Chemistry of Organomanganese(II) Compounds

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1. Introduction

In the recent years, the use of organometallics in organic synthesis has increased exponentially as the use of main group and transition metals like palladium, nickel, rhodium, and ruthenium has been of primary focus.[1] For a few years, sustainable development has played an increasingly important role in the strategy of the chemical industry. As a part of these preoccupations, the search for efficient, economic, and eco-friendly new synthetic methods is of vital concern. By comparison with the above-noted transition metals, manganese is very interesting since it is cheap and toxicologically benign. From this point of view, only iron is better. Many people are surprised to learn that, by its abundance, manganese is the twelfth element of the Earth's crust.[2] It is the second transition metal after iron. Moreover, a great part of the world reserves are composed of very high-grade ore (Mn $\geq$ 36%).

Compared to most organometallics derived from a transition metal, organomanganese(II) reagents are considerably more stable. Thus, they can be used very often at room temperature. This is significant since it is, therefore, possible to develop both catalytic and stoichiometric manganese-mediated reactions. Noteworthy, manganese can be easily removed, for instance, as manganese carbonate, during the final workup.

In 1937, Gilman and Bailie described the preparation of phenylmanganese iodide and diphenylmanganese from phenyllithium and manganese iodide.[3] These are the first examples of organomanganese(II) compounds reported in the literature. During the following 40 years, only sporadic reports concerning the preparation[4] and reactivity[5] of these compounds have been reported. In fact, the chemistry of organomanganese(II) reagents is relatively recent since the first detailed studies only appeared about 30 years ago. The present review deals primarily with this period.[6]

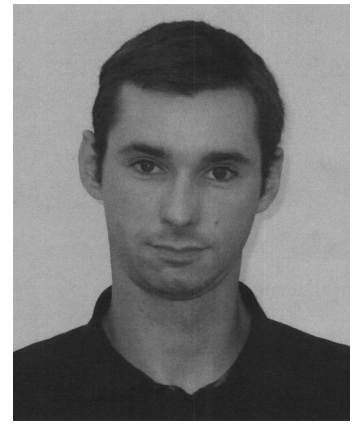
2. Preparation of Organomanganese Reagents

2.1. Introduction

In 1976, when we started our investigations of organomanganese(II) reagents in organic synthesis, only a few of these reagents were known (see section 1).[3–5] Accordingly, we had to study their preparation in order to have reliable and general procedures. In fact, most of the numerous organomanganese reagents currently known have been prepared by our group in the last 30 years by transmetalation from the corresponding organolithium or organomagnesium reagents.[7] In our view, these procedures are, at present, the best way to obtain organomanganese(II) reagents.

Recently, various attempts to prepare organomanganese compounds directly by oxidative addition of organic halides to manganese were reported. Such a method of preparation would be very useful since, in theory, it is straightforward and less expensive. In addition, functionalized organomanganese compounds would be easier to prepare in this way

Gérard Cahiez received his Ph.D. in 1973, at the University Pierre and Marie Curie (Paris VI) under the supervision of Professor Jean Francois Normant on the carbocupration of terminal alkynes (vinyl copper reagents). Then, he joined the CNRS. After a postdoctoral year in the Roussel Uclaf Laboratories (now Sanofi Aventis) on the chemistry of steroid, he came back to the University Pierre and Marie Curie before moving to the Ecole Supérieure de Chimie Organique et Minérale (ESCOM, Cergy−Pontoise) in 1993. He is now Director of Research at the CNRS (since 1980) and Professor of Chemistry at ESCOM (since 1993). Since 2000, he is also director of the UMR 8123 CNRS−University of Cergy Pontoise−ESCOM. The research developed since 1973 dealt with the use of organometallic reagents in organic synthesis and especially with the development of the chemistry of organomanganese reagents. His current interest is always focused on organomanganese chemistry but more generally on the search for new highly selective organometallic reactions, i.e., Mn-, Co-, and Fe-cross-coupling reactions, involving no toxic and expensive metal or additive.



Christophe Duplais was born June 15, 1980, in Caen, France. He graduated from Ecole Supérieure de Chimie Organique et Minérale (ESCOM) in 2004. For his Master's degree, he joined the research group of Prof. P. Knochel in Munich, Germany, as an exchange student in collaboration with Prof. G. Cahiez. Then he received his Ph.D. degree in 2008 from the Université of Cergy−Pontoise, France, under the supervision of Prof. G. Cahiez. His research focused on the preparation of functionalized organomanganese compounds and the use of iron, cobalt, and manganese salts as catalysts in cross-coupling reactions of Grignard reagents. He is currently pursuing his postdoctoral research in the laboratory of Prof. B. H. Lipshutz at the University of California, Santa Barbara.

Julien Buendia was born in Paris, in 1983. He studied chemistry for five years at Ecole Supérieure de Chimie Organique et Minérale (ESCOM) and at the University of Cergy−Pontoise (UCP). He received a B.S. in Mathematics from the UCP in 2004, then a Master's degree in Chemistry and Chemical Engineering from ESCOM, as well as an M.S. in Organic Chemistry from the UCP in 2006. For the latter degree, he joined the research group of Prof. G. Cahiez in Cergy−Pontoise, under whose supervision he is currently pursuing a Ph.D. in Organic Chemistry. His research work concerns copper- and manganese-mediated cross-coupling reactions. He is also interested in the preparation of symmetrical organozinc compounds and their use in organic synthesis. He received a GSK Award for Excellence in Organic Chemistry in 2005.

Scheme 1. Organomanganese Halides

$$RM + MnX_2 \longrightarrow RMnX \ (+ LiX \text{ or } MgXX')$$
(M= Li, MgX')

Scheme 2. Symmetrical Organomanganeses

$$2\ RM + MnX_2 \longrightarrow R_2Mn \ (+ 2\ LiX \text{ or } 2\ MgXX')$$
(M= Li, MgX')

Scheme 3. Organomanganates

$$3\ RM + MnX_2 \longrightarrow R_3MnM \ (+ 2\ LiX \text{ or } 2\ MgXX')$$
(M= Li, MgX')

$$4\ RM + MnX_2 \longrightarrow R_4MnM_2 \ (+ 2\ LiX \text{ or } 2\ MgXX')$$
(M= Li, MgX')

rather than by transmetalation, since the starting functionalized organolithium or organomagnesium reagents are not always trivial to prepare. Unfortunately, except in the case of the manganese-mediated Barbier and Reformatsky reactions, the current state of the art does not allow for the efficient and direct preparation of organomanganese reagents from massive manganese metal (see section 2.3).

2.2. Preparation of Organomanganese Compounds from Organomagnesium or Organolithium Reagents

2.2.1. General Considerations

According to the ratio RLi/MnX_2 or $RMgX'/MnX_2$, several types of organomanganese compounds can be prepared by transmetalation (Schemes 1, 2, and 3).

Manganese iodide, bromide, and chloride can be used to achieve the transmetalation reaction generally performed in ether or in tetrahydrofuran (THF). The starting manganese halide is generally chosen according to its solubility in the selected solvent, allowing rapid and efficient lithium−manganese or magnesium−manganese exchange. As shown hereafter, organomanganese halides are highly chemoselective. As an example, various cosolvents too reactive to be used with the starting organolithium or Grignard reagent (AcOEt, MeCN, CH_2Cl_2, etc.) can be added to the reaction mixture when the transmetalation step is complete.

Scheme 4

$$Mn \xrightarrow[2)\ RLi \text{ or } RMgX]{1)\ I_2,\ ether,\ r.t.} RMnI \ (+ LiI \text{ or } MgXI)$$
~ 100%

R= *s*-, *t*-alkyl T= -30 °C
R= *n*-alkyl, allyl, benzyl, aryl, alkenyl, alkynyl... T= -10 °C - r.t.

Scheme 5

$$Mn \xrightarrow[2)\ 2\ RLi \text{ or } 2\ RMgX,\ -30\ ^\circ C]{1)\ I_2,\ ether,\ r.t.} R_2Mn \ (+ 2\ LiI \text{ or } 2\ MgXI)$$
~ 100%

Commercial manganese chloride or bromide have to be dried in vacuo before use (200 °C, 10^{-2} torr, 3 h). A high-grade manganese bromide can also be readily prepared by addition of bromine to a suspension of manganese powder in anhydrous ethyl acetate at room temperature (the temperature should not exceed 40 °C).[8] Commercial manganese iodide is often too impure to be used as a starting material. Fortunately, it is easily obtained by addition of iodine to a suspension of manganese powder in anhydrous ether at room temperature. It is isolated by filtration in quantitative yield.[7b,c] This method of preparation was disclosed by Ducelliez in 1913.[9] Manganese iodide has to be stored in the absence of moisture in darkness.

A vast array of alkyl, alkenyl, alkynyl, allyl, benzyl, and aryl or heteroarylmanganese compounds can be prepared by transmetalation. In fact, the only limitation is the preparation of the starting organolithium or organomagnesium reagent. Organomanganese compounds are generally prepared fresh prior to use. It should be noted that a solution of methylmanganese chloride in THF can be stored for several months at room temperature without any degradation.[10]

2.2.2. Preparation by Transmetalation in Ether

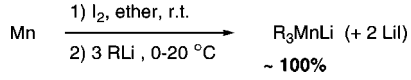
2.2.2.1. From Manganese Iodide.[7a−c] Manganese iodide is slightly soluble in ether. It reacts rapidly with organolithium or organomagnesium reagents to give the corresponding organomanganese compounds quantitatively. A very convenient way to obtain organomanganese iodides is to prepare manganese iodide by treating manganese with iodine in ether and then to perform the transmetalation according to a one-pot procedure (Scheme 4). It is thus possible to avoid the handling of manganese iodide, which is hygroscopic and light-sensitive.

The thermal stability of organomanganese iodides depends on the nature of the R group bonded to manganese. For example, secondary and tertiary alkylmanganese iodides have to be prepared and used below −30 °C to avoid their decomposition (β-hydrogen elimination). In the case of the more stable primary alkylmanganese iodides, it is possible to operate between −10 °C and room temperature. Finally, with aryl-, alkenyl-, and alkynylmanganese iodides, the transmetalation can be performed at room temperature.

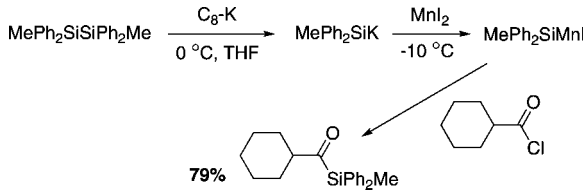
Dialkylmanganeses are less stable than the other alkylmanganese compounds. Thus, the transmetalation from organolithium or organomagnesium reagents has to be performed below −30 °C (Scheme 5).

Lithium organomanganates are the most stable organomanganese compounds. As shown in Scheme 6, they can be quantitatively prepared from the organolithium reagents

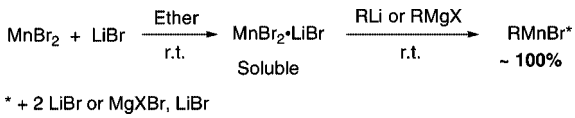
Scheme 6



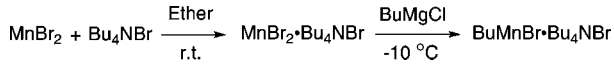
Scheme 7



Scheme 8



Scheme 9



between 0 °C and room temperature (the addition of RLi has to be performed at −40 °C when R = *s*- or *t*-alkyl). It should be noted that all attempts to prepare organomanganates R_3MnMgX from Grignard reagents in ether resulted in failure. However, this point is disputable since the characterization of such species is not obvious and no detailed study was done.[11]

One example of potassium−manganese exchange has been reported by Fürstner (Scheme 7).[12]

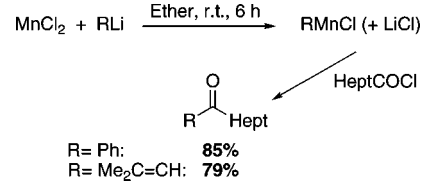
2.2.2.2. From Manganese Bromide.[7d,e] Manganese bromide is considerably less expensive than manganese iodide and is not light-sensitive. Because of its very slight solubility in ether, manganese bromide cannot be used conveniently in this solvent to prepare organomanganese reagents. Fortunately, in the presence of 1 or 2 equiv of anhydrous lithium bromide, a soluble ate-complex $MnBr_2$•LiBr or $MnBr_2$•2LiBr is formed at room temperature. This complex readily reacts, under mild conditions, with organolithium or organomagnesium reagents to give quantitatively the corresponding organomanganese bromides (Scheme 8). Currently, organomanganese bromides are the most suitable organomanganese halides to perform a reaction in ether.

It is important to underline that alkylmanganese bromides prepared from the ate-complex $MnBr_2$•LiBr and a Grignard reagent are more stable than the corresponding alkylmanganese iodides prepared from manganese iodide (see section 2.2.5).[7d] Symmetrical organomanganeses and organomanganates can be conveniently prepared from the complex $MnBr_2$•LiBr.

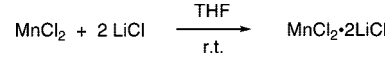
Finally, we discovered that it is also possible to form an ate-complex by treating manganese bromide with anhydrous tetrabutylammonium bromide in ether for 4 h.[7e] Further addition of a Grignard reagent thus affords the corresponding organomanganese reagent (Scheme 9).

2.2.2.3. From Manganese Chloride.[13] Manganese chloride is insoluble in ether, even in the presence of lithium halide. Consequently, the transmetalation takes place very slowly with Grignard reagents and gives poor results. With the more reactive organolithium compounds, the lithium−manganese exchange reaction occurs sluggishly at room temperature (6 h) and only a few stable aryl- and alkenyl-

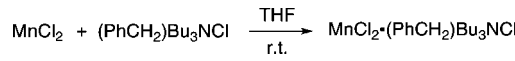
Scheme 10



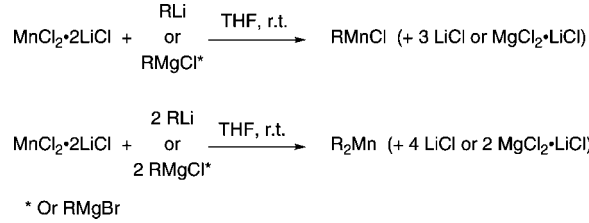
Scheme 11



Scheme 12



Scheme 13



manganese chlorides have been prepared successfully from manganese chloride (Scheme 10).

