ* transmetalation (simply treating with the salt of a less electropositive metal), which opens an easy access to new interesting organometallics and allows us to perform an efficient subsequent reaction. It is particularly noteworthy that the synthetic utility of *i*-PrMgCl·LiCl, with highly functionalized group tolerance and high levels of chemoselectivity has been considerably improved.



Scheme 11 Halogen-magnesium exchange at sp^2 carbon.[27]

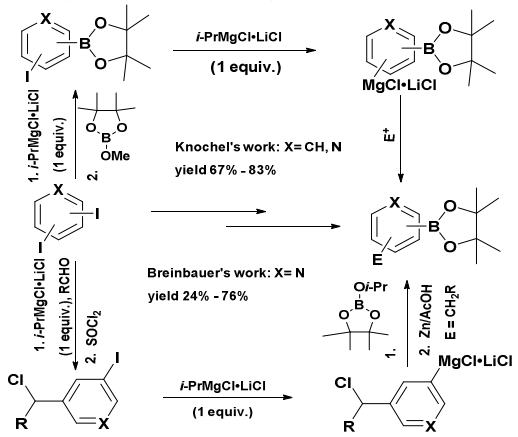
3.3.1 Functional group tolerance of halogen-magnesium exchange



Scheme 12 Exchange in the presence of acidic groups.[28-32]

Besides the classical functional groups mentioned above (e. g., alkyl, alkoxyl, CN, halides and carboxylic esters), substrates with many other sensitive or reactive functional groups can also undergo the halogen-magnesium exchange successfully employing the turbo Grignard reagent. For example, using the protocol of a stepwise deprotonation and exchange reaction, Knochel and co-workers described the generation of organomagnesium reagents from unprotected aromatic and heteroaromatic alcohols[28] and carboxylic acid derivatives[29] (top, Scheme 12). In both of the examples cited here, the first magnesium reagent (MeMgCl·LiCl) acted selectively

as a base, which was necessary to avoid the formation of the organomagnesium reagent before the complete deprotonation of the acidic moieties had occurred. Otherwise, the proton transfer from remaining acid groups could quench the desired organomagnesium species. The second reagent (*i*-PrMgCl·LiCl) then was used as a exchanged reagent to obtain the corresponding Grignard reagents, which displayed an excellent reactivity towards many electrophiles (e. g., acid chlorides, B(O*i*-Pr)$_3$, TsCN, allylic halides and aldehydes). Furthermore, this protocol has been successfully employed to heterocyclic systems like imidazoles,[30] uracils[31] and nucleosides[32] (bottom, Scheme 12).

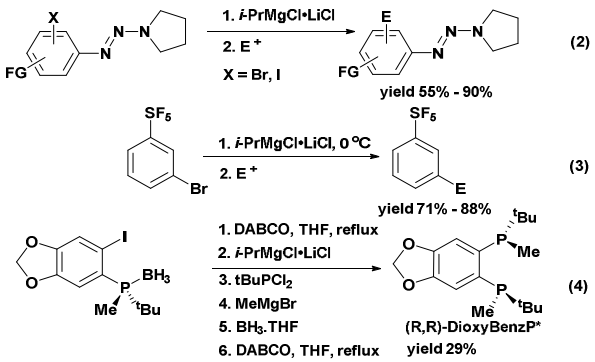


Scheme 13 Preparation of the (hetero)aryl boronic esters.[33]

The use of boronic esters as synthetic intermediates has attracted much research interest owing to their potential application in organic synthesis. In the case of the reaction of *para*-iodoboronic ester with *i*-PrMgCl, the unexpected isopropylboronate was achieved from the attack of *i*-PrMgCl at the boronic ester functionality. Fortunately, Knochel and co-workers[33a] found that iodine-magnesium exchange reactions were performed on the iodoaryl boronic esters by treatment with *i*-PrMgCl·LiCl in THF at -78 °C (top, Scheme 13). The obtained organomagnesium reagents were quenched with typical electrophiles (e. g., acid chlorides, 3-iodoenones, allylic halides and aldehydes) affording the desired products in good yields. It is interesting to note that iodoaryl boronic esters could be easily prepared *via* iodine-magnesium exchange starting from the corresponding diiodines in excellent yields. Later in 2013, Breinbauer and co-workers [33b] presented a general approach to the synthesis of 3,5-disubstituted pyridine boronic acid pinacol ester through changing the addition order of the electrophiles (bottom, Scheme 13). Analogously, highly functionalized (hetero)arylboronic esters were prepared readily from the corresponding magnesium chloride-lithium chloride complexes by other research groups[33c, 33d, 33e].

Knochel and co-workers [34] have shown that the treatment of iodo- or bromo- substituted aryltriazenes with *i*-PrMgCl·LiCl generated magnesiated derivatives which could react with various electrophiles (e. g., acid chlorides, 3-iodoenones, allylic halides and aldehydes) to afford polyfunctional triazenes (eqn. 2, Scheme 14). However, no formation of arylmagnesium reagents was observed when reacted with *i*-PrMgCl. Subsequently, the triazene moieties could be readily converted into the corresponding aryl azides and aryl iodides in moderate to excellent yields, which were versatile intermediates and could be further transformed into a range of more elaborated structures.

Stimulated by the unique charm and characters continuously, there is a growing focus on the synthesis of the highly fluorinated molecules in pharmaceutical and agrochemical research as well as material science. Although it is similar to the commonly-used CF_3



Scheme 14 Halogen-magnesium exchange of aromatic halides bearing triazene, SF_5 and P(Me)*t*-Bu functionality.[34-36]

function, SF_5 group is a more bulky substitute. However, the barely known organometallics bearing the SF_5 substituents are generally tolerated at low temperatures. Knochel and co-workers[35] have investigated the preparation of SF_5 substituted organomagesium reagents *via* bromine-magnesium exchange reactions starting from the commercial 1-bromo-3-pentafluorosulfanylbenzene (eqn. 3, Scheme 14). The resulting organometallics was used in several subsequent functionalizations such as addition to aldehydes or acid chloride, and Pd-catalyzed cross-coupling reactions.

