Transition Metal-Catalyzed Carbon−Carbon Bond Formation with Grignard Reagents − Novel Reactions with a Classic Reagent

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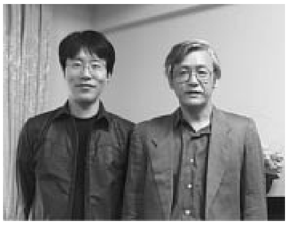
Organomagnesium compounds are among the most useful organometallic reagents in organic synthesis. Besides their classical nucleophilic reactions to carbonyl compounds, Grignard reagents gain versatile reactivity when combined with various transition metal salts. In this article, we review mainly our own studies on manganese-, iron-, chromium-, and cobalt-catalyzed carbon–carbon bond formation reactions using Grignard reagents. Other closely related research in this field is also discussed.

1. Introduction

Organomagnesium halides (RMgX) are one of the most classical organometallic species, and they were the first organometallic compounds to become useful in synthetic organic chemistry.[1] Since the discovery of the reaction of RMgX with carbonyl compounds by V. Grignard in 1900,[2] numerous efforts have been devoted to reveal the reactivity of such species and to develop new applications in the synthesis of natural and unnatural compounds. Grignard reagents continue to be synthetic tools of high importance for organic chemists and are frequently used in the laboratory. In addition, numerous industrial applications have been also reported.

The main reaction pattern of a Grignard reagent itself can be classified into (1) nucleophilic addition or substitution, (2) proton abstraction as a base, and (3) magnesium−halogen exchange reaction (Scheme 1). Recently, the use of iodine−magnesium exchange to prepare highly functionalized Grignard reagents has been a hot topic in organomagnesium chemistry.[3] In addition, Grig-



Hiroshi Shinokubo (left) was born in Kyoto, Japan, in 1969. He graduated from Kyoto University in 1992, and obtained his doctorate there in 1998. He was appointed as an Assistant Professor at Kyoto University in 1995. He worked with Professor Rick L. Danheiser at MIT from 1999 to 2000 as a visiting scientist. He was promoted to Associate Professor in 2003. He received the Japan Chemical Society Award for Young Chemists in 2004. His research interest is the development of new organic reactions.

Koichiro Oshima (right) was born in Hyogo, Japan, in 1947. He received his B.S. and Ph.D. degrees from Kyoto University in 1970 and 1975 under the guidance of Professor Hitosi Nozaki. He spent two and a half years as a postdoctoral fellow with Professor Barry Sharpless at MIT from 1975 to 1977, and became an Assistant Professor at Kyoto University in 1977. He was promoted to Lecturer in 1984, Associate Professor in 1986, and Professor in 1993. He has been involved in the development of organic reactions using organometallic reagents and in 1983 received the Award for Young Chemists from the Society of Synthetic Organic Chemistry, Japan. His current research interests include the development of new synthetic methods using radical reactions and organometallic reagents.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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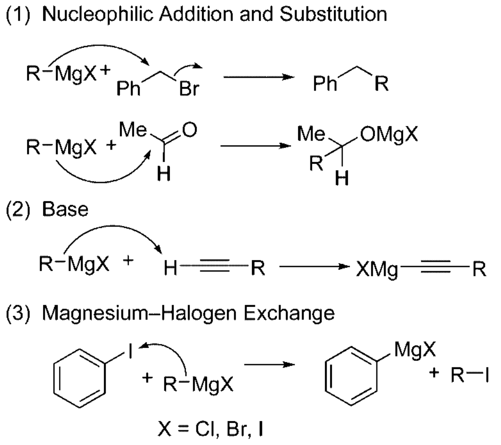
nard reagents, in some cases, undergo single-electron transfer to electron-deficient organic molecules.[4]



Scheme 1

The reactivity of Grignard reagents themselves is relatively simple, but their use in the absence of any additives may limit their range of applications. To explore further reactivity of Grignard reagents, their combination with catalytic amounts of transition metal salts has been extensively investigated. Kharasch revealed the basic reactions of a Grignard reagent in the presence of a variety of transition metal salts.[5] The introduction of transition metal catalysts has greatly expanded the reactivity of Grignard reagents and, therefore, their utility in organic synthesis; a variety of reactions of high synthetic value have been accomplished. In particular, the Tamao−Kumada−Corriu cross-coupling reaction under nickel catalysis, a parent of many other cross-coupling procedures, is a monumental example of a Grignard reaction that cannot be achieved without the use of transition metals.[6]

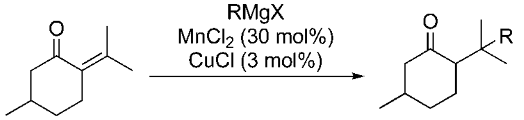
In recent years, we have been interested in the novel carbon−carbon bond formation reactions mediated by Grignard reagents in the presence of a variety of transition metal salts. In this account, we review mainly our own recent achievements in transition metal (Mn, Fe, Cr, and Co)-catalyzed reactions, but also include other closely related research in this area. Although other transition metals, such as Zr, Ti, Ni, Pd, and Cu, work together with Grignard reagents to mediate a number of carbon−carbon bond formation reactions, we do not cover the development of such reactions in this article.

2. Manganese Catalysis

Until recently, manganese-catalyzed carbon−carbon bond formation reactions have not been explored extensively. Normant and Cahiez investigated the preparation of triorganomanganate species and their reactions with carbonyl compounds. They revealed that organomanganese reagents undergo 1,4-addition reactions efficiently with α,β-enones in the presence of a copper catalyst.[7] Hosomi has developed the use of stoichiometric manganese reagents, triorganomanganates, as reducing agents for organic halides.[8] Manganese-catalyzed reactions with substrates other than carbonyl compounds, however, remained uninvestigated until very recently.