2.2.3. Preparation by Transmetalation in THF [7c,e]

Organomanganese compounds are more stable in THF than in ether (see section 2.2.5). Thus, numerous organomanganese reagents can be conveniently prepared and used in THF at room temperature. The transmetalation can be performed quantitatively by using manganese chloride or bromide. These salts are only slightly soluble in THF, but it is possible to dissolve them by adding lithium chloride or bromide to form a soluble ate-complex MnX_2•2LiX (X = Br or Cl). Manganese chloride is generally employed since it is a very cheap material (Scheme 11). Manganese iodide is not frequently used because it is much more expensive.

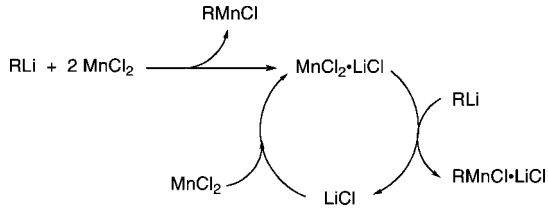
Similar results are obtained by mixing manganese chloride with benzyltrimethylammonium chloride in THF at room temperature (Scheme 12). Various tetraalkylammonium chlorides can be employed.[7e]

Organomanganese chlorides as well as symmetrical organomanganeses can be easily obtained from the complex $MnCl_2$•2LiCl and the corresponding organolithium or organomagnesium reagents (Scheme 13).

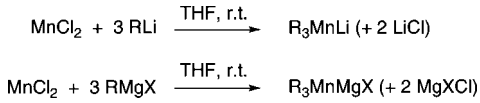
In THF, organolithium reagents can react directly with manganese chloride. Indeed, the lithium chloride produced from the beginning of the lithium−manganese transmetalation allows progressive dissolution of the insoluble manganese species (RMnCl and $MnCl_2$) present in the reaction mixture (Scheme 14).

For the preparation of organomanganates in THF, it is possible to use indifferently manganese chloride or the ate-complex $MnCl_2$•2LiCl. In both cases, organolithium or organomagnesium reagents give quantitatively the corresponding organomanganates R_3MnLi or R_3MnMgX at room temperature (Scheme 15).

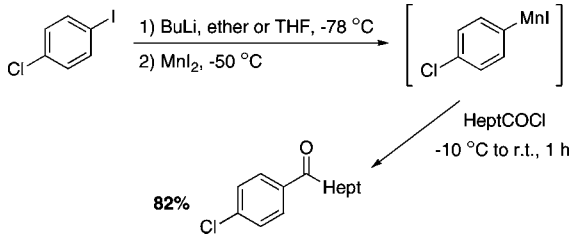
Scheme 14



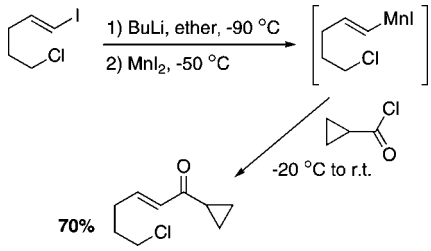
Scheme 15



Scheme 16



Scheme 17



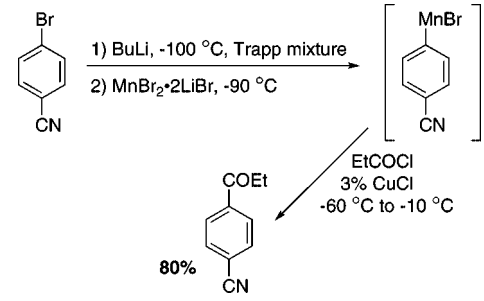
2.2.4. Preparation of Functionalized Organomanganese Derivatives

Organomanganese halides tolerate the presence of many functional groups (esters, nitriles, amides, etc.). Various reports showed that functionalized aryl- or alkenyllithium reagents can be readily prepared by halogen−lithium exchange at low temperature.[14] In 1997, Cahiez and Knochel developed a one-pot procedure to prepare functionalized organomanganese halides via the corresponding organolithium compounds.[15] Thus, they showed that 4-chlorophenyllithium, obtained by treating 4-chloroiodobenzene with butyllithium at −78 °C, reacts with manganese iodide, in ether or in THF at −50 °C, to give 4-chlorophenylmanganese iodide in excellent yield (Scheme 16).

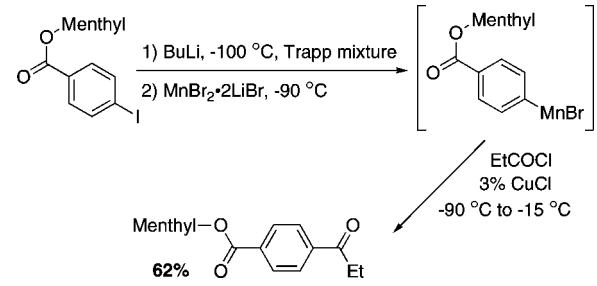
In the same way, it is also possible to prepare functionalized alkenylmanganese iodides in ether (Scheme 17).

With aryl halides bearing a more reactive functional group (CN, CO_2R), the lithium−halogen exchange has to be performed between −90 and −100 °C. However, the transmetalation does not occur at this temperature since manganese halides or their ate-complexes $MnX_2 \cdot 2LiX$ are completely insoluble. This drawback can be circumvented by working with the Trapp mixture (THF/ether/pentane, 4:4:1). Indeed, the complex $MnBr_2 \cdot 2LiBr$ is then soluble enough in the reaction mixture at −90 °C to react efficiently.[15] This procedure was applied to the preparation of functionalized arylmanganese bromides from 4-bromobenzonitrile or menthyl 4-iodobenzoate (Schemes 18 and 19). It is important to employ a hindered ester; thus, all attempts from ethyl- or methyl 4-iodobenzoates resulted in failure.

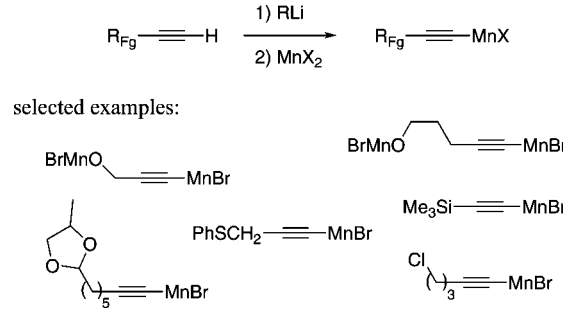
Scheme 18



Scheme 19



Scheme 20

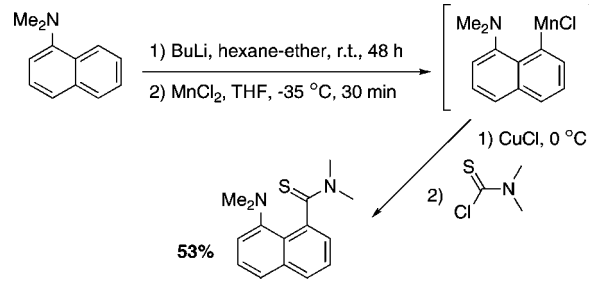


Likewise, various functionalized alkynylmanganese halides were prepared from the corresponding alkynyllithium compounds obtained by metalation of functionalized terminal alkynes (Scheme 20).[6c,f]

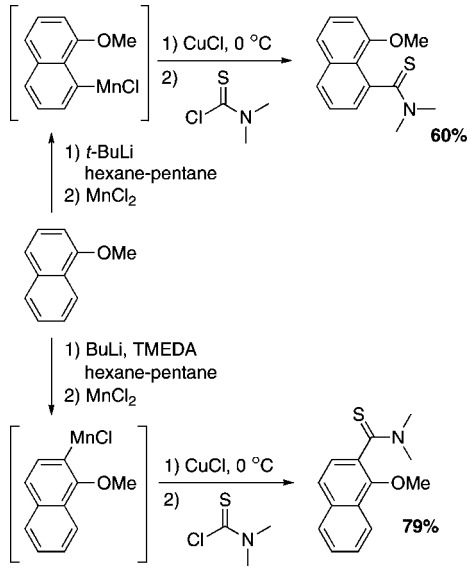
The preparation of 1,8-dimethylaminonaphthylmanganese chloride was described by Mannschreck according to a one-pot procedure.[16] 1-Dimethylaminonaphthalene is first metallated with butyllithium; then, the lithium−manganese exchange is achieved by adding manganese chloride (Scheme 21).

From 1-methoxynaphthalene, two regioisomers of the methoxynaphthylmanganese chloride can be obtained by changing the nature of the alkyllithium used for the metalation step (Scheme 22).

Scheme 21



Scheme 22



Scheme 23

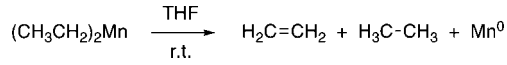


Table 1. Stability of RMnX Prepared in Ether or in THF

R from RMnX	limit of stability, T (°C)	
	RMnI prepared in ether	RMnCl prepared in THF
t-Bu	−35 °C	0 °C
i-Pr	−30 °C	10 °C
n-Bu	10 °C	25 °C
Me, Ph, Me_2C=CH	reflux	reflux

2.2.5. Stability of Organomanganese Reagents

The instability of many organometallics derived from a transition metal is a major drawback precluding their use as stoichiometric reagents in organic synthesis (e.g., R_2Pd, R_2Ni, R_2Fe)[1,17a–c] or obliges working at a low temperature (e.g., RCu).[17d–f] In the case of organomanganese reagents, the situation is more favorable since they are clearly more stable. Their stability decreases in the following order:

$$R_4MnLi_2 \text{ (or } (MgX)_2) \approx R_3MnLi \text{ (or MgX)} > RMnX \gg R_2Mn \quad (1)$$

Of course the nature of the R group is very important. In the early 1970s, Kochi studied the decomposition of dialkylmanganeses, the most unstable organomanganese reagents.[18] They decompose via a β-hydrogen elimination process like many alkyl transition metal derivatives to give a mixture of alkane and alkene (Scheme 23).

This mechanism explains that the number of available β-hydrogens is probably the most important factor regarding the stability of organomanganese reagents. There is a clear trend in stability in the case of the organomanganese iodides prepared in ether (Table 1). Thus, *t*-butylmanganese iodide has to be prepared and used below −35 °C, whereas the *n*-butyl analogue is almost stable at room temperature. In addition, organomanganese iodides having no β-hydrogen atom (aryl, alkenyl, methyl, etc.) can be heated in ether until reflux.

Organomanganese halides are more stable in THF than in ether.[19] This is likely due to the strong complexation of manganese to this solvent, which impedes the β-hydrogen elimination. Indeed, in THF, all organomanganese chlorides are stable around room temperature and can often be heated until reflux. It is interesting to note that the addition of 5 equiv of THF to an organomanganese iodide prepared in ether allows for an increase in its stability (Table 2).[20] The influence of dimethylformamide (DMF) as a ligand is even more marked; thus, in the presence of 5 equiv of DMF the isopropylmanganese iodide is stable until 35 °C.

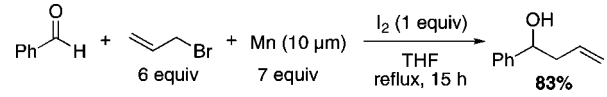
Table 2. Stability of *i*-PrMnI Prepared in Ether

ligand (5 equiv)	limit of stability, T (°C)
no ligand	−35 °C
THF	−5 °C
DMF	35 °C

Table 3. Stability of *i*-PrMnX Prepared in Ether from RMgX and MnX_2·2LiBr

i-PrMnX	limit of stability, T (°C)
i-PrMnI	−30 °C
i-PrMnBr·2LiBr	−10 °C
i-PrMnI·2LiBr	−10 °C

Scheme 24



As explained above, the use of secondary or tertiary alkylmanganese iodides prepared in ether is sometimes tedious because of their low stability. Fortunately, we disclosed that the organomanganese compounds prepared in ether from Grignard reagents and the soluble ate-complex $MnBr_2$·2LiBr are much more stable.[7d] A similar stabilizing effect is observed by using the ate-complex MnI_2·2LiBr, instead of manganese iodide (Table 3).[7e] This stabilization is due to the presence of both lithium and magnesium salts.

2.3. Preparation of Organomanganese Reagents from Manganese Metal

2.3.1. Oxidative Addition of Organic Halides to Commercial Manganese

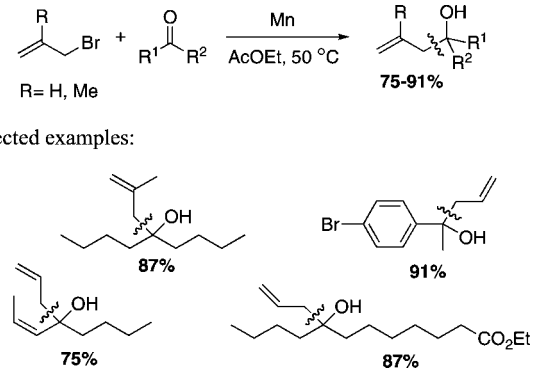
The preparation of organomanganese compounds by oxidative addition of organic halides to commercial manganese (massive metal) is potentially very attractive. It would avoid the preparation of the organolithium or organomagnesium precursors used for the transmetalation procedure presented above (see section 2.2). This is especially important to obtain organomanganese compounds bearing functional groups (ester, nitrile, etc.) that react with the corresponding lithium or magnesium derivatives.

In 1983, Hiyama described a new Barbier reaction, using micronized commercial manganese powder.[21] This one reacts with allyl bromide in the presence of an aldehyde or a ketone to afford the corresponding alcohols in good yields (Scheme 24).

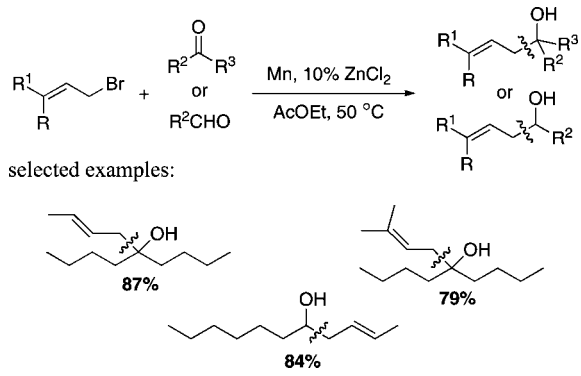
This procedure presents some significant limitations. First, it is necessary to heat the reaction mixture to reflux for 15 h. In addition, a large excess of reagents is required (7 equiv of Mn and 6 equiv of allyl bromide). Moreover, the substituted allylic halides like RCH=$CHCH_2X$ or R_2C=$CHCH_2X$ (R = alkyl) lead to poor yields.