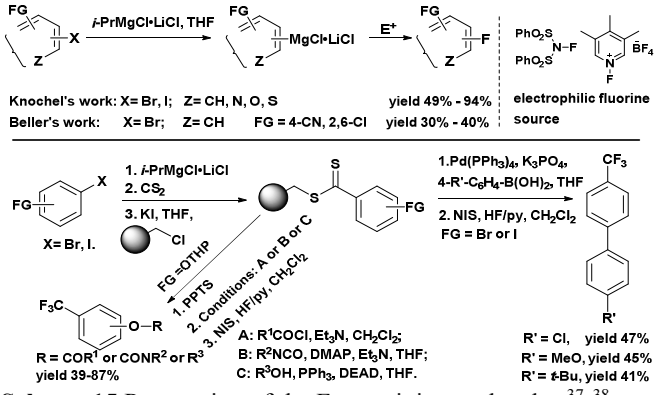
Although the P-chiral phosphine ligand is successfully employed for the first time in industry for the production of *L*-DOPA, that relatively little attention has been paid is mainly due to difficulties in synthesis and apprehension about the possible stereomutation at P-stereogenic centers. In 2012, Imamoto and Gridnev[36] demonstrated that the substrates bearing *tert*-butylmethylphosphino groups with DABCO and *i*-PrMgCl·LiCl afforded the organomagnesium intermediates, which could be finally converted into the conformationally rigid (*R*, *R*)-DioxyBenzP* (eqn. 4, Scheme 14). Remarkably, the yield was significantly lower when *sec*-butyllithium was used instead of *i*-PrMgCl·LiCl, probably because the generation of benzyne prevailed over the halogen-metal exchange reaction.

3.3.2 Diversity of subsequent functionalizations

A large variety of functional groups could be introduced as substituents and tolerate the halogen-magnesium exchange by using the turbo Grignard reagent *i*-PrMgCl·LiCl. Furthermore, the resulting organomagnesium chloride-lithium chloride complexes exhibited good to excellent reactivities to a broad range of electrophiles in succeeding transformations leading to highly diverse compounds that were so inaccessible. Some cases have been selected to further exemplify the benefits.

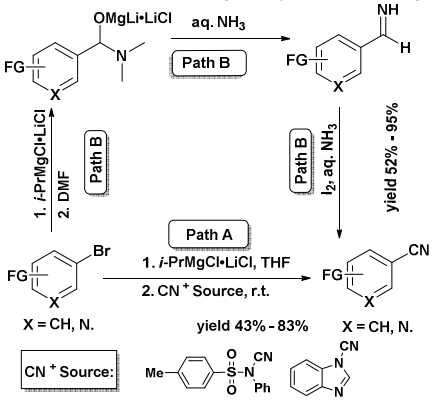
Traditional known methods for the direct introduction of a fluorine atom to aromatic or heterocyclic compounds usually require relatively harsh conditions that are incompatible with many functional groups. More specifically, the electrophilic fluorination of aryl magnesium compounds has been reported for simple Grignard reagents; however, it proceeded with moderate to poor yields.[37a] Recently, Knochel group[37b] and Beller group[37c] reported, almost at the same time, a convenient and efficient transformation of aryl and heteroaryl organomangesium chloride-lithium chloride complexes into the desired fluorinated products, respectively (top, Scheme 15). In Knochel's report, *N*-fluorobenzenesulfonimide (NSFI) was chosen as the fluorination reagent, and the fluorinated cosolvent

(e. g., perfluorodecalin) was found to be significantly beneficial for this transformation because the formed aryl radical might be able to abstract a fluorine atom from this cosolvent. In Beller's case, various electrophilic fluorinating reagents were examined. The use of *N*-fluoro-2,4,6-trimethylpyridinium salts gave the best yield of electrophilic fluorination, and the counteranions of the salt, which were not directly involved in the transfer of fluorine, had little or no independent influence on this chemical transformation.



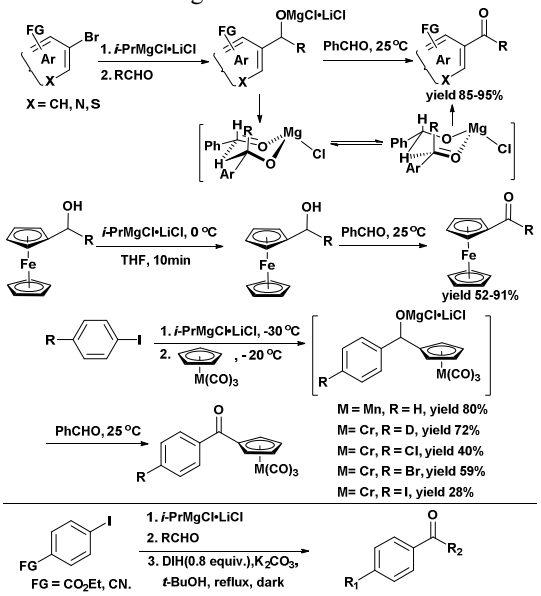
Scheme 15 Preparation of the F-containing molecules.[37, 38]

Similar to the incorporation of the fluorine atom, the introduction of trifluoromethyl group into organic molecules can substantially modify their physical, chemical, and biological properties. Bräse and co-workers[38] realized the first successful trifluoromethylation of immobilized arenes (bottom, Scheme 15). The organomagnesium reagents obtained from haloarenes and *i*-PrMgCl·LiCl were attached to a Merrifield resin through a novel dithioester linker system and subsequently modified by means of different transformations. In the final step fluorinating cleavage by using the suitable combination of *N*-iodosuccinimide (NIS) and HF/pyridine (Olah's reagent) enabled the release of target trifluoromethyl arene products from the resin in good yields and high purities.



Scheme 16 Electrophilic cyanation.[39]

Aryl and heteroaryl nitriles are one of the most important constituents of pharmaceuticals, agrochemicals, herbicides, dyes and natural products. In addition, the cyano group also serves as a key intermediate structure for a multitude of possible transformations into various useful functional groups. As an alternative to nucleophilic cyanation of aryl and heteroaryl halides, the electrophilic cyanation of reactive organometallic species is among the most promising strategies, which is still somewhat underdeveloped. Beller group[39a, 39b] and Togo group[39c] independently developed the successful cyanation of aryl and heteroaryl organomagnesium chloride-lithium chloride complexes by using different cyanating sources (Scheme 16). In Togo's system, from the mechanistic point, the aryl bromides reacted with *i*-PrMgCl·LiCl and then DMF was introduced into the initial step. By adding aq. NH_3 to the reaction mixture, the resulting adduct was converted into the corresponding aldimine. Finally aldimine reacted with equivalent iodine in the presence of NH_3 to furnish *N*-iodo aldimine, followed by β-elimination of HI by NH_3 to provide the desired nitriles analogues.