1,4-Addition to Enones

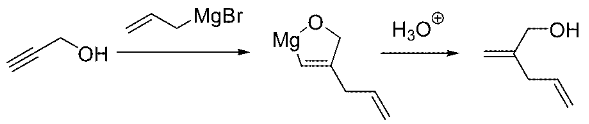
Besides stoichiometric reactions, Cahiez has also reported the 1,4-addition of Grignard reagents can be performed using a catalytic amount of MnCl$_2$ with the aid of a Cu co-catalyst (Scheme 2).[9]



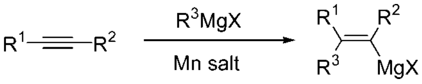
Scheme 2

Carbometallation

Carbometallation of carbon−carbon multiple bonds is an important process in organometallic chemistry from both theoretical and practical standpoints.[10] Uncatalyzed carbometallation with Grignard reagents is limited to reactive substrates such as alkynes bearing coordinating heteroatoms in adjacent positions.[11] Scheme 3 shows a typical example where allylmagnesium bromide reacts with propargyl alcohol giving vinylic magnesium species without the aid of catalysts. Manganese salts expand the scope and limitations of this process, and enable carbomagnesiation to occur for acetylenic linkages that otherwise do not react with organomagnesium species (Scheme 4). Manganese-catalyzed allylation, arylation, and alkylation of alkynes have been reviewed recently.[12]

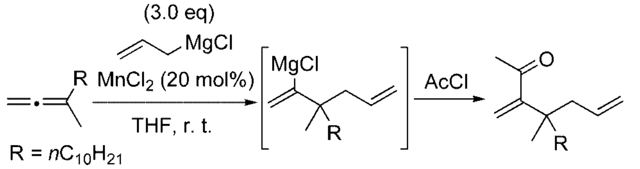


Scheme 3



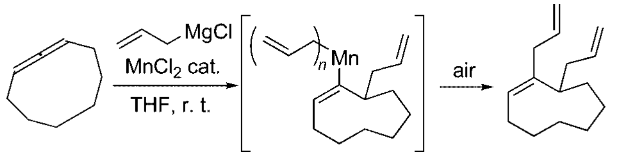
Scheme 4

Very recently, we reported that manganese chloride also catalyzes the addition of allylmagnesium chloride to allenes.[13] The allyl group is introduced regioselectively at the more-substituted carbon atom. It is quite notable that the use of 1,1-disubstituted allenes successfully provides alkenylmagnesium species having a quaternary carbon atom center. The resultant alkenylmagnesium can be trapped with various electrophiles, such as acetyl chloride, allyl bromide, iodine, and benzaldehyde (Scheme 5).



Scheme 5

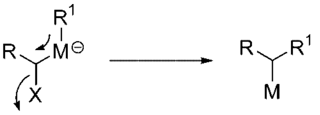
Interestingly, diallylation products are formed in the presence of molecular oxygen. A THF solution of allene was treated with allylmagnesium chloride (5.0 equiv.) in the presence of $MnCl_2$ (0.2 equiv.) under an argon atmosphere. The mixture was then exposed to air to provide the diallylated product (Scheme 6). We proposed that oxidation of manganese to a higher oxidation state facilitates reductive elimination to provide the diallylated product.



Scheme 6

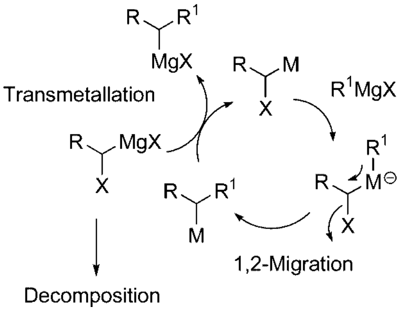
Alkylative Metallation via a 1,2-Alkyl Shift

1,2-Migration of an alkyl group on the metal center to the adjacent carbon atom in metal carbenoid species is a typical reaction of ate-type organometallic species (Scheme 7).[14] This process has been utilized successfully in the alkylation of α-haloalkylmetals (e.g., M = Mg,[15] Zn,[16] B,[17] or Cu[18]) and allows the facile introduction of an alkyl group to the organometallic reagents. This process enables complex metallic reagents to be prepared from relatively simple and easily accessible organometallic species. These reactions are usually conducted with the use of a stoichiometric amount of the central metal; the use of catalytic amounts of metal salts has not been investigated in depth. If, however, 1,2-migration of the alkyl group and transmetallation proceed considerable faster than the decomposition of carbenoid species (such as carbene formation, rearrangement, and dimerization), the process would result in alkylation of α-haloalkylmetals catalytically with regard to the central metal (Scheme 8).



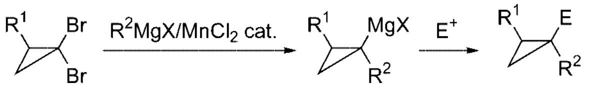
Scheme 7

Initially, we investigated the reaction of stoichiometric trialkylmanganates (R_3MnLi or R_3MnMgX) with *gem*-dibromo compounds. We found that treatment of *gem*-dibromocyclopropanes with R_3MnLi or R_3MnMgX furnished the desired alkylated products cleanly and in good yields. This satisfying result prompted us to explore the catalytic 1,2-alkyl migration reaction.



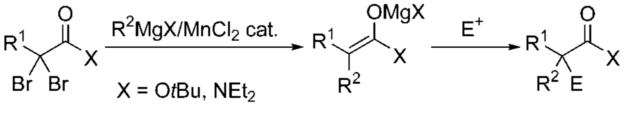
Scheme 8

After a series of experiments, we found that alkylation of dihalo compounds via 1,2-alkyl shifts can be achieved in the presence of a catalytic amount of manganese salts. Efficient alkylative metallation of *gem*-dibromocyclopropane proceeds when using a catalytic amount of manganese chloride (Scheme 9).[19] In the absence of manganese chloride, the reaction of butylmagnesium bromide with *gem*-dibromocyclopropanes provides only allenes in excellent yields via carbenoid rearrangement. This fact indicates that the transmetallation and 1,2-shift processes in the catalytic cycle shown in Scheme 8 are significantly faster than the rearrangement of the magnesium carbenoid. The same transformation (halogen−metal exchange and a subsequent 1,2-shift) can be also accomplished using diorganocuprates or triorganozincates. Catalytic use, however, has not been reported for transition metals other than manganese.