In 1989, we disclosed that commercial massive coarse-ground manganese, easily available and cheap, can efficiently

Scheme 25



Scheme 26



be used to prepare organomanganese compounds from reactive organic halides such as allylic halides or α-halogenoesters.[22] The choice of the solvent is decisive; thus, in the case of allyl or methallyl bromides, we tried several common solvents and found that only ethyl acetate led to satisfactory results (Scheme 25). The reaction is performed in the presence of a ketone to trap the organomanganese reagent as soon as it is formed (Barbier conditions).

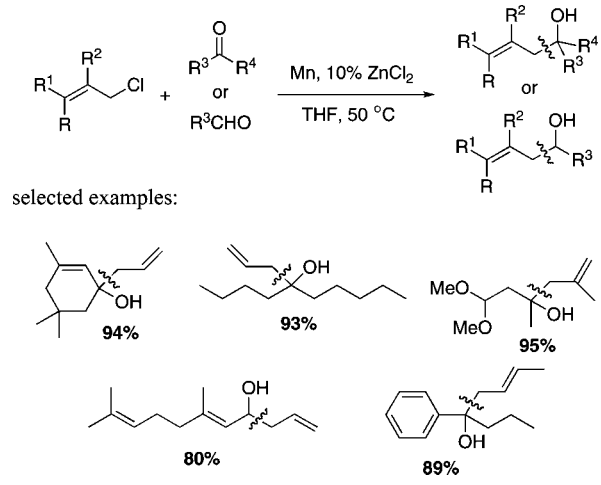
Good yields are obtained but this method cannot be extended to γ-substituted allylic halides such as crotyl bromide. Moreover, the use of aldehydes instead of ketones leads to poor yields. We found that the reaction takes place smoothly when 10% zinc chloride is added to the manganese suspension before adding the allylic halide and the carbonyl compound. A manganese/zinc couple is probably the reactive species. It should be noted that various metallic salts like cadmium, mercury, or copper(II) chlorides can be used successfully in place of zinc chloride.[22] By using this procedure, it is possible to extend the reaction to crotyl and prenyl bromides. In addition, ketones as well as aldehydes give the corresponding homoallylic alcohols in good yields (Scheme 26).

By using manganese activated by addition of 10% zinc chloride, it is also possible to perform the reaction in THF. In this case, allyl, methallyl, crotyl, and prenyl bromides can be used successfully. It should be noted that allylic chlorides also react efficiently (Scheme 27).

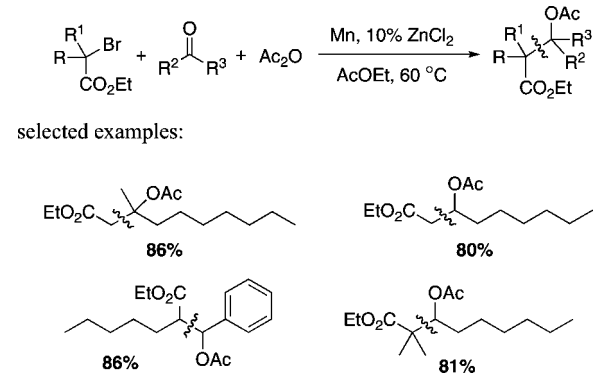
We showed that such a zinc/manganese couple allows one to perform a manganese-mediated Reformatsky reaction in ethyl acetate.[22] In the presence of acetic anhydride, good yields of β-acetoxyesters are obtained from ketones or aldehydes (Scheme 28).

Afterward, Takai found that manganese can also be activated by adding catalytic amounts of both $PbCl_2$ and Me_3SiCl (Scheme 29).[23] The latter probably strips the surface

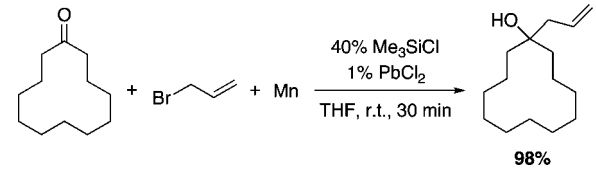
Scheme 27



Scheme 28



Scheme 29

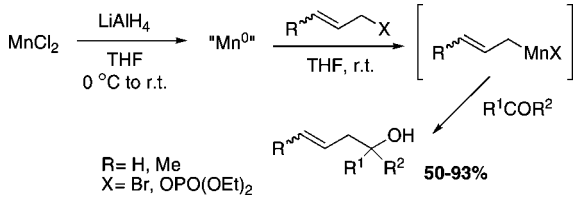


of the metal by removing the manganese oxide coating. On the other hand, the role of lead chloride in this reaction has not been clearly explained; a manganese/lead couple could be involved.

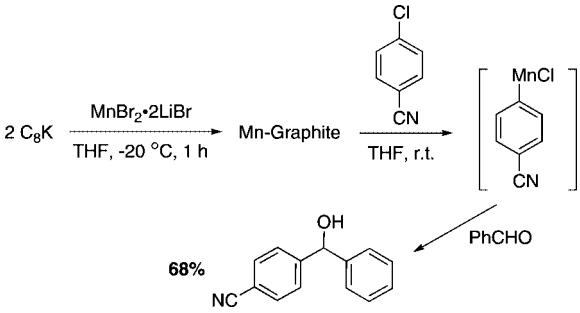
2.3.2. Oxidative Addition of Organic Halides to Activated Manganese Prepared from Manganese Halides

As previously shown (see section 2.3.1), massive commercial coarse-ground manganese only reacts with very reactive organic halides such as allylic halides or α-halogenoesters. It is well-known that the reactivity of a metal considerably increases when it is used as a very fine powder (dispersed metal, particles size < 1 μm). On the other hand, it is also established that a metal can be activated by using mechanical (e.g., with Mg, the dry-stirring procedure) or chemical methods (e.g., with Mg, the activation by I_2 or a 1,2-dihaloethane), in part to remove the metal oxide coating.[24] On the basis of these considerations, Rieke showed that it is possible to obtain very reactive metal powders by reducing a metal salt with potassium in THF.[25] In this solvent, sodium or lithium naphthalenide also led to excellent results. The resulting activated metal, so-called Rieke metal, is highly reactive. Indeed, the size of the metallic particles is very

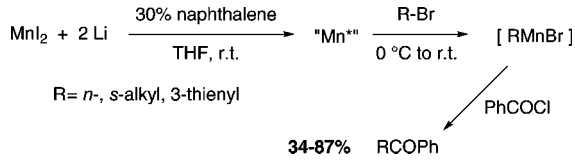
Scheme 30



Scheme 31



Scheme 32



small and the dispersed metal is used in situ to avoid the passivation processes.

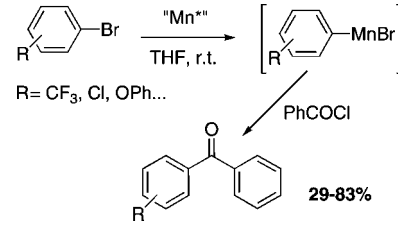
To increase the reactivity of manganese toward organic halides, several procedures involving an activated manganese were reported. The first, in 1982, was proposed by Hiyama.[26] He showed that manganese chloride can be efficiently reduced by lithium aluminum hydride (molar ratio = 1:1) in THF at 0 °C. Allyl and crotyl bromides react successfully but unsatisfactory results were obtained with prenyl bromide or allyl chloride (Scheme 30). From a practical point of view, this procedure is not very attractive since the manganese powder thus obtained is not more reactive than the commercial massive coarse-ground metal.

An interesting procedure was proposed by Fürstner in 1996: the reduction of the soluble ate-complex $MnBr_2 \cdot 2LiBr$ by potassium graphite C_8K.[27] The manganese graphite thus obtained smoothly reacts with allyl, alkenyl, and aryl halides (Scheme 31). Moreover, this new form of activated manganese allows for the preparation of various functionalized organomanganese halides (nitrile, sulfonamide).

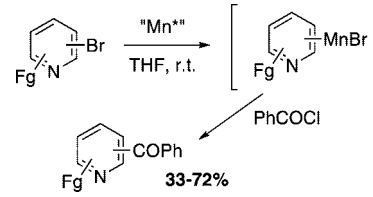
In another approach described by Rieke, manganese halides can be efficiently reduced with 2 equiv of lithium in the presence of naphthalene (0.3 equiv) as an electron carrier.[28] The highly reactive manganese powder thus obtained easily undergoes the oxidative addition of simple primary or secondary alkylbromides, as well as 3-bromothiophene under mild conditions (Scheme 32). The nature of the starting manganese halide is crucial since the oxidative addition rate is clearly faster when using manganese iodide (3 equiv) or bromide (4 equiv) rather than manganese chloride.[29] It should be noted that the excess of activated manganese must be consumed, i.e., by adding 1,2-dibromoethane before using the organomanganese reagent for synthetic applications.

The procedure has been applied to the preparation of arylmanganese halides (Scheme 33).[29]

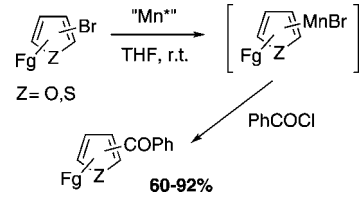
Scheme 33



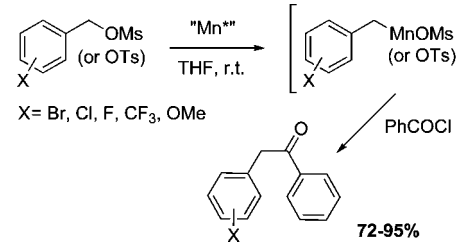
Scheme 34



Scheme 35



Scheme 36



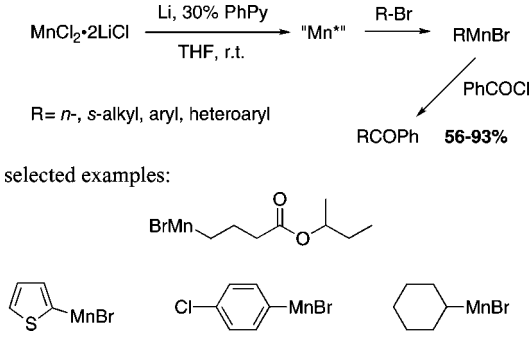
Interestingly, Rieke manganese can be used to prepare heteroarylmanganese halides.[30] The oxidative addition occurs chemoselectively with functionalized heteroaryl bromides bearing an ether, an ester, or a chlorine atom (Schemes 34 and 35).

Rieke also found that benzyl sulfonates react successfully (Scheme 36).[31]

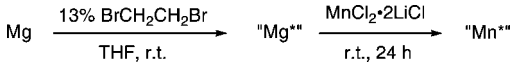
It should be emphasized that the Rieke procedure involves the use of naphthalene, which is very difficult to eliminate during the final workup. To avoid this drawback, we have replaced naphthalene by 2-phenylpyridine (PhPy), as a new electron carrier.[32]

In THF, activated manganese is readily obtained by treating a solution of the ate-complex $MnCl_2 \cdot 2LiCl$ with 2 equiv of lithium in the presence of 2-phenylpyridine (0.3 equiv). Further oxidative addition of primary or secondary alkyl as well as aryl or heteroaryl bromides leads to excellent yields of the expected organomanganese bromides. For large-scale preparative chemistry, this procedure offers several advantages. As expected, phenylpyridine is easily eliminated and recycled during the final workup by simple acidic washing. In addition, the activated manganese is prepared from the very cheap manganese chloride, whereas expensive manganese iodide is generally used in the Rieke procedure. The greater synthetic potential of the lithium phenylpyridine procedure is exemplified by the preparation of a primary alkylmanganese bromide bearing an ester group (Scheme 37).

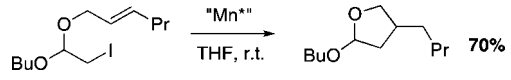
Scheme 37



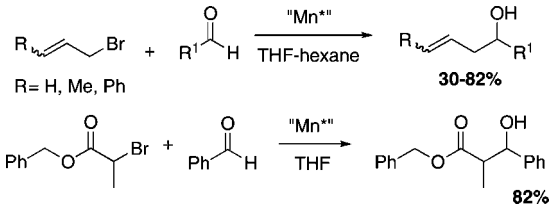
Scheme 38



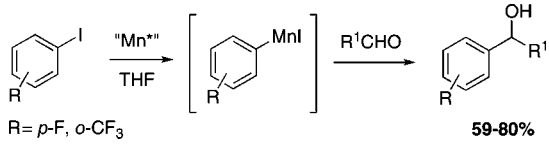
Scheme 39



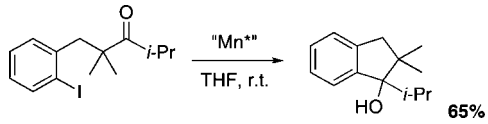
Scheme 40



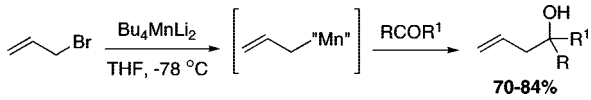
Scheme 41



Scheme 42



Scheme 43



Oshima reported that magnesium can also reduce the ate-complex $MnCl_2 \cdot 2LiCl$ in THF (Scheme 38).[33]

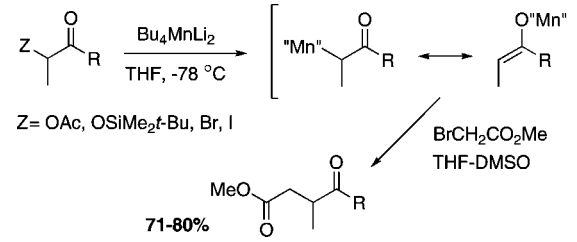
The activated manganese thus prepared was used in cyclization reactions (Scheme 39). These reactions will be presented later (see section 9.3).