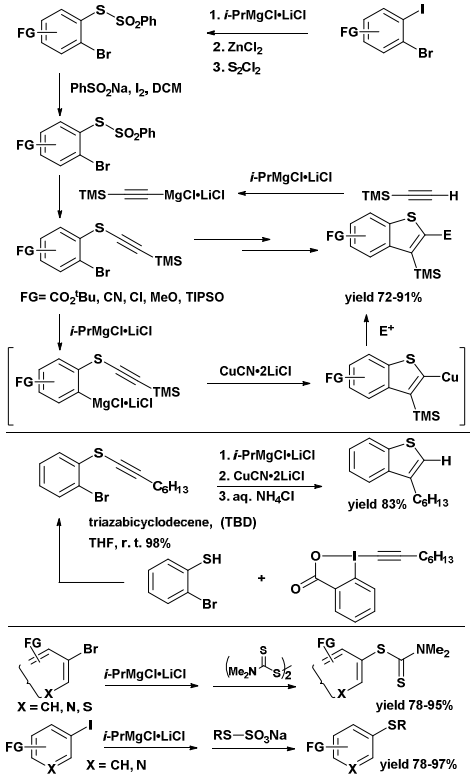
Scheme 17 Tandem nucleophilic addition and oxidation.[40]

Compared to the conventional metal-based two-step procedure, one-pot multi-step synthesis of ketones directly from aldehydes has received much attention in recent years. In 2007, Knochel and co-workers[40a] described the tandem nucleophilic addition and magnesium-Oppenauer oxidation as an approach to synthesize aryl and metallocenyl ketones at room temperature (top, Scheme 17). In the absence of LiCl, the reaction did not go to completion and several byproducts were observed. The authors suggested the intermolecular hydride transfer from the resulting magnesium alkoxides to an excess of benzaldehyde probably *via* a six-membered ring transition state. Moreover, the presence and composition of LiCl not only solubilized the resulting magnesium alkoxides, but also activated the carbonyl function of benzaldehyde as a Lewis acid. In a more recent paper on this topic, Togo and co-worlers[40b] also examined the practical one-pot preparation of ketones by the reaction of aryl halides with *i*-PrMgCl·LiCl followed by treatment with aldehydes and subsequent oxidation with 1,3-diiodo-5,5-dimethylhydantoin (DIH) to provide the desired products (bottom, Scheme 17).

Benzo[*b*]thiophenes and their related sulfur-containing aromatic derivatives, which are core skeletons frequently found in new electronic materials as well as in biologically active molecules, are generally prepared by two approaches, either *via* annulation of an aromatic ring onto a thiophene moiety or *via* construction of a thiophene ring onto an aromatic moiety.

In 2012, Knochel and co-workers[41a] reported an intramolecular-sequential copper-catalyzed method for the synthesis of functionalized benzo[*b*]thiophenes (top, Scheme 18). Initially, the magnesiation of the TMS-substituted alkynyl(aryl)thioethers was achieved *via* bromine-magnesium exchange using *i*-PrMgCl·LiCl. Then, an addition of

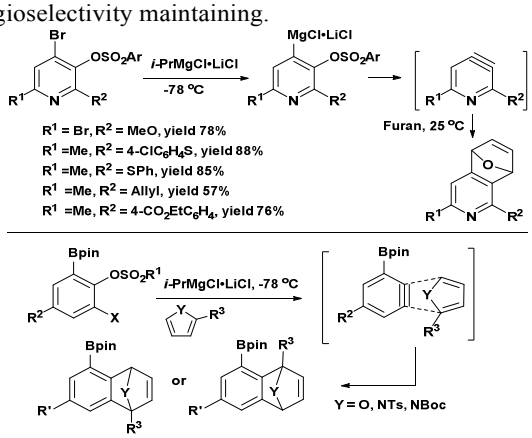
CuCN·2LiCl facilitated the transmetalation and subsequent intramolecular carbocupration. However, in the absence of the copper catalyst no cyclization was observed. Finally, quenching of the resulting organocuprate intermediates with various electrophiles provided highly diversified benzothiophene derivatives. The utility of the trimethylsilyl group held the opportunities to introduce different functional groups onto the aryl group or transform it into different functional groups through known methods. It was noteworthy that the starting *ortho*-substituted bromoiodoarenes were prepared in three straightforward steps as shown in Scheme 18.



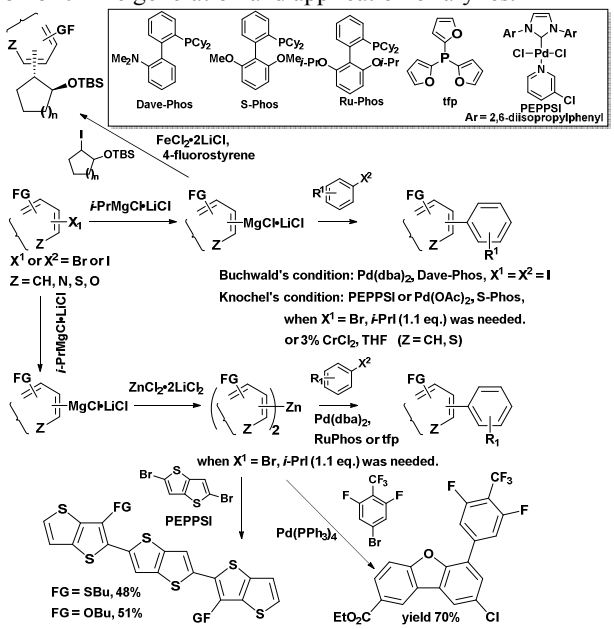
Scheme 18 Preparation of the sulfur-containing molecules.[41]

Most recently, Waser and co-workers[41b] described a facile and efficient one-pot direct synthesis of thioalkynes from thiols using ethynyl benziodoxolonehypervalent iodine reagents and further examined the transformation into the benzothiophene using the Knochel's protocol (middle, Scheme 18). Similarly, Knochel and co-workers[41c] reported that a diverse array of aryl and heteroaryl magnesium reagents reacted in the presence of LiCl with tetramethylthiuram disulfide affording the expected dithiocarbamates in good yields, which could be readily transformed into thiol, thiol salt or thioether. Very recently, Reeves group[41d] disclosed the first general and direct synthesis of aryl sulfides from the Bunte salts as electrophiles and the corresponding organomagnesium chloride-lithium chloride complexes, which were obtained though halogen-magnesium exchange reactions.

Arynes and heteroarynes are highly reactive intermediates due to the strained nature of the ring, which have numerous applications in organic synthesis. A very attractive approach is the Diels-Alders reaction between arynes and dienes of aromatic five-membered heterocycles, particularly furan and its derivatives. Recently, the halogen-magnesium exchange with *i*-PrMgCl·LiCl was applied to the generation and synthesis of highly functionalized benzynes by Knochel and co-workers (top, Scheme 19).[42a] Thus, 4-chlorobezenesulfonic acid pyridinyl esters were treated with *i*-PrMgCl·LiCl, and the reactions were completed at -78 °C within 0.5 to 6 h to give rise to 2-magnesiated aryl sulfonates. After the elimination of 4-$ClC_6H_4SO_3MgCl$ at room temperature, functionalized 3,4-pyridynes were formed and trapped with furan in 57-88% yields. Analogously, Akai and co-workers[42b, 42c] reported the regioselective Diels-Alder cyclization of 3-borylbenzynes between furans and substituted furans or pyrroles, furnishing the formation of fused ring systems (bottom, Scheme 19). Extensive studies[42c] revealed that the use of more active *i*-PrMgCl·LiCl slightly improved the yields of cycloadducts with the regioselectivity maintaining.