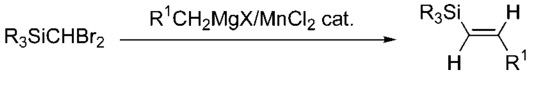
Scheme 9

In a similar manner, the organic group of various Grignard reagents can be introduced efficiently to dibromoacetates and dibromoacetamides. The reaction tolerates ester and amide groups and provides magnesium enolate species that can be further employed for carbon−carbon bond formation upon their reaction with a variety of electrophiles (Scheme 10).[20] This protocol eventually enables double alkylation at the α-position of acetates and acetamides. The use of α,α-dibromo β-lactam as a substrate also furnished doubly alkylated products in good yields.

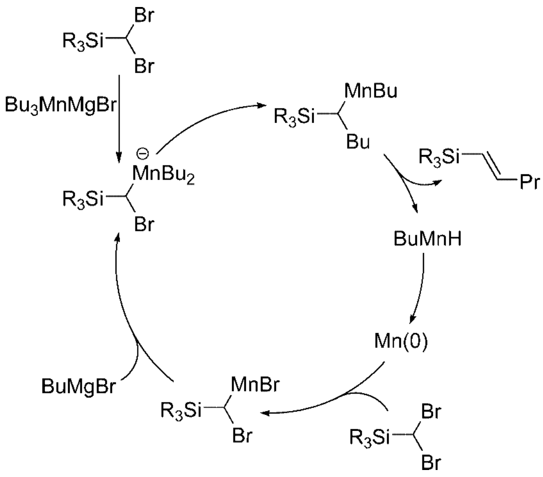


Scheme 10

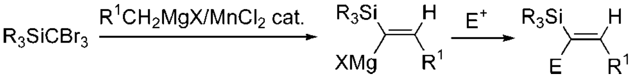
In the alkylation of dibromomethyltrialkylsilanes, (*E*)-alkenylsilanes were obtained with high stereoselectivity by β-elimination of the resulting organomanganese compounds (Scheme 11).[21] The β-elimination of Mn−H should, however, provide low-valent manganese species. Because Mn^{II} species are required for the continuation of the cycle, we proposed a different type of catalytic cycle, in which low-valent manganese inserts oxidatively into the carbon−bromine bond to regenerate the manganese carbenoid species (Scheme 12). In addition, the use of tribromomethylsilane as a substrate furnished alkenylmagnesium species by bromine−metal exchange of the initially formed 1-bromo-1-silylalkenes. The vinylic metal could be trapped using electrophiles (Scheme 13).



Scheme 11



Scheme 12

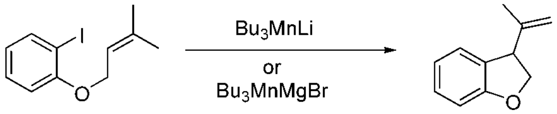


Scheme 13

Radical Cyclization

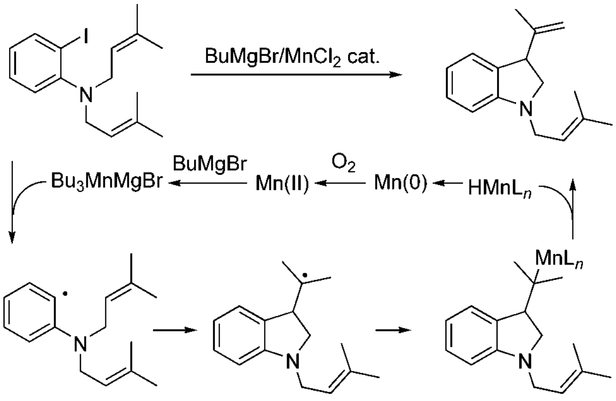
Radical cyclization has become a powerful tool for the preparation of five-membered cyclic compounds.[22] The reaction often employs tributyltin hydride as a radical mediator. As a result, however, of the toxicity of tin reagents and the difficulty in removing tin residues from the products, alternative reagents for tin compounds have been investigated extensively recently.[23]

We have reported that trialkylmanganate induces a radical cyclization of allyl *o*-iodophenyl ethers, *N*,*N*-diallyl-*o*-iodoaniline, and iodo acetals (Scheme 14). The reaction has been proposed to proceed through a radical species that is formed by single-electron transfer from the electron-rich manganese atom in the ate complex to the substrate.[24] The driving force of this electron transfer process is the cancellation of the formal negative charge on manganese in the ate-type species. The reaction is successful for providing dihydrobenzofuran, indoline, and tetrahydrofuran derivatives. It is, however, desirable to reduce the quantity of transition metal salts ($MnCl_2$) required from the viewpoints of cost and the environment.



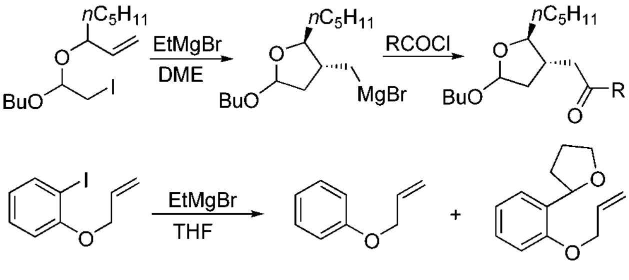
Scheme 14

The same transformation can be conducted efficiently using a catalytic amount of $MnCl_2$ (Scheme 15). Interestingly, the catalytic version of the reaction requires the presence of molecular oxygen; otherwise, the reaction terminates with β-elimination of *n*BuMnH, which is then converted into low-valent manganese species. The role of molecular oxygen is to oxidize the Mn(0) species to Mn^{II}, which is necessary for the continuation of the catalytic cycle.



Scheme 15

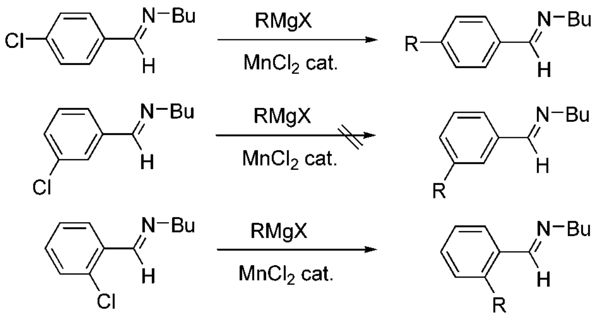
We have also reported that EtMgBr itself can induce the radical cyclization of iodo acetals to provide cyclized organomagnesium species, which further react with a variety of electrophiles, such as acyl chlorides (Scheme 16). Without the assistance of the manganese catalyst, however, Grignard reagents cannot cyclize allyl iodophenyl ethers. Instead of the radical cyclization, iodine−magnesium exchange proceeds with subsequent coupling with THF.