Barbier and Reformatsky reactions can also be achieved by using this activated manganese (Scheme 40).[34]

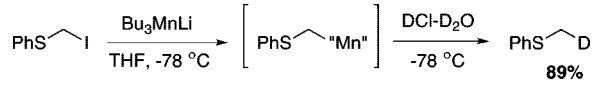
Oshima showed that the activated manganese, prepared by reduction of the ate-complex $MnCl_2 \cdot 2LiCl$ with magnesium, reacts with aryl iodides.[34] However, only aryl iodides bearing an electron-withdrawing group lead to satisfactory results (Scheme 41).

A cyclization via an intramolecular Barbier reaction was also described (Scheme 42).

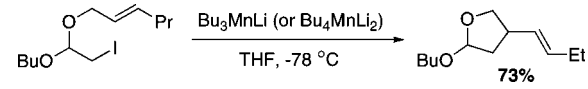
Scheme 44



Scheme 45



Scheme 46



2.4. Preparation of Organomanganese Reagents by Halogen−Manganese Exchange with Tri- or Tetraalkylmanganates

Examples of preparation of organomanganese reagents by halogen−manganese exchange are scarce. In 1997, Hosomi showed that treatment of allylic or propargylic bromides by the manganate Bu_4MnLi_2, in THF at −78 °C, leads to allylic or propargylic manganese species (Scheme 43).[35]

Under similar conditions, α-acetoxy-, silyloxy-, or halogenoketones can be converted into the corresponding manganese enolates (Scheme 44).[36] Although this reaction seems quite similar to the classical halogen−metal exchange, its mechanism is undoubtely more complex and has not been clearly established.

Iodomethyl sulfides react similarly with lithium tributylmanganate (Scheme 45).[37]

Oshima studied the reaction of organomanganates Bu_3MnLi or Bu_4MnLi_2 with various ε-unsaturated organic iodides (Scheme 46).[6h,38] These reactions will be presented later (see section 9.3).

3. Addition to Carbonyl Compounds and Related Derivatives

3.1. Reactivity of Organomanganese Halides toward Carbonyl Compounds and Related Derivatives

Organomanganese halides add to aldehydes, ketones, carbon dioxide, sulfur dioxide, and isocyanates (Scheme 47).[39] They behave like soft Grignard reagents.

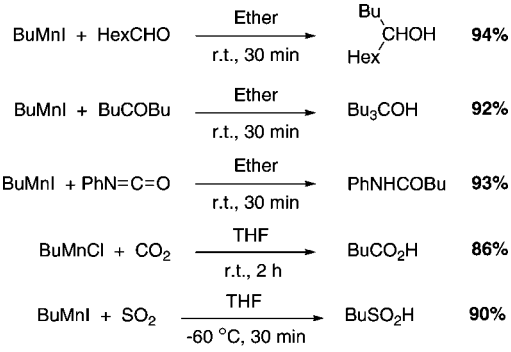
On the other hand, they do not add to esters, nitriles, or amides (Scheme 48).

Alkyl formates, which are more reactive than the other carboxylic acid esters, react smoothly (Scheme 49).[39b]

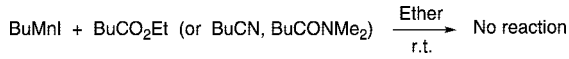
3.2. Chemo- and Regioselective 1,2-Addition to Aldehydes and Ketones

In ether, organomanganese compounds react easily under mild conditions with ketones and aldehydes to give the corresponding alcohols in excellent yields (Table 4). A vast array of organomanganese halides can be used successfully.[40]

Scheme 47



Scheme 48



Scheme 49

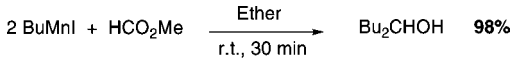
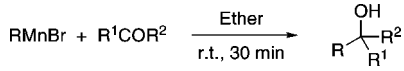
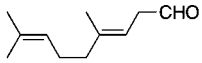
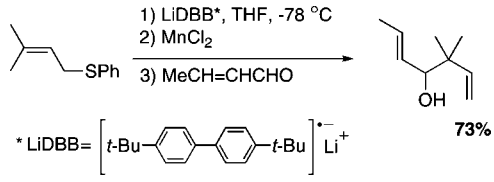


Table 4. 1,2-Addition of RMnBr to Aldehydes and Ketones



R	R^1COR^2	yield (%)
Bu	HexCHO	93
Ph	"	94
Me_2CH=CH	"	98
Bu	Et_2CHCHO	95
Hept	*t*-BuCHO	87
Me	PhCHO	93
"		91
Bu	PrCOPr	98
BuC≡C	"	95
Bu	PhCOPr	89
"	Me_2C=CHCOMe	91
"		86

Scheme 50

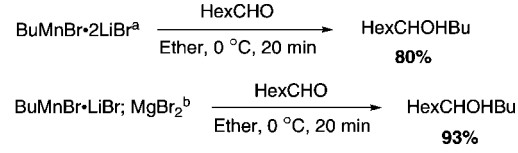


Allylic organomanganese chlorides react at their more substituted side. They can be prepared from the corresponding Grignard reagent, as well as from an allylic sulfide via the organolithium compound as shown in Scheme 50.[41]

Further investigations showed that the 1,2-addition reaction to aldehydes in ether can indifferently be performed with organomanganese reagents prepared from organolithium or organomagnesium reagents. In both cases, the reaction is complete after 20 min at 0 °C. As a rule, the yield of alcohol is slightly higher when the organomanganese halide is prepared from a Grignard reagent (Scheme 51).[42]

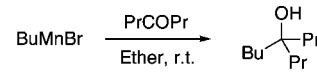
This difference is probably due to an electrophilic activation of the carbonyl group. Indeed, in the case of a ketone, the reaction rate and the final yield are clearly higher when the reaction is achieved in the presence of magnesium salts (Scheme 52).

Scheme 51



[a] From BuLi + $MnBr_2$•LiBr. [b] From BuMgBr + $MnBr_2$•LiBr

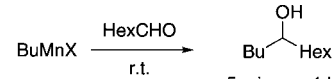
Scheme 52



	10 min	30 min	2.5 h	6 h
BuMnBr•2LiBr[a]:	**34%**	**53%**	**63%**	**80%**
BuMnBr•LiBr; $MgBr_2$[b]:	**80%**	**90%**	**93%**	**93%**

[a] From BuLi + $MnBr_2$•LiBr. [b] From BuMgBr + $MnBr_2$•LiBr

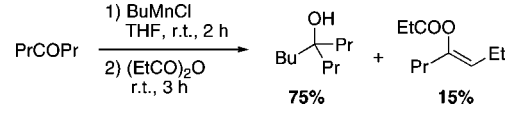
Scheme 53



	5 min	1 h
BuMnBr, ether[a]:	**97%**	-
BuMnBr, THF[b]:	**54%**	**92%**

[a] From BuMgBr + $MnBr_2$•LiBr. [b] From BuMgCl + $MnCl_2$•2LiCl

Scheme 54



In THF, the reaction is much slower. Thus, at room temperature, the 1,2-addition occurs almost instantaneously with an aldehyde in ether, whereas in THF the reaction requires ca. 1 h (Scheme 53).

With ketones, which are less reactive, the 1,2-addition is very slow in THF (1.5−2 h at r.t.) and the deprotonation of the ketone is generally observed as a side reaction (5−25%, Scheme 54).

Interestingly, organomanganese halides selectively react with an aldehyde in the presence of a ketone. The difference of reactivity is enough to allow the reaction to be carried out at room temperature. As shown by the results presented in Table 5, the addition can be performed in ether or in THF, and the chemoselectivity is superior to 99% in all cases.

The excellent results obtained during the competition experiments are confirmed by the highly selective conversion of the 11-ketotridecanal to the corresponding ketoalcohol depicted in Scheme 55.[42]

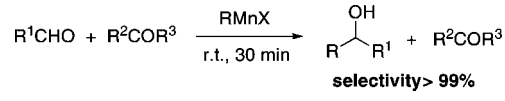
Of course, the 1,2-addition of organomanganese halides to ketones or aldehydes can be performed selectively in the presence of less reactive functional groups such as an ester, a nitrile, or an alkyl halide (Scheme 56).[6f,40]

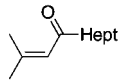
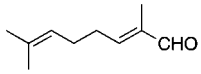
A chemoselective 1,2-addition of vinylmanganese iodide was used by Ireland for the synthesis of chlorothricolide (Scheme 57).[43]

Surprisingly, organomanganese compounds can be added regioselectively to unsymmetrical diketones (Scheme 58). The discrimination results from a difference of steric hindrance between the two carbonyl groups.[6c,f]

Organomanganese halides are more sensitive to steric than to electronic effects. Thus, in the example presented in Scheme 59, the conjugated carbonyl group, which is

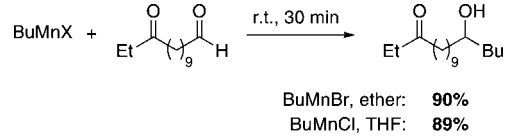
Table 5. Highly Selective Addition of RMnX to Aldehydes in the Presence of Ketones



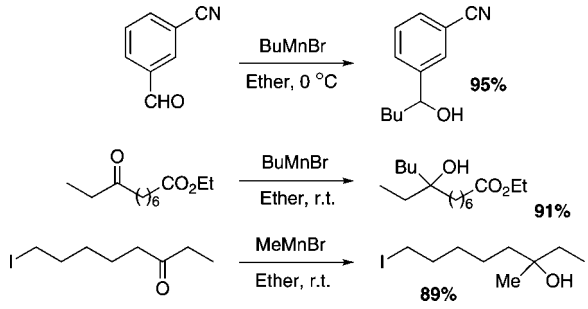
R^1CHO	R^2COR^3	R	yield (%)[a] of alcohol RMnBr[b]	RMnCl[c]
HexCHO	PrCOPr	Bu	93	90
"	PentCOMe	"	96	95
"	PhCOPr	"	95	90
"		"	90	95
"	PrCOPr	Me	95	88
"	"	Ph	94	88
"	"	Me_2C=CH	98	88
"	"	BuC≡C	80	72
	"	Me	90	91
PhCHO	"	Me	90	93
HexCHO	"	Hept	87	86

[a] Recovered yield of ketone ≥ 99%. [b] RMnBr prepared in diethylether from RLi. [c] RMnCl prepared in THF from RLi or RMgBr.

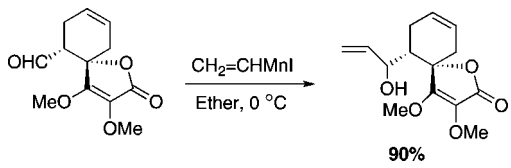
Scheme 55



Scheme 56



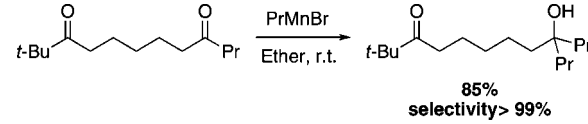
Scheme 57



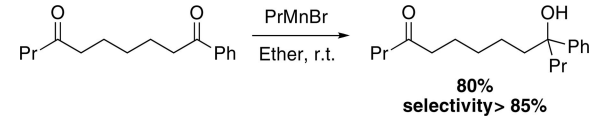
deactivated but more accessible, preferentially undergoes the 1,2-addition.[6c,f]

The discrimination can also result from the formation of a chelate with one of the two carbonyl groups and a neighboring complexing group such as Me_2N (Scheme 60).[44]

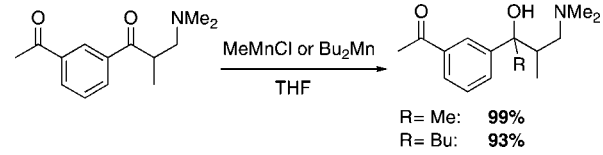
Scheme 58



Scheme 59



Scheme 60



Scheme 61

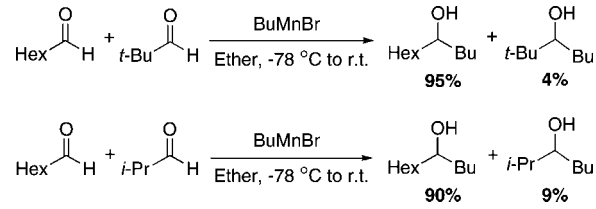
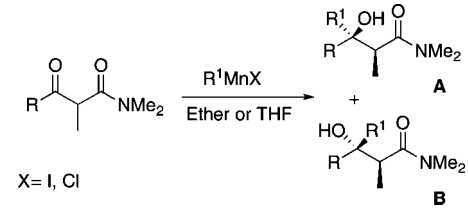


Table 6. Addition of RMnX to 2-Methyl-3-*oxo*-Amides



R	R^1	yield (%)	A/B
Ph	Me	93	>99:1
Ph	Bu	98	>99:1
Ph	*i*-Pr	83	>99:1
Me	Ph	83	1:99
Et	Ph	52	7:93

The aldehyde−aldehyde competition experiments described in Scheme 61 are remarkable. Again, the less hindered carbonyl group reacts preferentially in spite of the very high reactivity of the two aldehydes. The selectivity is not as good as in the examples reported above, but it is exceptional for such a competition.[6c,f]

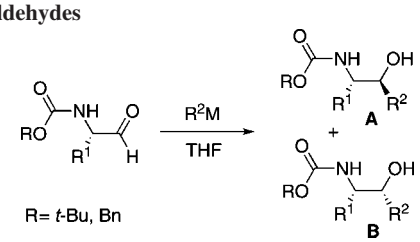
3.3. Diastereoselective 1,2-Addition

Oshima reported the diastereoselective addition of organomanganese compounds to racemic 2-methyl-3-*oxo*-amides (Table 6).[45]

The corresponding 3-alkyl (or aryl)-3-hydroxy-2-methyl amides are obtained in good yields. It should be pointed out that alkylmanganese compounds give one diastereomer whereas phenylmanganese mainly gives the other.