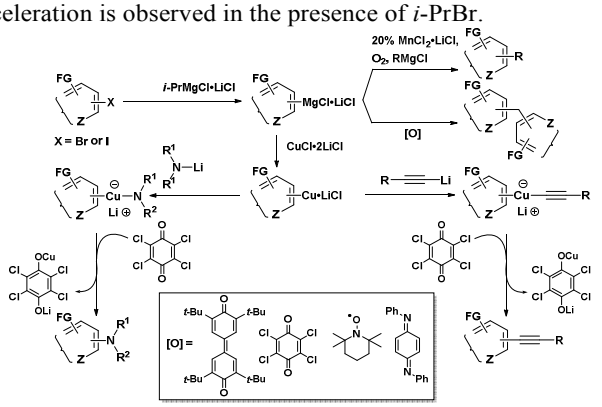
Scheme 19 The generation and application of arynes.[42]



Scheme 20 Cross coupling catalyzed by transition metal.[43]

The transition metal catalyzed cross coupling of an organometallic reagent with a related electrophile has proven to be highly valuable chemical transformations in modern organic synthesis, offering new methods to achieve C–C bond formations. After the successful development of mild and selective methods for the preparation of organomagnesium compounds using *i*-PrMgCl·LiCl, these resulting organomagnesium chloride-lithium chloride complexes have been successfully applied in transition metal catalyzed cross coupling reactions,[43] such as Kumada-Corriu coupling,[43a, 43b, 43c] Negishi coupling[43d, 43e, 43f, 43g] and $C(sp^2)$–$C(sp^3)$ coupling of 2-

iodocycloalcohol derivatives with (hetero)aryl Grignard reagents[43h] (Scheme 20). Interestingly, both Kumada-Corriu coupling and Negishi coupling can be accelerated by the presence or addition of *i*-PrI or other alkyl iodides, but no rate acceleration is observed in the presence of *i*-PrBr.



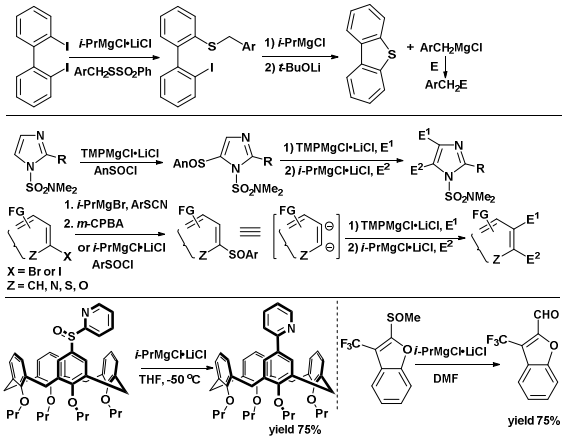
Scheme 21 Oxidative coupling between two organometallic reagents.[23a, 44, 45]

The oxidative coupling between two organometallic reagents, in which an extra oxidant is needed to accept two redundant electrons, could serve as a useful complement to classical transition metal catalysed cross coupling of an organometallic reagent with a related electrophile, even eventually replace this traditional chemistry in some contexts.[44] In this context (Scheme 21), several research groups have investigated the use of 3,3',5,5'-tetra-*tert*-butyldiphenoquionone,[23a] chloranil,[23a] TEMPO,[45a] and *N,N'*-diphenyl-*p*-benzoquiononediimine[45b] as organic oxidants in the simple preparation of functionalized biaryls and dienes through metal-free homocoupling of sp^2 hybridized organomagnesium reagents complexed by LiCl. By carefully choosing the nature of the organic groups in different organomagnesium reagents, Cahiez and co-workers[45c] reported a $MnCl_2$ catalyzed oxidative heterocoupling reaction between 2-cyanophenylmagnesium chloride-lithium chloride complex and traditional Grignard reagents with oxygen as an oxidant.

On the other hand, the transmetalation of organomagnesium chloride-lithium chloride complex with CuCl·2LiCl provided the corresponding copper derivatives. The subsequent reaction with a lithium amide or an alkynyl lithium compound resulted in the formation of the lithium amidocuprate or the lithium aryl(alkynyl)cuprate. These intermediates could be oxidized with chloranil to afford oxidative amination products[45d, 45e, 45f, 45g] and oxidative Sonogashira-type products.[45h]

3.3.3 Diversity of other leaving groups

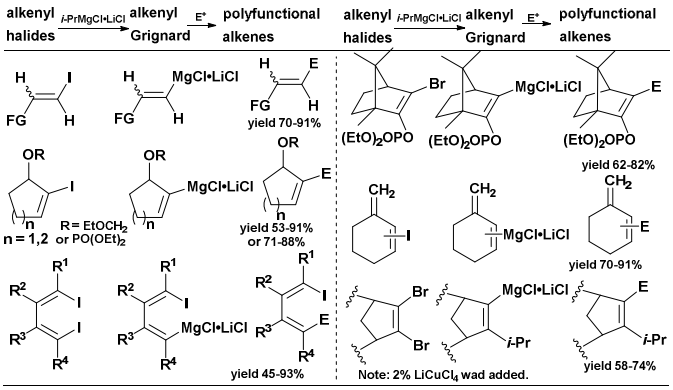
Among the most common methods for preparing organomagnesium reagents, halogen-magnesium exchange reactions are still problematic as many organic bromides and especially iodides suffer from dehalogenation reactions due to their thermal or photoinstability. To overcome these difficulties, the use of non-halogenated compounds in the exchange reactions has been the target of diverse investigations. A novel intramolecular sulfur-magnesium exchange was reported by Knochel and co-wokers[46a] and allowed the preparation of functionalized benzylic magnesium reagents, which were rather tedious if prepared by the magnesium insertion into benzylic bromides, because of the unwanted side products from the Wurtz homocoupling and the difficult activation of the magnesium. Remarkably, the role of *t*-BuOLi might be explained tentatively through the formation of magnesiated intermediates (RMg(O*t*-Bu)Cl$^-$Li$^+$), which encountered the similar coordination mode to that in *i*-PrMgCl·LiCl. Then, the more reactive magnesiate intermediates further underwent the intramolecular sulfur-magnesium exchange reactions, furnishing the benzylic magnesium reagents and the stable cyclic dibenzothiophene (top, Scheme 22).



Scheme 22 Other magnesium exchange reactions.[46]

Another possible substitute for halogenated organic substances is sulfoxide, which is also suitable for exchange reactions in the generation of organomagnesium reagents. Knochel and co-workers[46b, 46c, 46d, 46e, 46f] discovered that diverse aromatic or heteroaromatic sulfoxide derivatives as synthetic equivalents of the bis-carbanionic synthon obtained by convenient one- or two-steps syntheses, permitted an expedient two-step difunctionalization with two different electrophiles by directed metalation and sulfoxide-magnesium exchange (middle, Scheme 22). In the first step, the sulfoxide played the role of a directing metalation group with TMPMgCl·LiCl as a base. In the second step, it became a leaving group and underwent a regioselective sulfoxide-magnesium exchange with *i*-PrMgCl·LiCl. Furthermore, the exchange reactions based on the sulfoxide group were extended to other systems and allowed the preparation of substituted calixarenes[46g] and benzofurans[46h] in good yields (bottom, Scheme 22).