Scheme 16

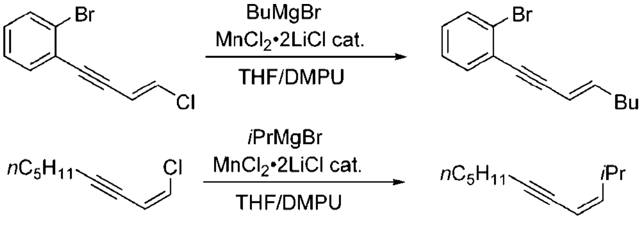
Cross-Coupling

Cahiez has demonstrated (Scheme 17) that manganese chloride can be an alternative for palladium and nickel catalysts for mediating cross-coupling reactions between Grignard reagents and aromatic halides under mild conditions (0 °C to room temperature).[25] In the presence of manganese chloride (10 mol %), alkyl and aryl Grignard reagents can be cross-coupled with a variety of activated aromatic chlorides that feature an electron-withdrawing group (CN, CH=NR, oxazoline). This reaction exhibits marked chemoselectivity. The position of the activating group is crucial: the reaction of *ortho*- and *para*-chlorobenzaldimines yields the desired coupling products, but the *meta* isomer does not. In some cases, even fluorides can be employed in the reaction, even though they are generally the most robust organic halides in the palladium- and nickel-catalyzed procedures. Although the reaction mechanism has yet to be clearly elucidated, a mechanism similar to those established for palladium- or nickel-catalyzed cross-coupling reactions (i.e., oxidative addition of Mn(0) to the C−X bond, transmetallation, and reductive elimination) has been postulated.



Scheme 17

The manganese-catalyzed cross-coupling reaction exhibits a remarkable reactivity for conjugated chloroenynes and chlorodienes.[26] In a THF/DMPU solvent system, Grignard reagents can be coupled selectively with conjugated alkenyl chlorides, whereas aromatic bromides and non-conjugated alkenyl chlorides remain unchanged during the reaction (Scheme 18). The reaction proceeds in a stereospecific manner. Thus, the (*E*) and (*Z*) isomers of 1-chloronona-1-en-3-yne yield the corresponding (*E*) and (*Z*) isomers of the coupling product without isomerization of their carbon−carbon double bonds.



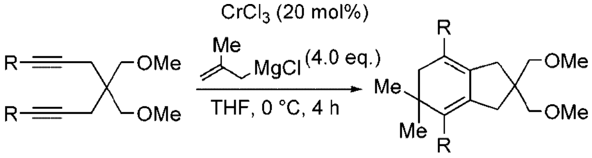
Scheme 18

3. Chromium Catalysis

Organochromium reagents play significant roles in organic synthesis. The Nozaki−Hiyama−Kishi reaction involving allyl- or alkenylchromium species has served as a pivotal reaction in many total syntheses of naturally occurring compounds.[27] Arene−chromium complexes provide a regio- and stereoselective method to construct aromatic compounds.[28] The use of chromium catalysts in the reaction with Grignard reagents, however, has not been investigated. We have investigated the reactivity of allylchromate reagents with unsaturated molecules, and have developed chromium-catalyzed reactions using Grignard reagents.

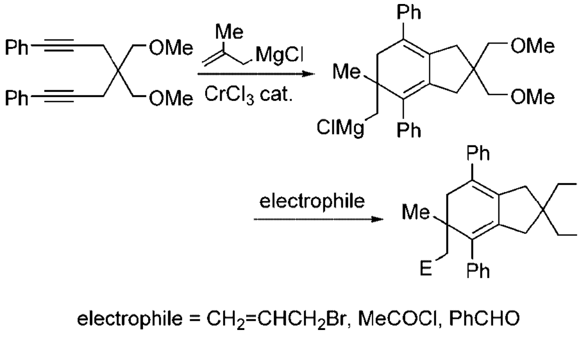
Carbometallation-Induced Cyclization of 1,6-Diynes and 1,6-Enynes

Among a number of organochromium species, organochromium ate complexes have received little attention in synthetic organic chemistry.[29] Recently, we examined the reactivity of tetraallylchromates toward unsaturated molecules, and found that chromium induces the [2+2+2] annulation of 1,6-diynes.[30] Furthermore, we have demonstrated that treatment of 1,6-diynes with methallylmagnesium chloride in the presence of a catalytic amount of $CrCl_3$ provides the annulation products in good yields (Scheme 19).



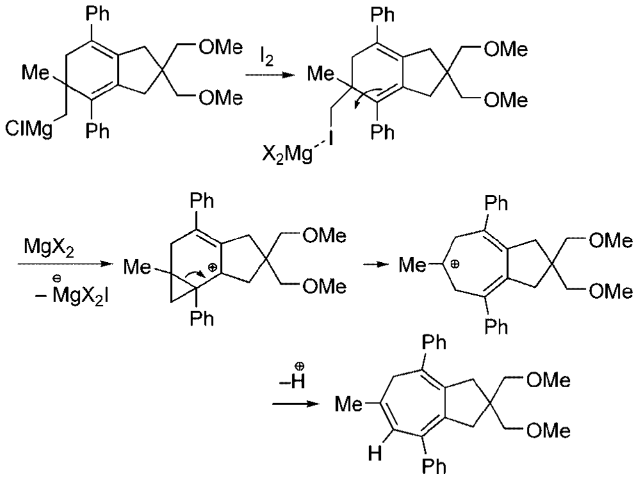
Scheme 19

The intermediate cyclohexadienylmethylmagnesium species reacts with various electrophiles efficiently (Scheme 20). Interestingly, the reaction with iodine yielded exclusively the cycloheptatriene derivative. This [3+2+2] annulation product is proposed to be formed via the cationic intermediate that is generated from the initial product by the action of magnesium halide acting as a Lewis acid (Scheme 21).