Reetz showed that methyl and butylmanganese bromides react with the enantiopure *N*-protected α-aminoaldehydes depicted in Table 7 to give the 1,2-addition products in good yields. Organomanganese reagents give a better diastereoselectivity than the organolithium or organomagnesium reagents.[46]

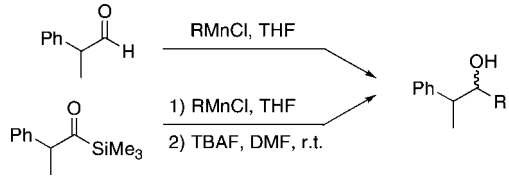
Table 7. Reaction of RMnX with *N*-BOC or *N*-CBZ Protected α-Aminoaldehydes

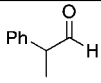
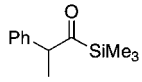


R	R^1	R^2M	conversion[a] (%)	A/B
t-Bu	Me	MeMnBr	90	95:5
$PhCH_2$	Me	BuMnBr	82	93:7
t-Bu	Me	BuMnBr	82	86:14
t-Bu	$PhCH_2$	MeMnBr	85	89:11
t-Bu	$PhCH_2$	MeMgI	66	54:46
t-Bu	*i*-Bu	MeMnBr	97	96:4
t-Bu	*i*-Bu	MeLi	85	39:61

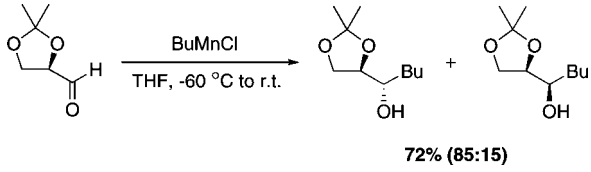
[a] The yield is not reported.

Table 8. Diastereoselective Addition of RMnX to Aldehydes and Acylsilanes



substrate	R	yield (%)	*syn*/*anti*
	Me	95	96:4
	Bu	75	≥ 99:1
	Allyl	85	93:7
	Me	75	96:4
	Bu	70	97:3
	Allyl	83	76:24

Scheme 62



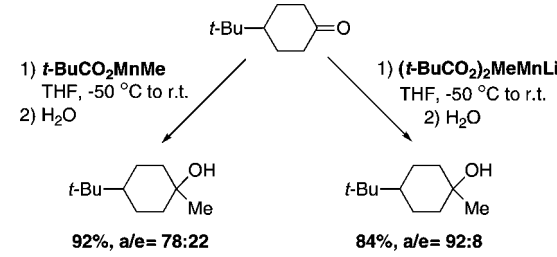
Cahiez, Knochel, and Ricci reported the diastereoselective addition of organomanganese halides to 2-phenylpropanal and the corresponding α-chiral acylsilane (Table 8).[47]

Interestingly, organomanganese halides add to 2,3-*O*-isopropylideneglyceraldehyde, a well-known chiral starting material in asymmetric synthesis, to give mainly the *anti*-alcohol (Scheme 62). The diastereoselectivity is higher than that reported in the literature for other organometallic reagents.[47]

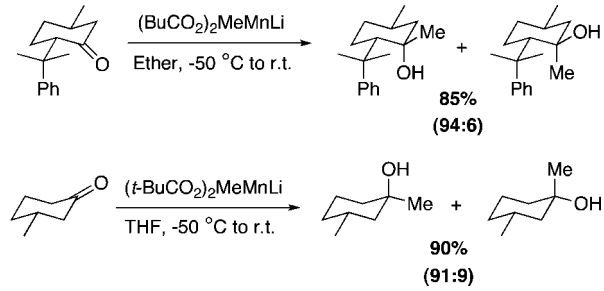
In 1992, Reetz described the diastereoselective addition of a new alkylmanganese reagent *tert*-$BuCO_2MnMe$ to 4-*tert*-butylcyclohexanone.[48] Later, during our investigations, we demonstrated that the reagent used by Reetz is not the organomanganese reagent *tert*-$BuCO_2MnMe$ but probably the heteroorganomanganate (*tert*-$BuCO_2)_2MeMnLi$ (Scheme 63).[49]

As a rule, such heteroorganomanganates promote superior diastereoselectivities (Scheme 64).[49]

Scheme 63



Scheme 64



Scheme 65

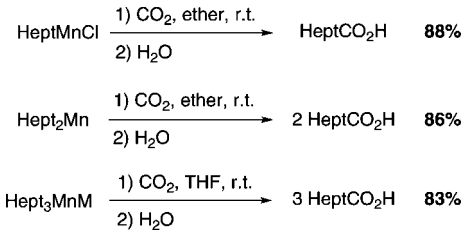
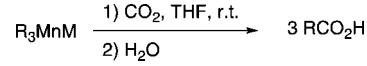


Table 9. Carbonation of Organomanganates



R_3MnM	yield (%)
$Bu_3MnMgCl$	86
Ph_3MnLi	89
$Mesityl_3MnLi$	76
$(Me_2C{=}CH)_3MnLi$	96
$(BuC{\equiv}C)_3MnLi$	83

3.4. Reaction with Carbon Dioxide

The carbonation of organomanganese reagents was reported in 1979.[39b] Organomanganese halides, symmetrical organomanganeses, and organomanganates were used successfully (Scheme 65). It is interesting to note that all R groups bonded to manganese participate in the reaction.

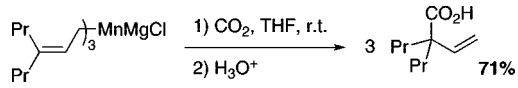
In all cases, the reaction can be performed at room temperature since the resulting manganese carboxylate does not react with the starting organomanganese compound. It is a clear advantage compared to the organolithium or organomagnesium reagents, which must be carbonated at a low temperature to prevent the formation of side products and to control an important exothermic effect.

The scope of the reaction is broad and numerous carboxylic acids can be prepared in good yields under mild conditions (Table 9).

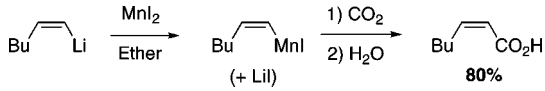
Interestingly, allylic organomanganese compounds selectively react at their more substituted side (Scheme 66).

Alkenylmanganese halides react stereospecifically to give the corresponding α,β-ethylenic carboxylic acids in good yields (Scheme 67).

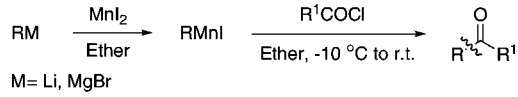
Scheme 66



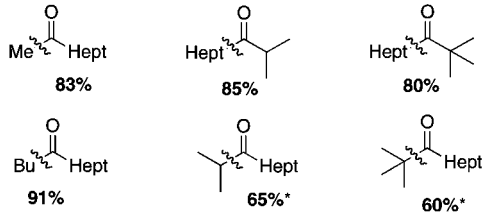
Scheme 67



Scheme 68



selected examples:



* 1.5 equivalents of RMnI were used

4. Acylation of Organomanganese Compounds

Acylation was the first reaction studied when we embarked upon the chemistry of organomanganese coupounds. Initial attempts were performed by using organomanganese reagents prepared from manganese iodide. Later, our know-how concerning the preparation of these organometallics improved, and we then turned to the use of organomanganese bromides or chlorides prepared in ether or in THF. Finally, we disclosed the manganese-catalyzed acylation of Grignard reagents, a very interesting procedure for large-scale applications. As exemplified below, the scope of the manganese-mediated preparations of ketones described herein is extensive, since the acylation procedures involving organomanganese reagents are highly chemoselective. During all our investigations, we have prepared more than 1000 simple and functionalized ketones.

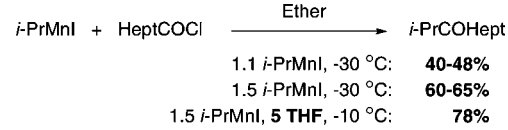
4.1. Preparation of Ketones from Organomanganese Halides and Carboxylic Acid Chlorides in Ether

4.1.1. From Organomanganese Iodides

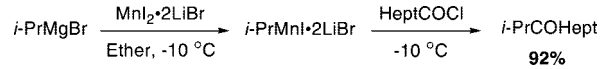
Our first results concerning the acylation of organomanganese compounds were reported in 1976.[50] The ketones are obtained in good yields from organomanganese iodides and stoichiometric amounts of carboxylic acid chlorides in diethylether (Scheme 68).

As shown in Scheme 68, aliphatic ketones are easily prepared from linear or branched carboxylic acid chlorides. The reaction is generally performed between −10 °C and room temperature and is operational down to −50 °C. Primary alkylmanganese compounds lead to good-to-excellent yields. However, only moderate yields are obtained with secondary and tertiary alkylmanganese iodides that are clearly less stable (see section 2.2.5). It should be pointed out that the formation of the 1,2-addition product is never observed.

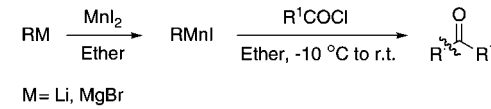
Scheme 69



Scheme 70



Scheme 71



selected examples:

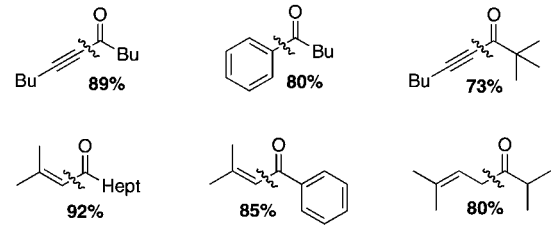


Table 10. Acylation of Organomanganese Compounds Prepared from MnI_2 in Ether

RMnI (A) R_2Mn (B) R_3MnLi (or MgX) (C)

"RMn" ("RMn"/R^1COCl)	R	R^1	yield (%)
A (1:1)	Bu≡C	Bu	89
B (1:2)	Bu≡C	Bu	80
C (1:3)	Bu≡C	Bu	70−75
A (1:1)	Bu	Hept	90
B (1:2)	Bu	Hept	85
C (1:3)	Bu	Hept	75−80

With the unstable secondary and tertiary alkylmanganese iodides, it is possible to improve the yield by using an excess of organometallic reagent (1.5 equiv) or by adding THF as a ligand (5 equiv, Scheme 69).[20]

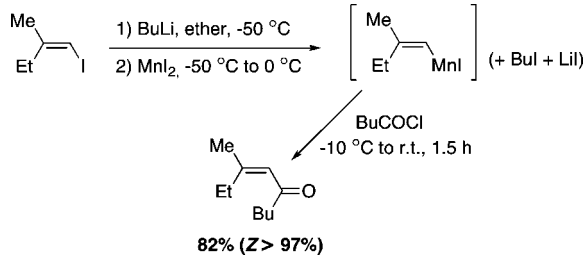
To date, however, the best way is to prepare secondary or tertiary alkylmanganese iodides from the corresponding Grignard reagents by using the complex MnI_2•2LiBr instead of MnI_2. The organometallics thus obtained are more stable and can be acylated efficiently at −10 °C (Scheme 70).[7e]

The procedure described above is very general, and was successfully extended to allyl-, alkenyl-, alkynyl-, and arylmanganese iodides (Scheme 71). The acylation smoothly takes place at 0 °C to afford good yields of unsaturated ketones.[7a,b]

The results presented in Table 10 illustrate that symmetrical organomanganeses and organomanganates prepared from manganese iodide in ether also lead to good yields of ketones (Table 10). It should be emphasized that all the R groups bonded to manganese are acylated.

Interestingly, (*Z*)-alkenylmanganese iodides can be obtained stereoselectively from the corresponding lithium reagent prepared by lithium−iodine exchange from the (*Z*)-alkenyl iodides (Scheme 72).[50] The acylation of these

Scheme 72. Stereoselective Acylation of Alkenylmanganese Iodide



organomanganese reagents yields the expected conjugated enones in good yield and with an excellent stereochemical purity.[6a] The reaction takes place chemoselectively in the presence of the butyl iodide resulting from the lithium−iodine exchange.

The chemoselectivity of organomanganese iodides is well-demonstrated by the impressive number of functionalized ketones synthesized from functionalized carboxylic acid chlorides.[7a,b,51] As shown in Scheme 73, various reactive functional groups are tolerated. Thus, it is easy to prepare various halogenoketones, ketoethers, and ketosulfides as well as ketoesters, ketonitriles, or even unsymmetrical diketones. In all cases, no side reaction is observed.

The preparation of mono- and dichloromethylketones from mono- or dichloroacetylchlorides deserves to be underlined since these ketones are generally too reactive to be obtained efficiently by acylation of an organometallic compound (Scheme 74).[7b]

Good yields of symmetrical 1,6-diketones were obtained from the carboxylic acid chloride depicted in Scheme 75.[51]

The reaction was successfully extended to heterocyclic carboxylic acid chlorides derived from furan or thiophene (Scheme 76).

Various cycloheptatrienyl ketones were also prepared (Scheme 77).[52]

The acylation of organomanganese iodides by carboxylic acid chlorides is a very clean reaction. Thus, the formation of tertiary alcohol as a side product is never observed. This result is surprising since organomanganese iodides easily react with ketones in ether (see section 3). Further investigations showed that the ketone and the manganese salts (MnICl) produced during the reaction form a complex.[53] This complex is then destroyed during the final aqueous workup.

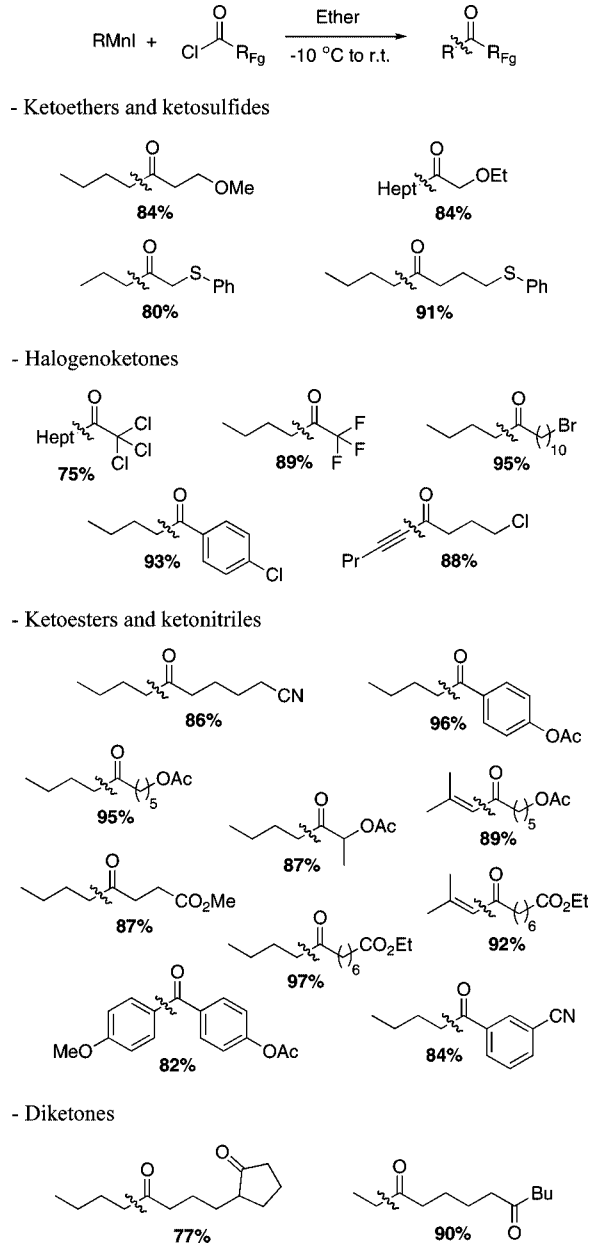
For instance, the reaction of butylmanganese iodide with pentanoyl chloride in ether leads to a sticky precipitate (Scheme 78). No trace of 5-nonanone was detected in the ethereal phase. On the other hand, the ketone is obtained in 93% yield after hydrolysis. Let us remark that the 5-nonanone can be quantitatively displaced from the complex BuCOBu·MnICl, under anhydrous conditions, by adding triethylamine (15 equiv) or acetone (10 equiv).