3.3.4 Other sp^2 carbon sources



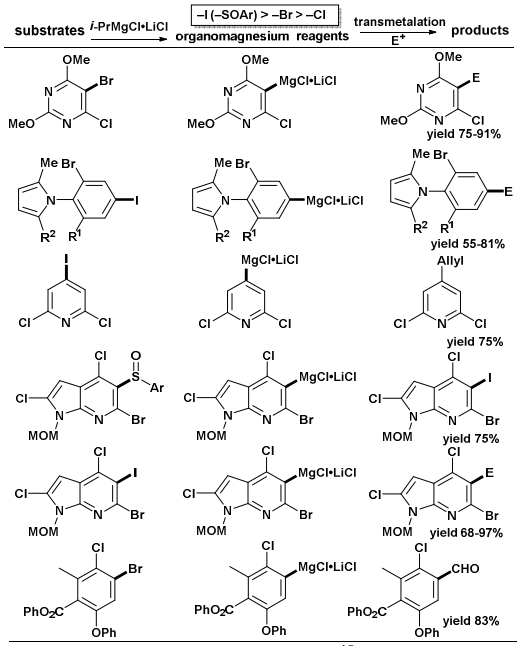
Scheme 23 The generation and application of alkenyl Grignard reagents.[47]

So far as we know, the iodine-magnesium exchange of alkenyl iodides with traditional Grignard reagents is relatively

slower than the similar one using aryl or heteroaryl iodides, which implies that either the use of more reactive Grignard reagents or the presence of chelating groups would be advantageous. The important breakthrough in the development of the turbo Grignard reagent was accomplished by Prof. Knochel, while his group and others[47] have explored the stereoselective preparation of functionalized acyclic and cyclic alkenylmagnesium reagents with retention of the double bond configuration by using highly reactive *i*-PrMgCl·LiCl, which can subsequently react with various electrophiles to provide polyfunctional alkenes with good yields and excellent stereoselectivity (Scheme 23).

3.3.5 Chem- and regio-selectivity of exchange reaction using *i*-PrMgCl·LiCl

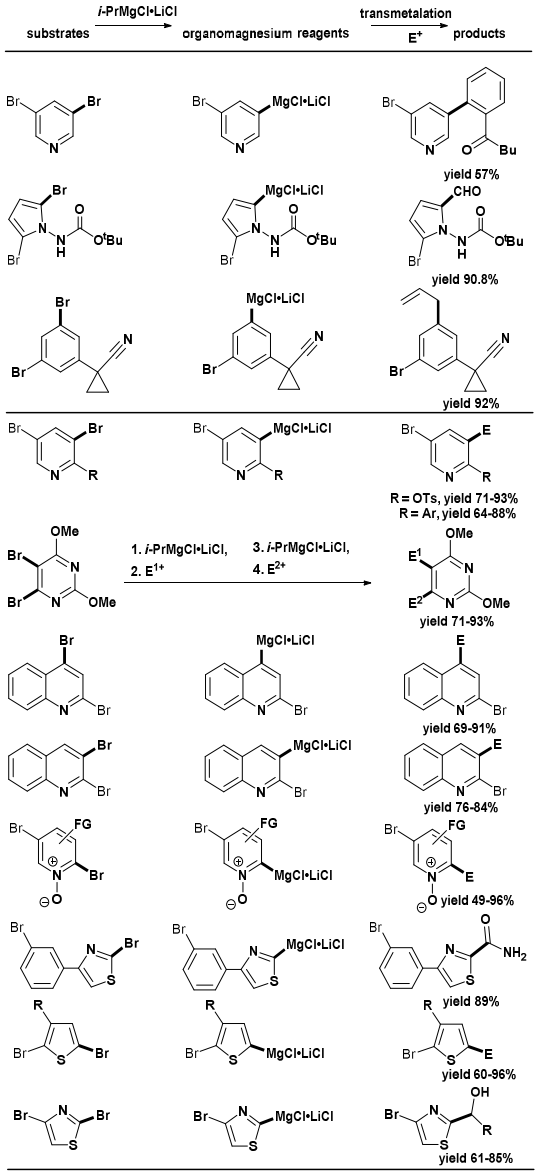
With only one exchangeable halide or other leaving group in the starting materials the position of the initial magnesiation is obvious. If more than one exchangeable halide or heteroatom is in the molecule, the presence and nature of substituents and halides (or heteroatoms) would influence the position of the initial halogen (heteroatom)-magnesium exchange. In addition, chemo- and regioselective multi- (mono-, di-, etc.) functionalization are particularly important, with fundamental starting materials carrying functional groups that offer multiple reactive positions.



Scheme 24 Leaving group dependence.[48]

If the exchangeable halides or heteroatoms are different, the excellent chemoselective reactivity of one leaving group in the presence of others could be observed (–I (–SOAr) > –Br > –Cl),[48] in line with the kinetic investigations[17d] of the leaving group dependence (Scheme 24).

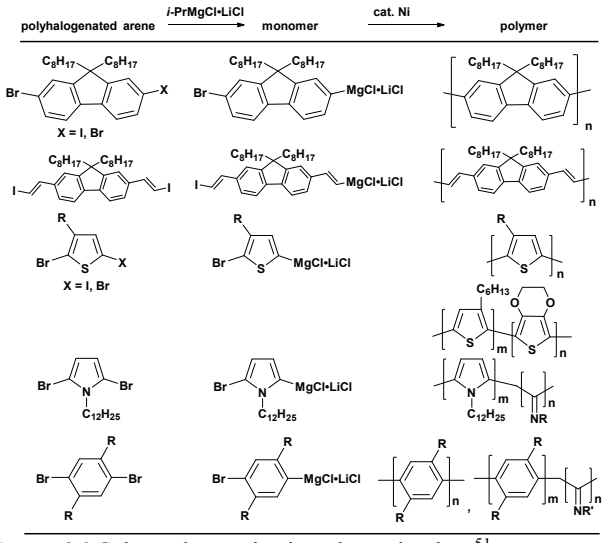
If the exchangeable halides and heteroatoms are same, the corresponding halogen (heteroatom)-magnesium exchange can be divided into two distinct parts. In the first case, the positions of two leaving groups in starting materials are symmetrical, so the initial magnesiation product would have been identical to the one provided (top, Scheme 25).[49] In another case, non-symmetrical starting materials containing multiple leaving groups using *i*-PrMgCl·LiCl lead to smooth and regioselective magnesiation of various aromatics and heterocycles with a broad functional group compatibility (bottom, Scheme 25).[48a, 48b, 50] As a result, the corresponding organomagnesium derivatives can be formed predominantly or even exclusively. The high regioselectivity can be observed *via* discrimination by electronic effects and chelating properties of substituents, in accordance with the theoretical prediction.[17] On the other hand, the steric discrimination is also responsible for the achievement in high regioselectivity for the halogen-magnesium exchange with *i*-PrMgCl·LiCl. For example, Knochel and co-workers[50e] have demonstrated the highly regioselective generation of 3-substituted thienylmagnesium derivatives using *i*-PrMgCl·LiCl in combination with $(Me_2NCH_2CH_2)O$ or $(Me_2NCH_2CH_2)NMe$. Furthermore, the resulting 3-substituted thienyl magnesium reagents could possibly be used in regioregular cross-coupling polymerizations.