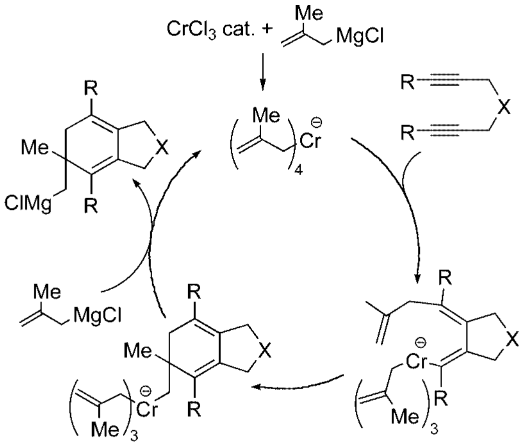


Scheme 20

A plausible catalytic cycle is proposed to occur as depicted in Scheme 22. The [2+2+2] allyl/alkyne annulation



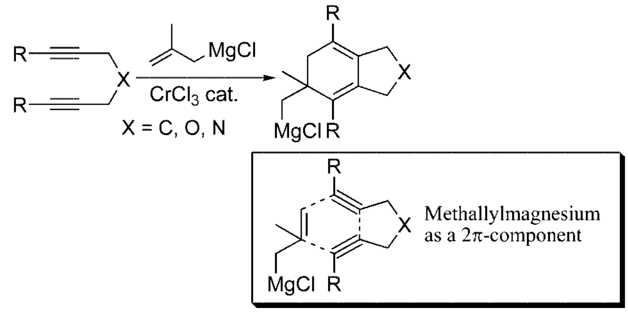
Scheme 21



Scheme 22

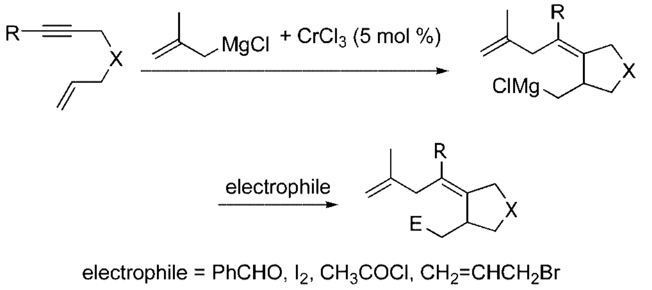
begins with allylation of an alkyne ligand on the metal.[31] The allylchromation of the carbon−carbon triple bond triggers the cyclization to yield the dienylchromium. The subsequent insertion of the terminal alkene into the carbon−chromium bond provides cyclohexadienylmethylchromium. Transmetallation from chromium to magnesium furnishes the cyclic magnesium compound and regenerates the allylic chromium species.

The reaction can be regarded as a [2+2+2] annulation reaction of 1,6-diynes with methallylmagnesium chloride. The methallyl group acts as a two-carbon component in this formal cycloaddition process (Scheme 23).



Scheme 23

The combination of methallylmagnesium chloride and $CrCl_3$ also effects the efficient cyclization of 1,6-enynes (Scheme 24).[32] The resulting cyclic organomagnesium species can be utilized for further functionalization. These cyclization reactions with 1,6-diynes and 1,6-enynes, however, cannot employ allylic Grignard reagents other than methallylmagnesium chloride, such as allylmagnesium chloride.



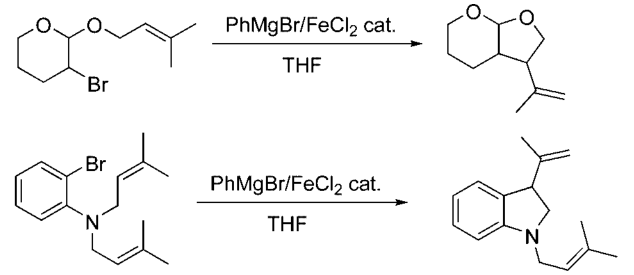
Scheme 24

3. Iron Catalysis

Recently, much attention has been paid to iron-catalyzed reactions because most iron salts are nontoxic and inexpensive. Iron catalysts might be employed as alternatives for more-expensive precious metals, such as palladium, or toxic metals, such as nickel. Because of the low toxicity of magnesium reagents, combining Grignard reagents with iron catalysts could be used to develop environmentally benign carbon−carbon bond forming processes.

Radical Cyclization

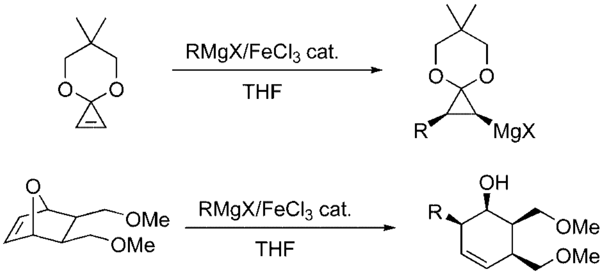
We have demonstrated that phenylmagnesium bromide can initiate a radical cyclization of halo acetals and allyl *o*-halophenyl ethers in the presence of a catalytic amount of $FeCl_2$ (Scheme 25).[33] The manganese-catalyzed radical cyclization (Scheme 15) employs iodo acetals and *o*-iodophenyl ethers; the corresponding bromides do not afford the desired cyclized products efficiently. On the other hand, the $PhMgBr/FeCl_2$ combination can be used to cyclize bromo acetals in good yields. The reaction is proposed to be initiated by single-electron transfer from either $Ph_3Fe(MgBr)$ or $Ph_4Fe(MgBr)_2$.



Scheme 25

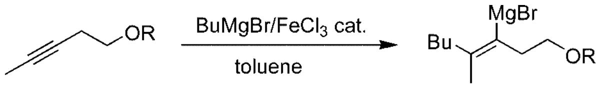
Carbometallation

A Grignard reagent usually does not add to an alkenyl linkage without the aid of transition metals.11 Nakamura has demonstrated that a combination of $FeCl_3$ with Grignard reagents achieves efficient introduction of organic groups to cyclopropenes (Scheme 26).[34] The system also enables alkylative ring-opening of 7-oxa[2.2.1]bicyclohept-2-enes to yield stereochemically well-defined cyclohexene derivatives. A sequence of carbometallation of the carbon−carbon double bond and β-alkoxy elimination is proposed as one plausible mechanism.