This complexation, however, considerably slows down the 1,2-addition of the organomanganese reagent to the carbonyl group. Thus, butylmanganese iodide adds to uncomplexed 5-nonanone in 15−20 min at room temperature to give 90% yield of tertiary alcohol, whereas the complexed ketone only leads to 63% after 36 h (Scheme 79).

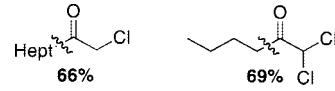
4.1.2. From Organomanganese Bromides

Organomanganese bromides prepared in ether from the soluble ate-complex $MnBr_2 \cdot 2LiBr$ are very interesting since they are less expensive than the iodide analogues. They

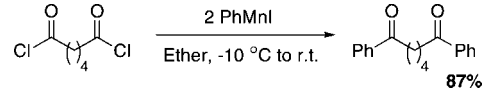
Scheme 73. Chemoselective Preparation of Ketones by Acylation of RMnI with Functionalized Carboxylic Acid Chlorides



Scheme 74. Acylation of Organomanganese Iodides with Chloro- and Dichloroacetylchlorides



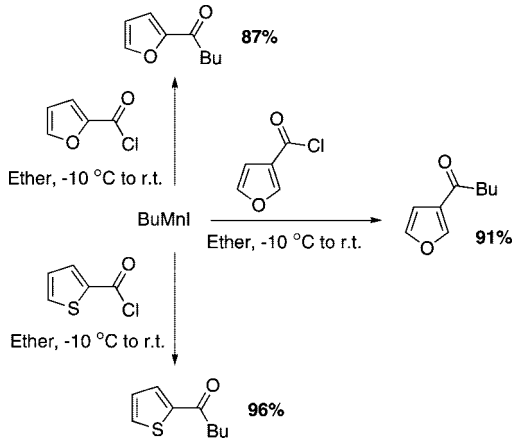
Scheme 75



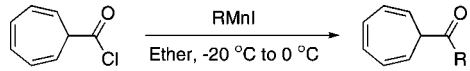
readily react with carboxylic acid chlorides under mild conditions to afford the corresponding ketones in excellent yields (Table 11).[7d,e,13]

Secondary and tertiary alkylmanganese bromides prepared from a Grignard reagent are stable enough to be acylated efficiently at −10 °C. Various branched ketones can thus be prepared in excellent yields (Scheme 80).[7e,13]

Scheme 76

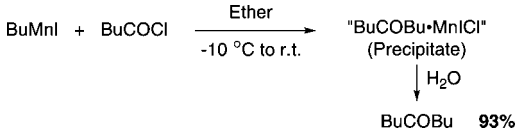


Scheme 77

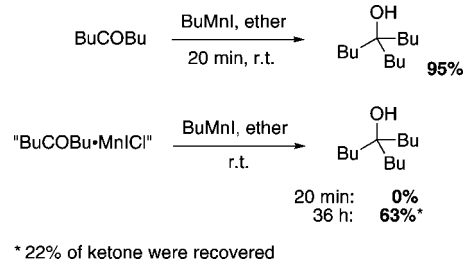


R= Ph: **75%**; Me: **60%**; *c*-Pr: **50%**

Scheme 78

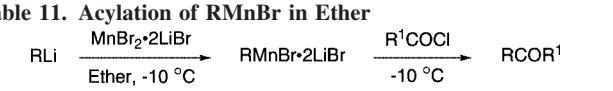


Scheme 79



* 22% of ketone were recovered

Table 11. Acylation of RMnBr in Ether



R	R^1	yield (%)
Bu	Hept	97
Me_2C=CH	Hept	87
Bu	Me_2C=CH	95
Ph	Bu	95
Bu	Ph	92
BuC≡C	Bu	95

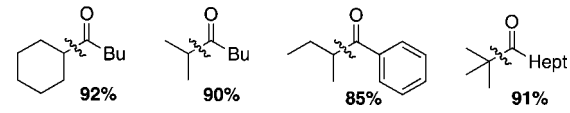
Moreover, the preparation of organomanganese compounds from $MnBr_2$ instead of MnI_2 allows one to avoid the presence of iodine during the final workup. This is very important for the preparation of iodine-sensitive products. Thus, all our attempts to prepare the polyunsaturated ketone described in Scheme 81 resulted in failure from 1-hexynylmanganese iodide, whereas the corresponding bromide gives a good yield.[7d]

This procedure is thus especially suitable for the preparation of conjugated polyunsaturated ketones (Scheme 82).[13]

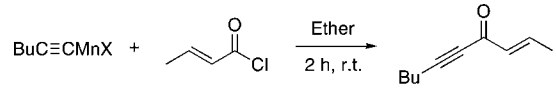
Numerous acetylenic ketones were obtained from alkynylmanganese bromides (Schemes 83 and 84).[6c,f] Moreover,

Scheme 80

selected examples:



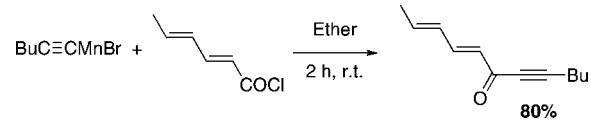
Scheme 81



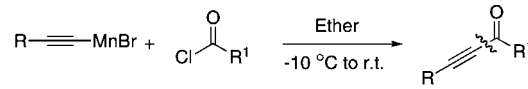
From MnI_2: **0%***
From $MnBr_2$: **87%**

* Only polymeric material was obtained

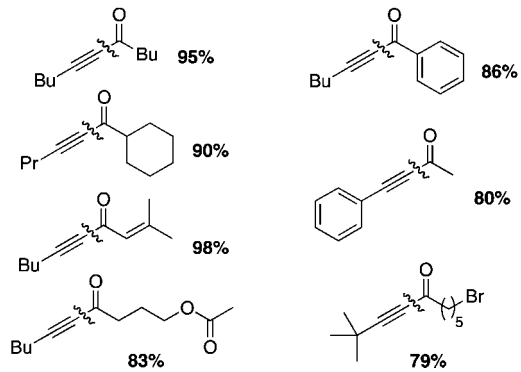
Scheme 82



Scheme 83



selected examples:



functionalized alkynylmanganese bromides can also be employed successfully (Scheme 84).

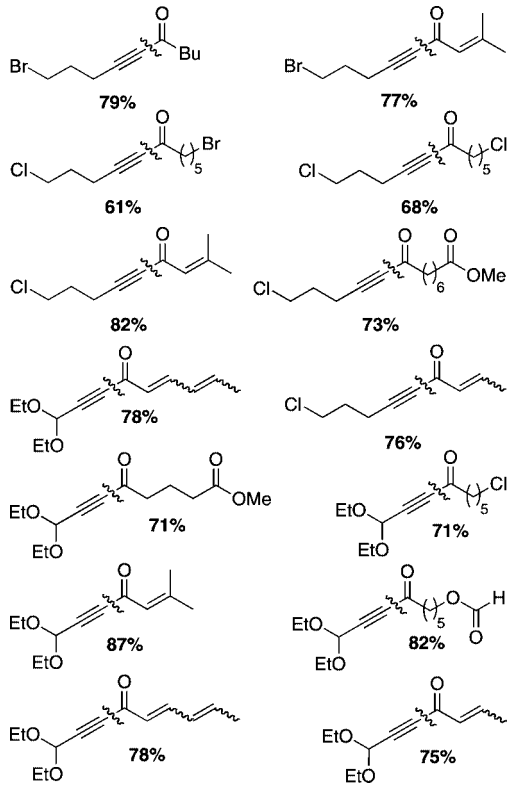
It is interesting to note that the organomanganese alcoholate derived from propargylic alcohol undergoes a double acylation to give a ketoester in good yield (Scheme 85).[13]

Finally, we have recently described the acylation of functionalized organomanganese compounds prepared from various aryl or alkenyl iodides or bromides via the corresponding organolithium reagents (lithium−halogen exchange).[15] Thus, highly polyfunctionalized ketones were obtained in satisfactory yields (Schemes 86 and 87).

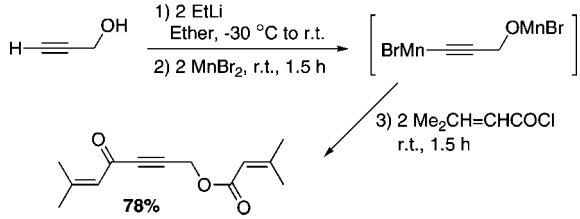
4.2. Preparation of Ketones from Carboxylic Acid Chlorides in THF

The acylation of organomanganese compounds was also performed in THF.[19] In this solvent, organomanganese chlorides are easily prepared from the soluble ate-complex $MnCl_2$•2LiCl and react with acid chlorides to give the desired ketones (Scheme 88).

Scheme 84. Preparation of Acetylenic Ketones from Functionalized Alkynylmanganese Bromides



Scheme 85



Linear and branched aliphatic acid chlorides, as well as the less reactive conjugated aromatic and ethylenic acid chlorides, lead to the corresponding ketones in excellent yields. On the other hand, alkyl-, alkenyl-, and alkynylmanganese chlorides as well as allylic organomanganese reagents were used successfully. In THF, the reaction is also highly chemoselective (Scheme 89).[19]

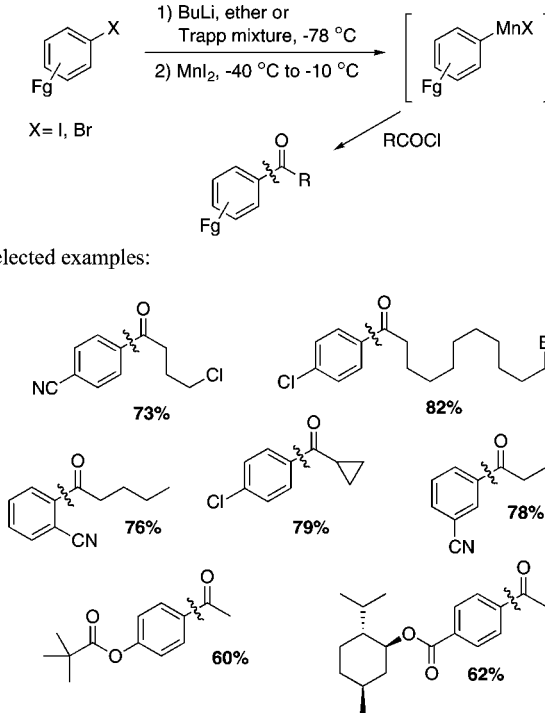
In THF, methyl-, aryl-, and secondary and tertiary alkylmanganese halides give lower yields than in ether. Fortunately, these limitations were circumvented (Table 12) by performing the reaction in the presence of a catalytic amount of copper chloride (3%). A dramatic influence is observed in the case of the *tert*-butylmanganese chloride since the yield jumps from 0% to 92%.[19]

4.3. Acylation with Other Carboxylic Acid Derivatives

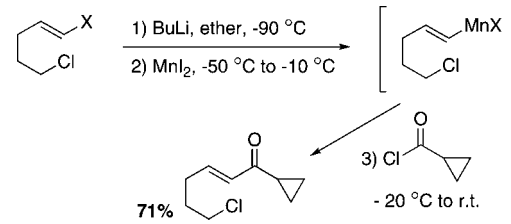
Carboxylic acid anhydrides smoothly react with organomanganese halides under mild conditions in ether or in THF to afford ketones in good yields (Scheme 90).[20,54]

Mixed carbonic−carboxylic anhydrides are easily prepared from the corresponding carboxylic acid and ethyl chloroformate in quantitative yields (Scheme 91). These acylating agents are prepared under milder conditions than the corresponding carboxylic acid chlorides. It is especially interesting in the case of acid-sensitive carboxylic acids. Thus, they have been widely employed for the synthesis of peptides.