Scheme 25 Exchange reactions of polyhalogenated arenes and heteroarenes.[48a, 48b, 49, 50]

Actually, many other research groups have indeed explored the use of the turbo Grignard reagent in the synthesis of a variety of aryl and heteroaryl conjugated oligomers and

polymers.[51] Polymerization was conducted *via* Kumada-type cross-coupling reactions with catalytic amount of nickel(II) species. The addition of LiCl to the isopropylmagnesium chloride facilitated the formation of the mono-magnesiated monomer *via* the halogen-magnesium exchange and subsequent Grignard metathesis polymerization (GRIM) of less reactive conjugated monomers (Scheme 26). In comparison to other methods, the Grignard metathesis polymerization (GRIM) is essentially advantageous and particularly attractive for industries, since the use of both cryogenic temperatures and highly reactive metals is unnecessary.



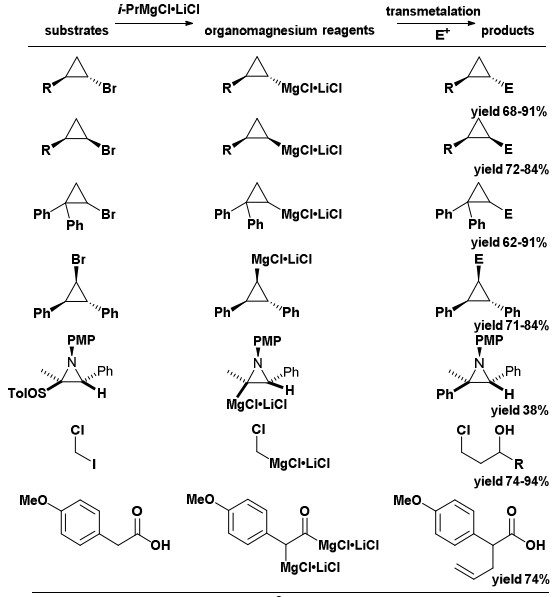
Scheme 26 Grignard metathesis polymerization.[51]

3.4 Preparation of sp^3 hybridized organomagnesium reagents

The halogen (or sulfoxide)-magnesium exchange on sp^3-hybridized carbon is a scientifically challenging research subject, since the gain of energy is less important (the resulting organomagnesium reagent and *i*-PrMgCl·LiCl have the same hybridization). As described in Scheme 27, Knochel and co-workers[52a] investigated the bromine-magnesium exchange of cyclopropyl derivatives without a chelating or an electron withdrawing group, in which the s-character of the carbon-halogen bond was increased compared to non-strained aliphatic systems. The reactivity of *i*-PrMgCl·LiCl in THF was found to be relatively low, however, the utilization of a THF/dioxane mixture led to an increased reactivity due to the enforcement of an anionic Schlenk equilibrium. The formed organomagnesium reagents were quenched with various electrophiles, furnishing the expected functionalized cyclopropanes with complete retention of configuration in good yields.

In related work, Bull and co-workers[52b] described the generation of unstabilized α-aziridino organomagnesium reagents *via* a sulfoxide-magnesium exchange, which could subsequently undergo the Negishi-type cross coupling. It was noted that the utilization of *i*-PrMgCl could give a dramatically improved yield of the desired product (61%) compared with that of *i*-PrMgCl·LiCl (38%).

Soon after that, Clososki and co-workers reported[52c] the generation of the mixed lithium-magnesium carbenoid $ClCH_2MgCl·LiCl$ through an iodine-magnesium exchange of chloroiodomethane with *i*-PrMgCl·LiCl and subsequent application of this *in situ* generated reagents in the synthesis of chlorohydrins. On the other hand, some aliphatic organic substances had a relative acidic proton that could be removed by very strong bases such as Grignard reagents. Mori and co-workers[52d] exploited the relative acidity of the proton at the α-position of arylacetic acids and provided a direct deprotonation intermediate with *i*-PrMgCl·LiCl and subsequently trapped with an allyl bromide, although an elevated temperature (60 °C) was required.



Scheme 27 Preparation of sp^3 hybridized organomagnesium reagents.[52]

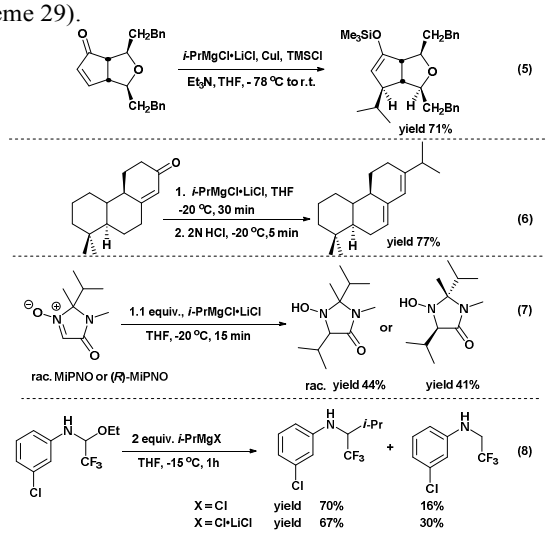
4. Direct substitution or addition of the turbo Grignard reagent

As mentioned above, in most cases the complex *i*-PrMgCl·LiCl has exhibited a dramatically increased rate and efficiency compared to *i*-PrMgCl for obtaining a variety of functionalized organomagnesium reagents. This may be explained by the structure of the turbo Grignard reagent, as outlined in Scheme 1, which displays an extra negative charge on the magnesium center enhancing the nucleophilic character of the isopropyl group.