Scheme 26

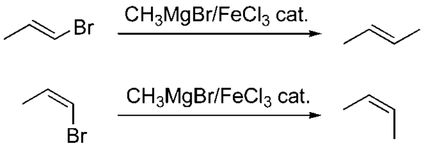
Hosomi and Hojo have also reported the use of $FeCl_3$ as a catalyst for carbomagnesiation of alkynes having a heteroatom-directing group (Scheme 27),[35] but using organolithium reagents, instead of Grignard reagents, afforded better yields. The use of organolithium species is beneficial for trapping the resulting alkenyllithiums with various electrophiles.



Scheme 27

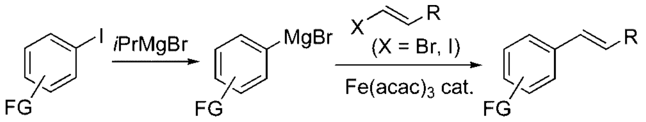
Cross-Coupling

Iron-catalyzed cross-coupling reactions seem to have the potentially to be very useful catalytic transformations in organic synthesis. Kochi originally proposed the use of iron salts for cross-coupling of Grignard reagents with organic halides (Scheme 28),[36] but once the Tamao−Kumada−Corriu coupling protocol was discovered using nickel catalysts, the iron-catalyzed cross-coupling remained unexplored for a long period. In this procedure, alkenyl halides must be used in large excess in most cases (3−5 equiv.) and the yields based on the Grignard reagents are moderate.



Scheme 28

Cahiez has pointed out the importance that the solvent system has on the iron-catalyzed cross-coupling reaction.[37] He demonstrated that iron chloride can be an effective alternative to palladium and nickel catalysts for cross-coupling reactions between Grignard reagents and alkenyl halides in the presence of *N*-methylpyrrolidone (NMP). Later, this protocol was combined successfully with Knochel's chemoselective magnesium−iodine exchange reaction to provide organic chemists with an efficient procedure for synthesizing highly functionalized styrene derivatives (Scheme 29).



Scheme 29

The iron-catalyzed cross-coupling protocol was further polished by Fürstner.[38] The iron-catalyzed coupling procedure employs a wide range of substrates including aryl iodides, bromides, chlorides, triflates, and tosylates (Scheme 30). The use of an iron salen complex (Figure 1) is recommended for *sec*-alkyl Grignard reagents. Successful coupling is also accomplished using heteroaromatic halides. It is quite noteworthy that the reaction proceeds at lower temperatures and over shorter reaction periods than those of the corresponding nickel-catalyzed cross-coupling reaction. The fact that aryl chlorides, triflates, and tosylates are better substrates than the corresponding bromides or iodides is also remarkable. Taking advantage of this unique reactivity, the one-pot synthesis of unsymmetrical 2,6-disubstituted pyridines can be achieved with high efficacy by consecutive cross-coupling reactions (Scheme 31). This protocol has been applied to the beautiful synthesis of the odoriferous alkaloid (*R*)-(+)-muscopyridine by also using ring-closing metathesis.[39]

$$\mathrm{ArX} \ + \ \mathrm{RMgX} \xrightarrow{\mathrm{Fe(acac)_3\ cat.}} \mathrm{ArR}$$

(X = I, Br, Cl, OTf, OTs)

(R = aryl, alkyl)

Scheme 30

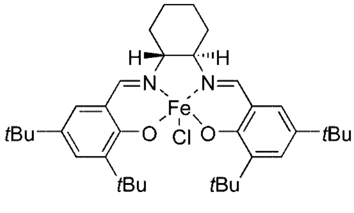
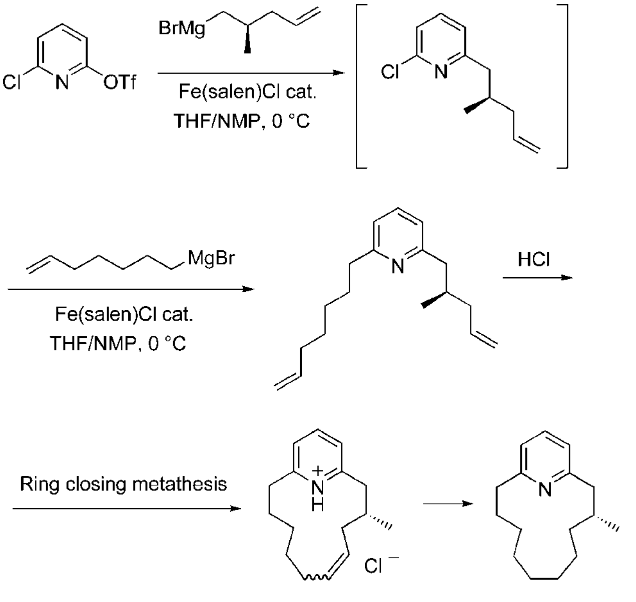


Figure 1. Iron−salen complex for cross-coupling of *sec*-alkyl Grignard reagents

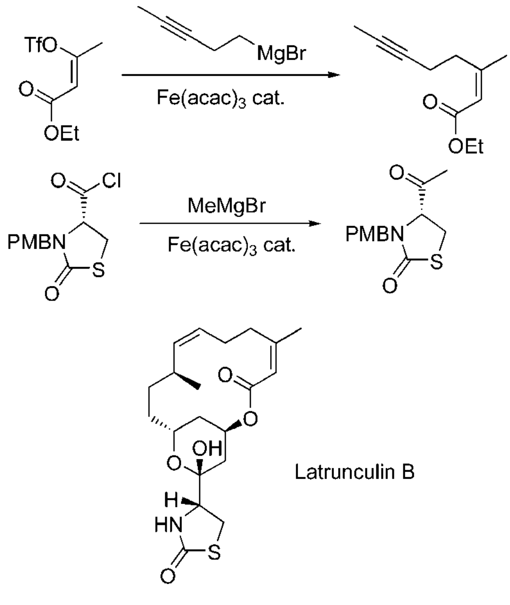


(R)-(+)-muscopyridine

Scheme 31

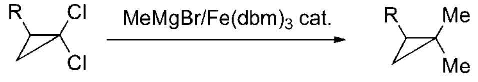
For the reaction mechanism of this cross-coupling reaction, it has been suggested that a highly reactive low-valent iron species [$Fe(MgX)_2$], an "inorganic Grignard reagent", is involved. In its reaction with Grignard reagents, iron chloride is reduced to [$Fe(MgX)_2$], which bears a formal negative charge at the iron center. The Fe(−II) species then inserts into the Ar−X bond to provide [ArFe(MgX)], which is further converted into [$ArFeR(MgX)_2$] upon the reaction with RMgX. Eventually, the coupling product Ar−R is yielded after reductive elimination of [$ArFeR(MgX)_2$].