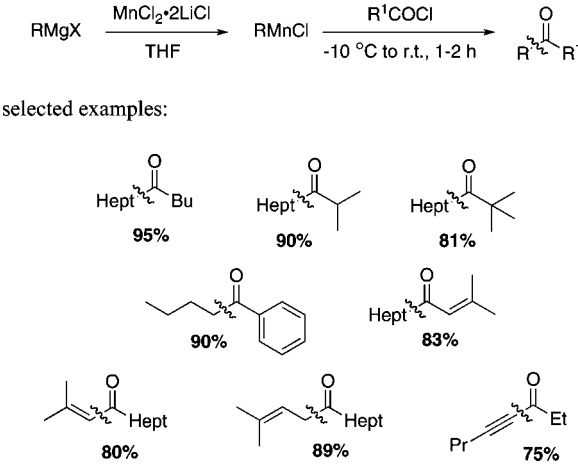
Scheme 86



Scheme 87



Scheme 88



In ether, they can be used in place of carboxylic acid chlorides and give similar results (Scheme 92).[20]

On the other hand, in THF, they lead to the ketones in only moderate and irreproducible yields (20−40%), since the formation of the ethyl ester R^1CO_2Et competes seriously. This is often the main product (Scheme 93).[20]

We have shown that good yields of ketones can be obtained by using an organomanganese chloride prepared

Scheme 89

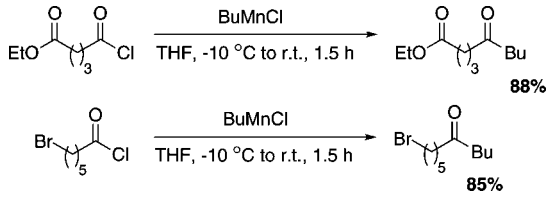
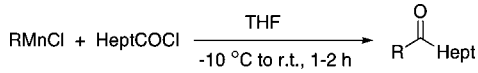
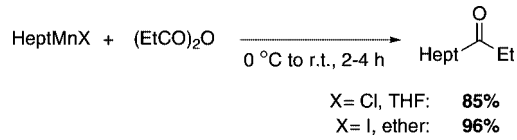


Table 12. Cu-Catalyzed Acylation of RMnCl in THF

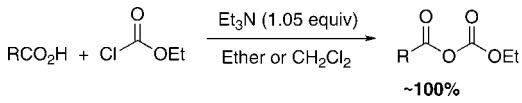


	yield (%)	
R	without CuCl	with CuCl (3%)
Me	40	91
i-Pr	69	93
t-Bu	0	92
Ph	75	92

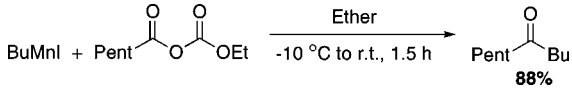
Scheme 90



Scheme 91



Scheme 92



Scheme 93

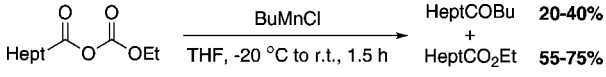
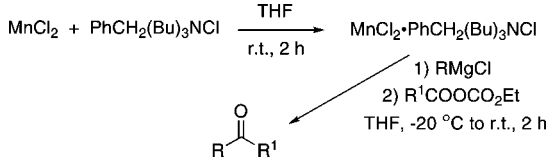


Table 13. Acylation of RMnCl by RCOOCO$_2$Et in the Presence of PhCH$_2$(Bu)$_3$NCl

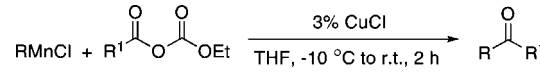


R	R^1	yield (%)
Bu	Hept	79
Ph	Hept	68
Hept	*i*-Pr	78
Bu	Ph	85
i-Pr	Ph	79
Hept	Me$_2$C=CH	83

from the complex MnCl$_2$·R$_4$NCl previously mentioned (Scheme 12). Indeed, in the presence of a tetraalkylammonium chloride, the acylation occurs almost instantaneously (Table 13).[7e]

Another way to improve the yield of ketone from mixed carbonic−carboxylic anhydrides is to achieve the reaction in the presence of a catalytic amount of copper chloride (Table 14).[13]

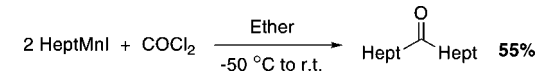
Table 14. Acylation of RMnCl by RCOOCO$_2$Et in the Presence of 3% CuCl



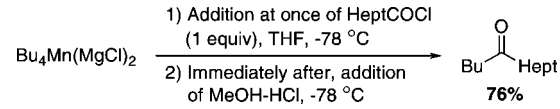
R[a]	R^1	yield (%)
Bu	Hept	81
Bu	Me$_2$C=CH	76
t-Bu	Hept	76
Ph	Hept	78

[a] RMnCl was indifferently prepared from RLi or RMgX and MnCl$_2$·2LiCl.

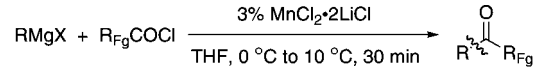
Scheme 94



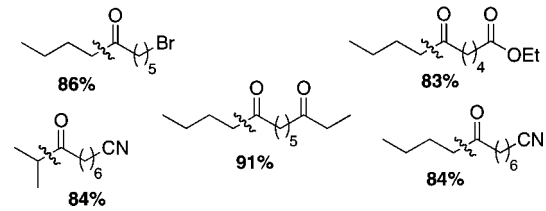
Scheme 95



Scheme 96



selected examples:



Finally, symmetrical ketones were also synthesized from phosgene (Scheme 94).[55]

4.4. Manganese-Catalyzed Acylation of Grignard Reagents

As shown above (Table 10), organomanganese compounds R$_2$Mn, R$_3$MnLi, or R$_3$MnMgX as well as R$_4$MnLi$_2$ or R$_4$Mn(MgX)$_2$ can also be efficiently acylated. In the case of an organomanganate R$_4$Mn(MgX)$_2$, we evidenced that the acylation of the first R group bonded to manganese takes place almost instantaneously, even at −78 °C in THF (Scheme 95).[56]

This preliminary experiment initiated a study that resulted in the discovery of a very efficient method for the preparation of ketones by manganese-catalyzed acylation of Grignard reagents. Good yields were thus obtained under very mild conditions (Table 15).[56]

It is important to underline that the success of this reaction closely depends on the rate of the addition of the Grignard reagent. The following catalytic cycle involving a manganate R$_4$Mn(MgX)$_2$ as the key intermediate was proposed (Figure 1).

This catalytic procedure allows the preparation of various functionalized ketones in good yields from the corresponding carboxylic acid chlorides (Scheme 96).

The reaction is sensitive to steric hindrance. Thus, tertiary alkylketones are only obtained in moderate-to-poor yields.

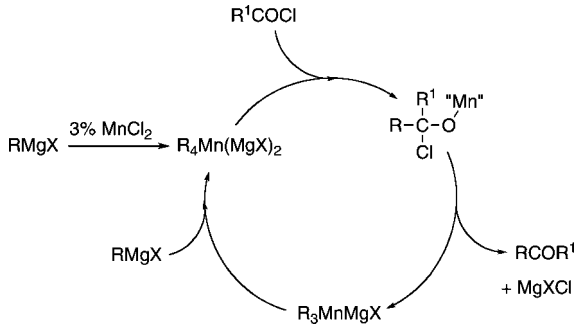
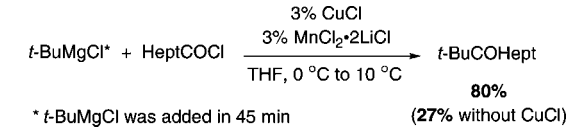


Figure 1. Mechanism of the Mn-catalyzed acylation of RMgX.

Scheme 97



Scheme 98

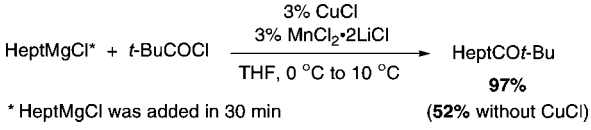
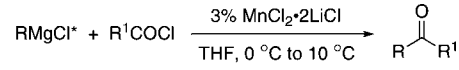


Table 15. Mn-Catalyzed Acylation of RMgX



* RMgCl is added dropwise for 30 to 45 min

R	R^1	yield (%)
Bu	Hept	87
Hept	*i*-Pr	94
Hept	*t*-Bu	52
Hept	$Me_2C{=}CH$	79
Bu	Ph	85
i-Pr	Hept	74
$Me_2C{=}CH$	Hept	73
Ph	Bu	85
i-Pent	*i*-Bu	83

It is possible to circumvent this drawback by using a copper−manganese cocatalysis.

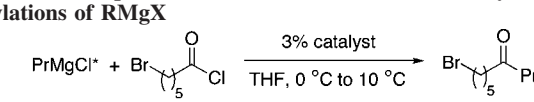
This catalysis is efficient in the case of tertiary alkylmagnesium reagents (Scheme 97) but also in the case of branched carboxylic acid chlorides (Scheme 98).[56b]

The manganese-catalyzed procedure is especially convenient for large-scale preparative applications since it is very simple to carry out (Table 15, Schemes 96−98). It should be noted that manganese chloride is a very cheap catalyst. From an economical point of view, only the iron-catalyzed acylation of Grignard reagents supports the comparison. However, the manganese-catalyzed reaction allows one to work at a higher concentration (Table 16).[57]

4.5. Preparation of Esters by Acylation of Organomanganese Halides with Ethyl Chloroformate

Ethyl chloroformate was also used as an acylating reagent. The reaction with organomanganese iodides in diethylether leads to good yields of esters (Scheme 99).[55]

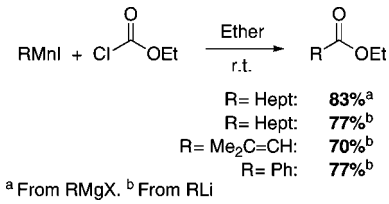
Table 16. Comparison between the Mn- and Fe-Catalyzed Acylations of RMgX



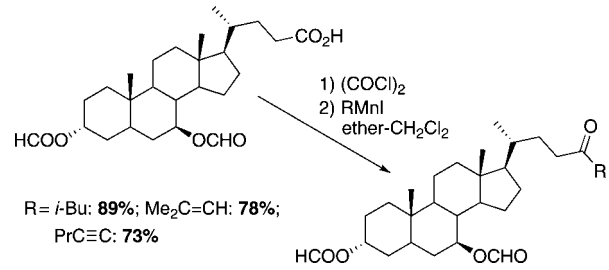
* PrMgCl was added in 30 min

catalyst	concentration of the reaction mixture	yield (%)
$Fe(acac)_3$	0.4 M	91
$Fe(acac)_3$	1.2 M	38
$MnCl_2$•2LiCl	1.2 M	86

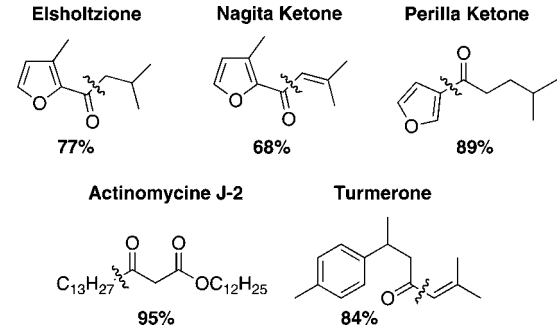
Scheme 99



Scheme 100



Scheme 101



4.6. Applications of the Acylation of Organomanganese Compounds in Organic Synthesis

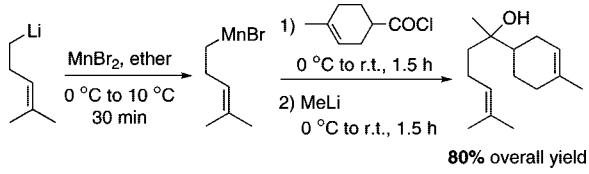
As illustrated above, organomanganese compounds are acylated very chemoselectively. This characteristic was used in the synthesis of various natural compounds, fragrances, or bioactive products. The first applications relate to the synthesis of ketosteroids (Scheme 100).[58]

Excellent yields were obtained in spite of the presence of formyloxy groups. It should be noted that the chemoselectivity of organomanganese reagents allows one to work with a mixture ether−dichloromethane as a solvent in order to solubilize the starting carboxylic acid chloride.

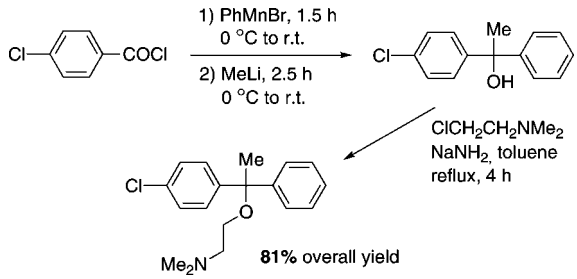
Various natural ketones were prepared in good yields by acylation of organomanganese iodides (Scheme 101).[8,59]

(±)-α-Bisabolol was prepared according to a one-pot acylation/1,2-addition procedure via the 4-methyl-3-pentenylmanganese bromide (Scheme 102).[60]

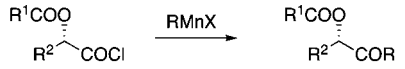
Scheme 102



Scheme 103



Scheme 104



X= Cl, Br
R^1= Me, *t*-Bu, Ph
R^2= Me, *i*-Pr, Ph, $PhCH_2$
R= Me, Bu, Hex, *i*-Pr, *t*-Bu, Ph, $Me_2C{=}CH$, PentC≡C

A similar procedure was applied to the synthesis of chlorphenoxamine, which is used as an antihistaminic (Scheme 103).[60]

Various chiral α-acyloxyketones were easily prepared in high yields and with an excellent enantiomeric purity from enantiopure chiral α-acyloxy carboxylic acid chlorides (Scheme 104).[61]

Finally, optically active δ-ketobutanolides were synthesized in good yields with excellent enantiomeric purity by acylation of the butyrolactone acid chloride prepared from natural (L)-glutamic acid (Scheme 105).[62]

Finally, organomanganese iodides were used in solid-phase synthesis for the chemoselective conversion of carboxylic acid chlorides to tertiary alcohols (one-pot acylation/1,2-addition procedure).[63]

5. Addition of Organomanganese Compounds to α,β-Unsaturated Carbonyl Derivatives

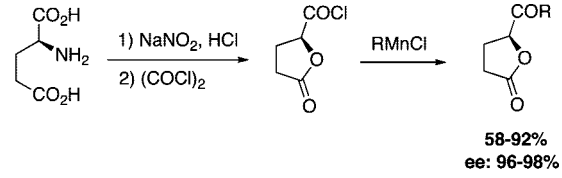
5.1. Reaction of Organomanganese Reagents with Various Michaël Acceptors

Organomanganese reagents react with cyclohexenone to give a mixture of products resulting from the 1,2- and 1,4-additions as well as the β-reductive dimerization.[64] The proportion between the three products is very dependent on several parameters: the nature of the organomanganese reagent, the solvent, the presence of metallic salts (LiX or MgX_2), and the temperature.

With organomanganese halides, the reaction has no preparative interest since it generally leads to a mixture of the three products (Scheme 106).