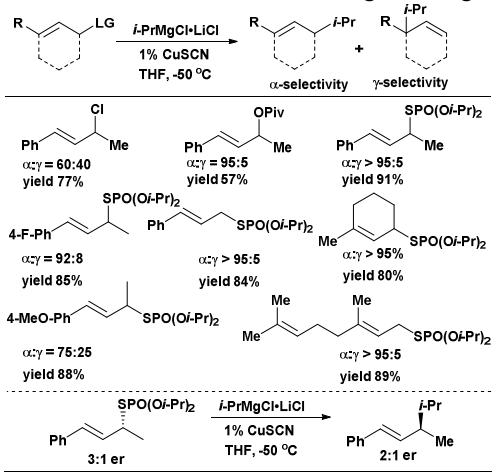
In 2005, Marsden and co-workers[53a] reported a copper-catalyzed addition of isopropylmagnesium chloride-lithium chloride complex to enone in the presence of chlorotrimethylsilane, which gave direct access to enol ether as a single diastereoisomer in a yield of 71% (eqn. 5, Scheme 28). Without a transition metal catalyst, Manzaneda and co-workers[53b] reported the 1,2-addition of α,β-unsaturated ketone with *i*-PrMgCl·LiCl and the further treatment with aquous HCl in THF gave the desired diene in a yield of 77% (eqn. 6, Scheme 28). In 2011, Chavant and co-workers[53c] prepared the isopropyl adduct through an addition of *i*-PrMgCl·LiCl onto the rac. or (*R*)-MiPNO with a moderate yield (eqn. 7, Scheme 28). In 2014, Deutsch and co-workers[53d] described that the nucleophilic addition of *i*-PrMgCl·LiCl to trifluoromethylated *N,O*-acetals could afford α-branched trifluoromethyl *N*-arylamine in a yield of 67% and the reduction product as a side-product in a yield of 30% (eqn. 8, Scheme 28).

It was worth mentioning that the yield of side-product was significantly higher with *i*-PrMgCl·LiCl (up to 30%) than with *i*-PrMgCl. This was presumably due to the higher degree of complexation in the presence of LiCl, which facilitated hydride

transfer to the substrates. In 2011, Wu and co-workers[54a] described a highly α-regioselective copper-catalyzed allylic alkylation of *i*-PrMgCl·LiCl utilizing diverse leaving groups (Scheme 29).



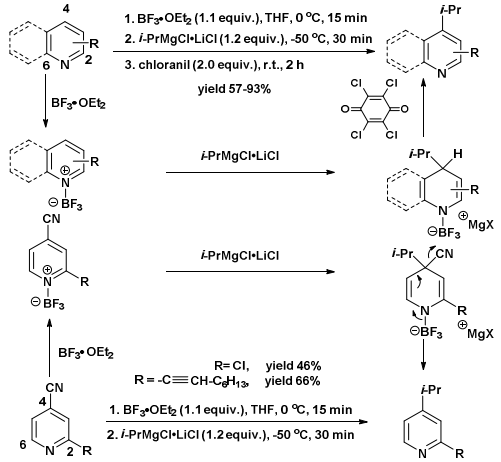
Scheme 28 Direct addition of the turbo Grignard reagent.[53]



Scheme 29 Direct allylic alkylation of the turbo Grignard reagent.[54]

The success of these reactions relied on the use of phosphorothioate esters as leaving groups and 1% CuSCN as a catalyst, enabling the generation of isopropylation products in good yields with excellent regioselectivities, *E*/*Z* selectivities and moderate levels of stereochemical fidelity. The order of α-regioselectivity ($SPO(Oi\text{-}Pr)_2$ > OPiv > Cl) mainly originated in the differences between the attractive electrostatic forces and the repelling steric interaction of the $SPO(Oi\text{-}Pr)_2$, OPiv and Cl groups on the Cu group.[54b]

The regioselective direct functionalization of simple and readily available pyridines affording structurally more complex pyridine derivatives is an extremely challenging task for organic synthetic chemists. In 2013, Knochel and co-workers[55a] reported a novel $BF_3{\cdot}OEt_2$ mediated direct isopropylation of functionalized pyridine derivatives with *i*-PrMgCl·LiCl, furnishing regioselectively 4-substituted desired products in 57-93% yields. The complexation of the pyridine nitrogen with BF_3 afforded the Lewis pair, which made the C(2), C(4) and C(6) position of the pyridine ring especially electrophilic. The regioselectivity of the subsequent Chichibabin-type nucleophilic addition of *i*-PrMgCl·LiCl could be explained by the steric hindrance by complexed BF_3 shielding the *ortho* position, and thus the C(4) position of the pyridine ring should be preferred. Finally, a suitable oxidative work up by chloranil was crucial to aromatize the 1,4-dihydropyridine intermediates to obtain the expected pyridine products (Scheme 30). Functional groups such as chloro, bromo, vinyl, phenyl, cyano and carbethoxy were tolerated under this condition. In addition, the same group[55b] found that if the C(4) position of the pyridine ring had already been occupied by a suitable leaving group, like CN group, the treatment of isonicotinonitrile derivatives with $BF_3{\cdot}OEt_2$ and *i*-PrMgCl·LiCl led to the generation of 4,4-disubstituted-1,4-dihydropyridine intermediates, which further underwent a non-oxidative rearomatization to give functionalized pyridine products.



Scheme 30 Direct isopropylation of pyridine derivatives.[55]

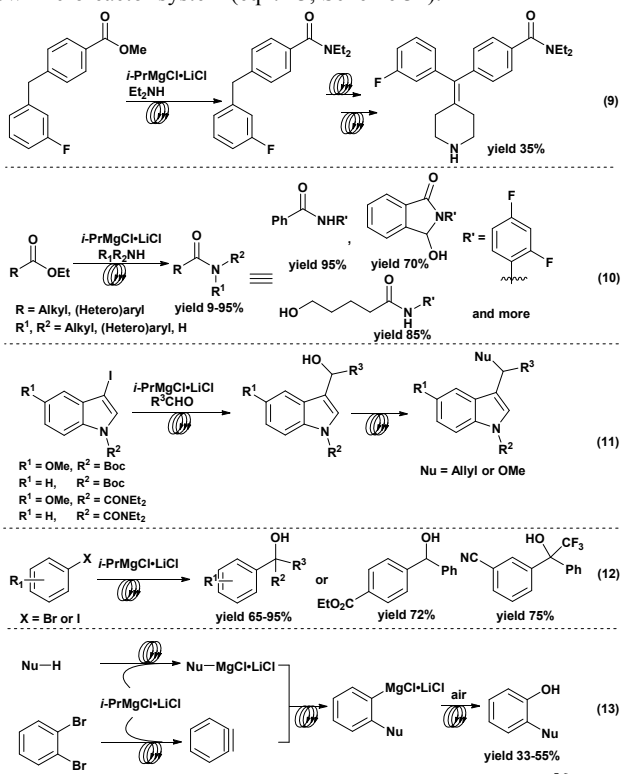
5. The turbo Grignard reagent in flow chemistry

The continuous flow technique as a machine-assisted approach is expected to make a fundamental or revolutionary change in organometallic chemistry. In fact, extensive studies on organometallic chemistry using flow microreactors have opened up new possibilities in organic synthesis and highly stimulated the correlative development in laboratory research and industrial production.