A recent total synthesis of latrunculin B clearly demonstrates the power of this iron-catalyzed cross-coupling (Scheme 32).[40] It is particularly noteworthy that an alkenyl triflate bearing a ester moiety can be cross-coupled with the Grignard reagent chemoselectively. $Fe(acac)_3$ also works well as a catalyst for the alkylation of an acid chloride with MeMgBr. The iron-catalyzed procedure is reported to be much more reliable and convenient than the uncatalyzed reaction of acyl chlorides.



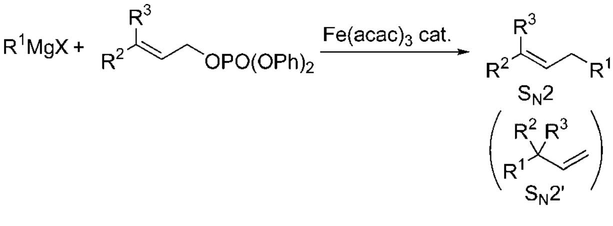
Scheme 32

Iron catalysis may be useful also in coupling between two sp^3-hybridized carbon atoms. The reaction of *gem*-dichlorocyclopropanes with methylmagnesium bromide in the presence of an iron catalyst provided dimethylated cyclopropanes, although the reaction mechanism was not elucidated (Scheme 33).[41]



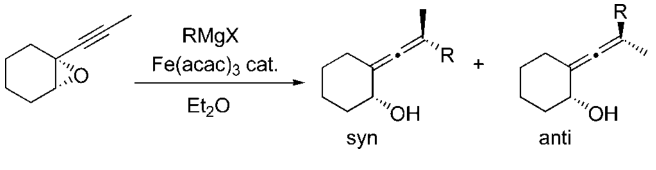
Scheme 33

Highly regioselective coupling of allyl phosphates with Grignard reagents can be accomplished under iron catalysis (Scheme 34).[42] In the presence of a catalytic amount of $Fe(acac)_3$, the reaction provides S_N2 substitution products with high selectivity over S_N2' products. In addition, a nickel salt was also reported to exhibit excellent S_N2 selectivity. On the other hand, the coupling proceeds in a S_N2' fashion in the presence of a catalytic amount of $CuCN{\cdot}2LiCl$.



Scheme 34

Very recently, Fürstner reported the S_N2'-selective ring-opening of propargyl epoxides with a variety of Grignard reagents in the presence of $Fe(acac)_3$ as the catalyst (Scheme 35).[43] The reaction successfully furnished allenyl alcohol bearing axial chirality at the allenyl moiety without loss of enantiomeric excess of the starting propargyl epoxides. Another salient feature of this reaction is that the syn-configured 2,3-allenols are formed as the major products. In contrast, organocopper reagents usually provide the anti-isomer predominantly.[44]



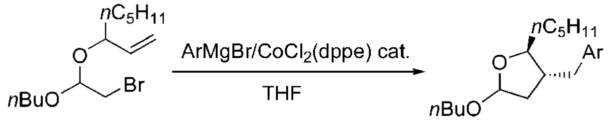
Scheme 35

4. Cobalt Catalysis

Cobalt-catalyzed reactions play important roles in organic synthesis. Cobalt carbonyl compounds serve as efficient catalysts for Vollhardt's [2+2+2] cyclotrimerization of alkynes and the Pauson−Khand reaction. Cobalt is also a key atom in hydroformylation and hydrosilylation reactions. The reaction of stoichiometric organocobalt species with organic halides and carbonyl compounds has been reviewed.[45] In recent years, cobalt-catalyzed carbon−carbon bond formation with organometallic reagents has received increasing attention.

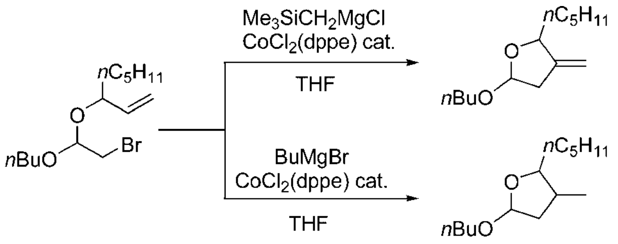
Radical Cyclization

As well as manganese and iron salts, cobalt salts also efficiently catalyze the radical cyclization of halo acetals when combined with Grignard reagents.[46] The reaction pattern, however, of cobalt-catalyzed radical cyclization is remarkable when compared to the corresponding manganese- and iron-catalyzed reactions. When using aromatic Grignard reagents, the aromatic group can be incorporated into the product after the cyclization (Scheme 36). Thus, under cobalt catalysis, radical cyclization and subsequent coupling with aromatic Grignard reagents can be achieved in a single operation. The choice of phosphane ligands to cobalt is crucial; the use of bis(diphenylphosphanyl)ethane afforded the best result. As for the reaction mechanism, single-electron transfer from low-valent cobalt species is proposed to be involved.