In 2010, Ley and co-workers (eqn. 9, Scheme 31)[56a] demonstrated a four-step continuous flow in synthesis of *N,N*-diethyl-4-(3-fluorophenylpiperidin-4-ylidenemethyl)-benzamide, whereby the initial step required the formation of diethyl amide using *i*-PrMgCl·LiCl. Similarly, Alcázar and co-workers subsequently realized the synthesis of amides mediated by the turbo Grignard reagent *via* flowing approach, which could be applied not only to various anilines and primary and secondary amines, but also to aliphatic and aromatic esters (eqn. 10, Scheme 31).[56b]

Additionally, several research groups[56c, 56d, 56e] have also provided clear and convincing evidences that *i*-PrMgCl·LiCl could act as a flow-compatible reagent for the in-line generation of organomagnesium intermediates *via* a halogen-magnesium exchange that could be subsequently converted *in situ* in these continuous flow processes (eqn. 11 and 12, Scheme 31). Particularly, Jamison and co-workers[56f] discovered that the benzyne intermediate could be achieved from 1,2-dibromobenzene through a halogen-magnesium exchange and an elimination process using continuous flow systems, which further underwent a selective addition of magnesiated nucleophiles, such as thiophenols and anilines. After the subsequent aerobic oxidation, the corresponding substituted phenol products were successfully obtained in moderate yields using the integrated

flow microreactor system (eqn. 13, Scheme 31).



Scheme 31 Application of continuous flow techniques.[56]

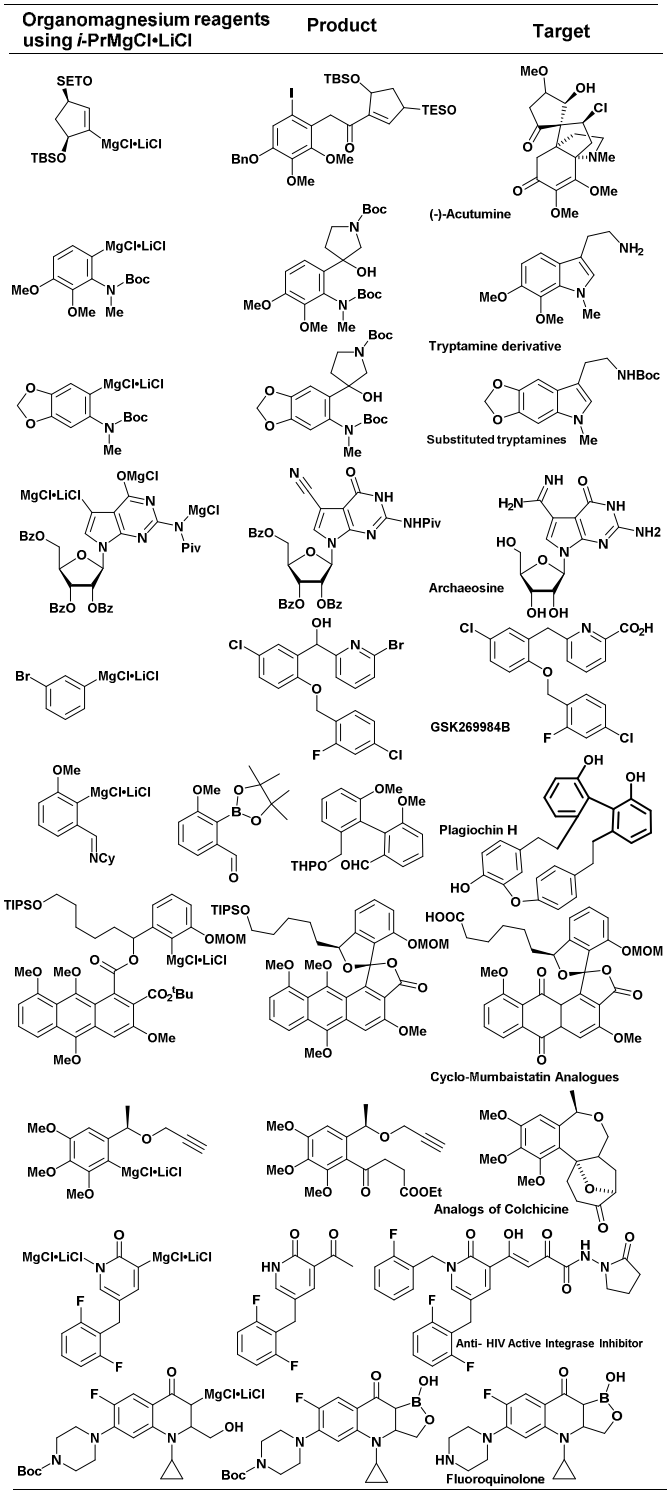
6. Practical application in natural products and pharmaceuticals

Many research teams have adopted the above-mentioned methodologies using *i*-PrMgCl·LiCl in the synthesis of natural products and biologically active molecules. Several outstanding examples[57] with a focus on this topic are summarized in Scheme 32. Obviously, a variety of valuable building blocks in both organic and medicinal chemistry, especially functionalized aromatic and heteroaromatic compounds, can be prepared easily with a broad range of functional group tolerance. In addition, its use at the start of the total synthesis requires large scale. Indeed and rather impressively, this compilation of selected examples in Scheme 32 clearly shows that these sequences using *i*-PrMgCl·LiCl can be considered for scale-up processes.

7. Conclusion and Outlook

The emergence of the turbo Grignard reagent *i*-PrMgCl·LiCl in chemical synthesis has opened new dimensions for preparative organic chemistry since its debut in 2004, which has attracted significant interest and shown great application potential either as an exchange reagent to obtain functionalized organomagnesium reagents or as a nucleophile to directly achieve the isopropylation products. Compared to conventional Grignard reagents, these reactions using *i*-PrMgCl·LiCl generally exhibit higher levels of reactivity and selectivity and more important result in excellent functional group tolerance under mild reaction conditions.

In this feature article, we have highlighted the basics of its performance evaluation and summarized the developments in ten years. Despite the aforementioned impressive progress, the



Scheme 32 Practical application in natural products and pharmaceuticals.[57]

turbo Grignard reagent as a tool in the minds and hands of creative synthetic chemists will always remain sharp as they attempt to solve more complex puzzles.

The potential advances, from our perspective, might occur in the following scenario: (1) The effect of metalation for turbo Grignard reagent will go far and beyond with delivery by the turbo Hauser bases through a deprotonation *via* *i*-PrMgCl·LiCl

and/or transmetalation with other metals. (2) The further novel applications of the turbo Grignard reagent will be anticipated, especially in the synthesis of complex natural products, pharmaceuticals and polymer materials. (3) To provide more guidance to synthetic application, an in-depth insight into the relationship between the microstructures of *i*-PrMgCl·LiCl and the apparent reactivities of substrates will be partly required. (4) The commercially available reagent will deserve a place in industry undoubtedly, for instance, its attempt in flow chemistry seems to be a promising beginning.

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