Scheme 36

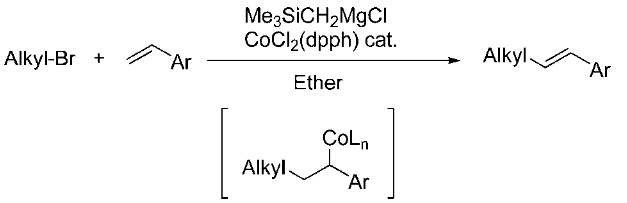
Unfortunately, alkylmagnesium species cannot be introduced in the products; instead, the reaction provides saturated products. In contrast, the use of Me_3SiCH_2MgCl totally changes the course of the reaction, with the reaction providing alkenyl products in good yields (Scheme 37).[47]



Scheme 37

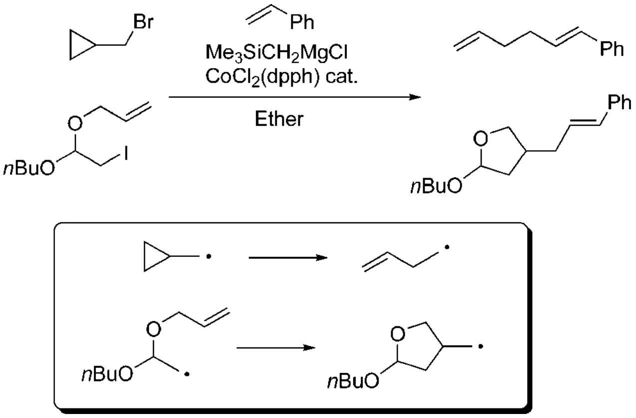
Heck-Type Reactions

Coupling between alkyl halides and styrenes and acrylate derivatives has been developed with a catalyst combination of $CoCl_2$ and bis(diphenylphosphanyl)hexane in the presence of Me_3SiCH_2MgCl (Scheme 38).[48] The reaction is proposed to proceed via the intermediacy of benzylcobalt. This reaction can be recognized as novel Heck-type reaction employing alkyl halides as the substrates. The conventional Heck reaction under palladium catalysis usually employs aryl halides as the coupling partner; alkyl halides cannot be utilized because of β-hydride elimination of the alkylpalladium intermediate, which is formed by oxidative addition of Pd^0 to the alkyl−X bond.



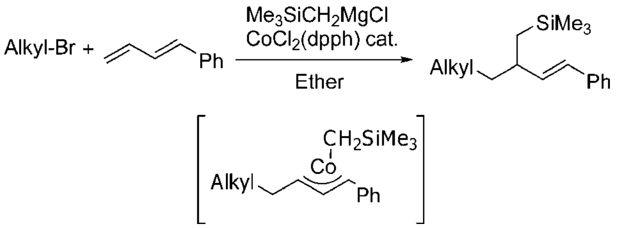
Scheme 38

A radical pathway has been postulated because the reaction of cyclopropylmethyl bromide or iodo allyl acetal provides rearranged products that can be accounted for by the presence of radical species as intermediates (Scheme 39). In a sense, the β-elimination problem is circumvented by employing an alkyl radical intermediate, which rapidly undergoes an addition reaction toward alkenes, rather than an alkylmetal species, which decomposes readily.



Scheme 39

The use of 1,3-dienes instead of styrenes provides three-component coupling products, homoallylsilanes, in good yields (Scheme 40).[49] Excellent regioselectivity is achieved with 1-phenyl-1,3-butadiene as the substrate. This reaction

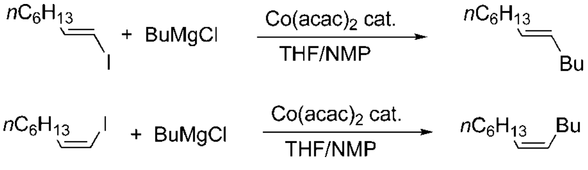


Scheme 40

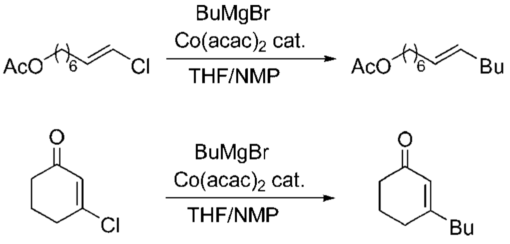
also involves radical species formed from alkyl halides. The reaction probably involves π-allylcobalt species that result from the addition of the alkyl radical to 1,3-dienes. The allylcobalt then undergoes reductive elimination, rather than β-elimination, to form the Heck-type product.

Cross-Coupling

In a fashion similar to that of the iron case, the ability of cobalt salts to catalyze cross-coupling of organic halides with Grignard reagents was recognized quite early. Recently, Cahiez et al. revisited cobalt catalysis for the cross-coupling reaction with Grignard reagents. Again, they found a similar improvement could be effected by using THF/NMP as the solvent system. The coupling proceeds in a stereospecific manner (Scheme 41). It is quite noteworthy that a highly chemoselective cross-coupling reaction is accomplished (Scheme 42). In addition, alkenyl chlorides gave reasonable yields in this Co-catalyzed coupling protocol.

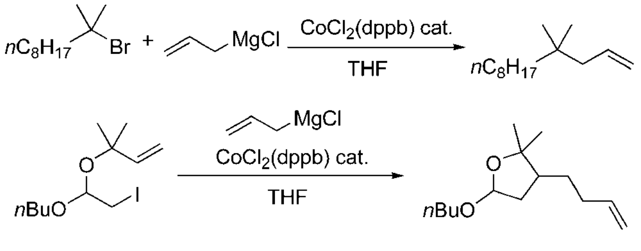


Scheme 41



Scheme 42

Cross-coupling of alkyl halides with allylic Grignard reagents has been developed recently using cobalt catalysis (Scheme 43).[50] A salient feature of this reaction is that the protocol enables the coupling of an allylic group with tertiary alkyl halides, furnishing quaternary sp^3-hybridized carbon atom centers. This reaction is likely to involve some radical species formed from alkyl halides, because the cyclization of allyl iodo acetals proceeded prior to coupling with the allyl moiety.



Scheme 43

5. Conclusion

A wide range of new reactions has been developed by the combination of Grignard reagents and transition metal catalysts. In particular, efficient cross-coupling of organic halides, including alkyl halides, with Grignard reagents is accomplished effectively when using some metals. In the near future, palladium and nickel catalysts may be substituted by other nontoxic and economical metals, such as iron. One of characteristics of the reactions reviewed in this account is the involvement of carbon-centered radical species. We believe that the combination of radical species and transition metal catalysis opens up novel possibilities in organic synthesis.

Acknowledgments

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