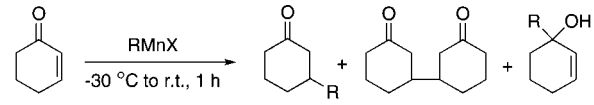
By using a symmetrical organomanganese reagent, the formation of the 1,2-addition product is generally not observed. As a rule, the 1,4- and β-reductive dimerization

Scheme 105



R= Me, Bu, Hex, $C_{12}H_{25}$, *i*-Pr, *t*-Bu, Ph, PentC≡C

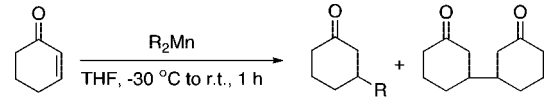
Scheme 106



MeMnBr, ether:	7%	25%	34%
BuMnBr[a], ether:	18%	27%	20%
BuMnBr[b], ether:	26%	35%	3%
BuMnCl[a], THF:	10%	0%	10%
i-PrMnCl[c], THF:	23%	33%	4%

[a] Prepared from BuLi. [b] Prepared from BuMgCl. [c] Prepared from *i*-PrMgCl.

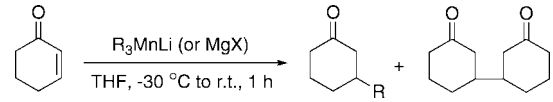
Scheme 107



Me_2Mn[a]:	40%	0%
Me_2Mn[b]:	72%	5%
Bu_2Mn[a]:	30%	50%
Bu_2Mn[b]:	70%	25%
i-Pr_2Mn[b]:	4%	83%
Ph_2Mn[b]:	62%	21%

[a] Prepared from RLi. [b] Prepared from RMgX.

Scheme 108



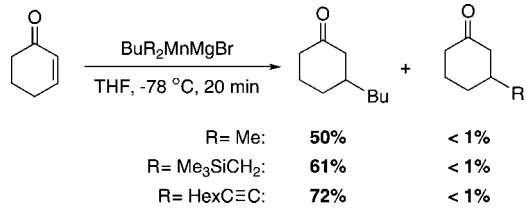
$Me_3MnMgCl$:	42%	21%
Bu_3MnLi:	18%	74%
$Bu_3MnMgCl$:	20%	74%
i-$Pr_3MnMgCl$:	13%	74%
$Ph_3MnMgCl$:	45%	16%

products are obtained as a mixture, but it is sometimes possible to obtain mainly one of the two products (Scheme 107).

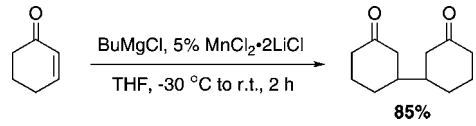
Lithium or magnesium organomanganates behave similarly. The formation of the β-reductive dimerization product is clearly favored with the trialkylmanganates subject to decompose by β-hydrogen elimination. It should be underlined that, in the case of organomanganates, the yields indicated in Scheme 108 are based on the transfer of only one of the three R groups.

Some years later, Oshima showed that, in the case of the cyclohexenone, it is possible to use heteroorganomanganates such as $BuR_2MnMgBr$ in order to transfer only the Bu group.[65] Thus, when R = Me, Me_3SiCH_2, or RC≡C, only the 3-butylcyclohexanone is obtained. Nevertheless, the yields are moderate and the scope of the reaction is very limited (Scheme 109).

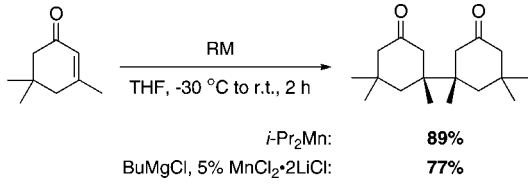
Scheme 109



Scheme 110



Scheme 111



It is very important to note that the report concerning the conjugate addition of organomanganese reagents to cyclohexenone described in 1984[66] should not be taken into account. Indeed, in the light of our results, the authors tried to repeat their experiments and they finally confirmed the results described above.

The β-reductive dimerization product was also obtained in satisfactory yield from 2-cyclohexenone by using an organomagnesium reagent in the presence of a catalytic amount of manganese salt (Scheme 110).[64] The manganese catalysis is very efficient since the 1,2-addition to cyclohexenone is completely avoided.

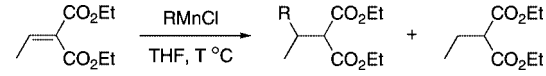
Unfortunately, the synthetic scope of this reaction is very limited. Thus, the β-reductive dimerization product is obtained in good yield from isophorone (Scheme 111), but all our attempts to extend the reaction to various enones such as 2- and 3-methylcyclohexenones, 1-acetylcyclohexene, and some β-mono- or β,β-bisubstituted acyclic enones resulted in low yields (< 30%) of 1,4- or β-reductive dimerization products.

The results presented above showed that organomanganese reagents are able to add in a 1,4-manner to conjugated enones. However, the reaction has no practical interest, since the yields are generally moderate and the 1,2-addition as well as the β-reductive dimerization compete seriously. To favor the conjugate addition, we thus decided to perform the reaction with a class of powerful Michaël acceptors, the alkylidene malonic esters.[7c] As expected, alkyl-, aryl-, alkenyl-, or even the less reactive alkynylmanganese chlorides readily react in THF to give satisfactory yields of conjugate addition product (Table 17). From secondary or tertiary alkylmanganese reagents having β-eliminable hydrogen atoms, the formation of the reduction product is partially (R = *i*-Pr) or mainly (R = *t*-Bu) observed.

Interestingly, functionalized organomanganese reagents can also be employed (Scheme 112).[15]

In some cases, Grignard reagents can also react with alkylidene malonic esters to give mainly the 1,4-addition product (Table 18). However, organomanganese reagents generally give higher yields, and the scope of the reaction is larger.[7c]

Table 17. Conjugate Addition of RMnX to Alkylidene Malonic Esters



R	*T*	1,4-addition (%)	reduction (%)
Me, Bu, Ph	−30 °C	85−89	
Me_2CH═CH, BuC≡C, allyl	20 °C	72−91	
i-Pr	−30 °C	70	11
t-Bu	−30 °C	10	40

Scheme 112

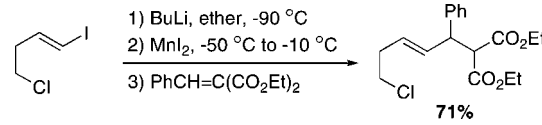
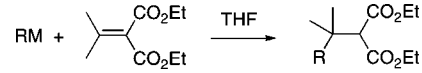
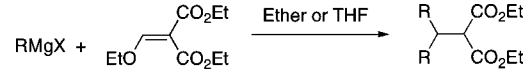


Table 18. Conjugate Addition to Alkylidene Malonic Esters: Comparison between RMgCl and RMnCl

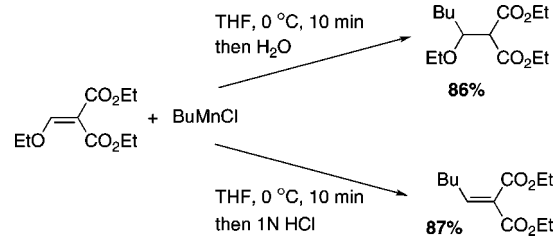


	yield (%) from	
R	RMgCl	RMnCl
Bu	62	74
Me	5	82
Ph	5	87

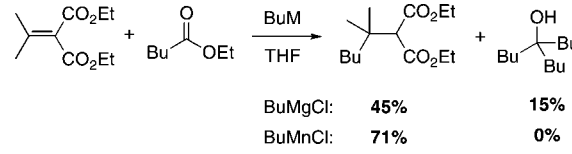
Scheme 113



Scheme 114



Scheme 115



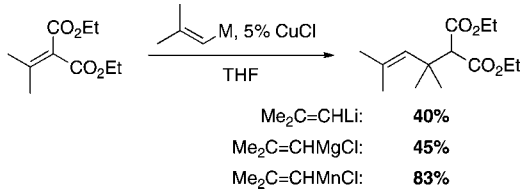
Moreover, from β-alkoxy alkylidene malonic esters, the Grignard reagents only give the double addition product (Scheme 113), even when an excess of ester is used.

On the contrary, the organomanganese reagents lead selectively to the monoaddition product (neutral hydrolysis). By treatment under acidic conditions, a new alkylidene malonic ester is thus prepared in good yield (Scheme 114).

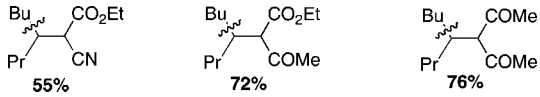
Finally, it should be pointed out that organomanganese compounds react more chemoselectively than the corresponding Grignard reagents (Scheme 115).[7c]

β,β-Disubstituted alkylidene malonic esters are clearly less reactive than their β-monosubstituted analogues. Thus, the conjugate addition of alkenyllithium, magnesium, and manganese reagents only occurs in the presence of copper

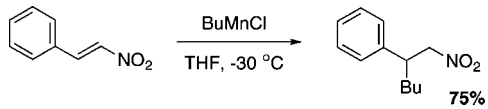
Scheme 116



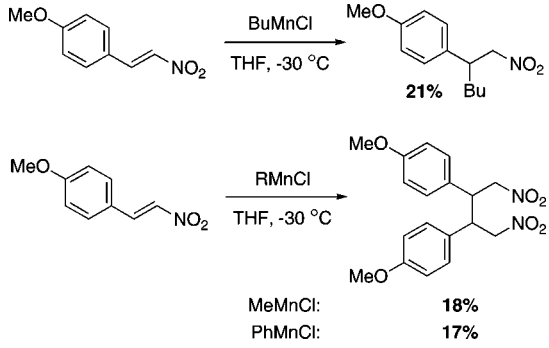
Scheme 117



Scheme 118



Scheme 119



chloride. However, in this case, organomanganese chlorides are still more efficient (Scheme 116).

It should be noticed that the reaction was successfully extended to various Michaël acceptors derived from alkylidene malonic esters (Scheme 117).[7c]

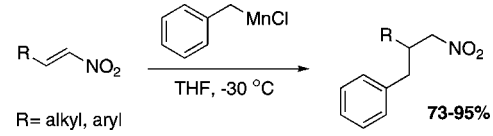
Conjugated nitroolefins are well-known to be versatile and powerful Michaël acceptors. However, the 1,4-addition of Grignard reagents gives poor results since the competitive 1,2-addition to the nitro group mainly occurs. Hassner tried to avoid the 1,2-addition by using organomanganese reagents.[67] The first experiments were encouraging, since BuMnCl reacts with nitrostyrene in THF at −30 °C, to give the 1,4-adduct in 75% yield (Scheme 118). Under these conditions, the 1,2-addition does not occur (<5%). The author showed that the addition of copper salts or Me_3SiCl to the reaction mixture has no significant influence on the course of the reaction.

Unfortunately, this method cannot be successfully extended to other nitroolefins such as 4-methoxy nitrostyrene. Thus, butylmanganese chloride adds on this substrate in poor yield, and methyl- or phenylmanganese chloride only give the β-reductive dimerization product (Scheme 119).

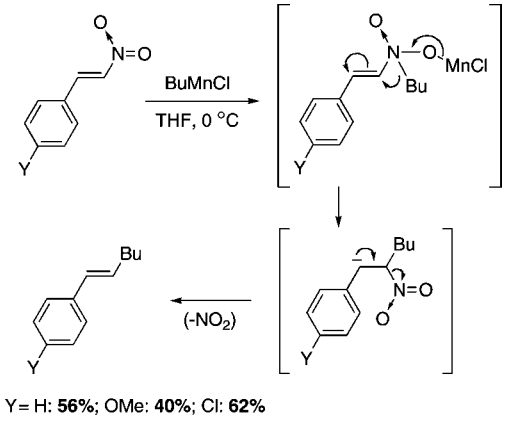
Benzylmanganese chloride leads to better yields (Scheme 120).

Curious results are obtained by treating various nitrostyrenes with butylmanganese chloride in the presence of 1 equiv of manganese salt ($MnCl_2 \cdot 2LiCl$). The reaction then leads, in moderate yields, to the (*E*)-olefins corresponding to the formal substitution of the NO_2 by a butyl group. Hassner has proposed the following mechanism (Scheme 121).[67]

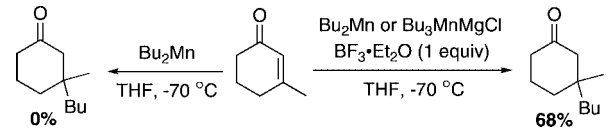
Scheme 120



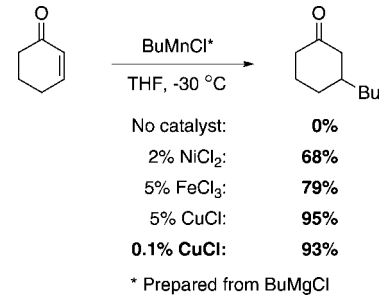
Scheme 121



Scheme 122



Scheme 123



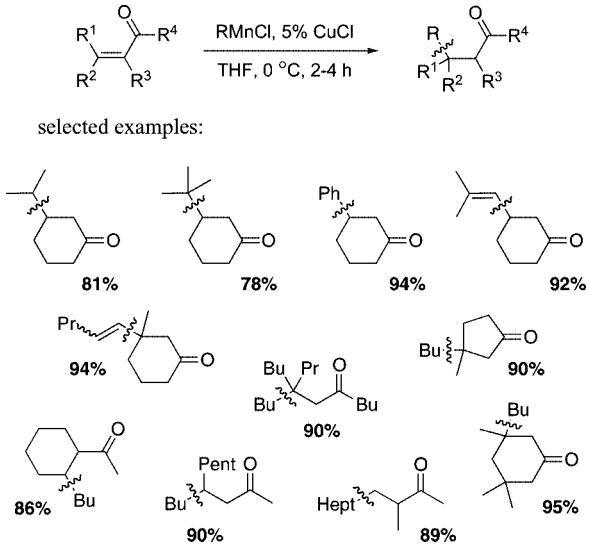
5.2. Copper-Catalyzed Conjugate Addition of Organomanganese Reagents to Conjugated Enones

In order to favor the 1,4-addition of organomanganese reagents to conjugated enones, we tried to perform the reaction in the presence of various Lewis acids.[68] Only $BF_3 \cdot Et_2O$ gave interesting results. However, the yields never exceeded 65−70% (Scheme 122).

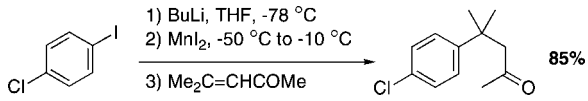
Very interesting results were obtained in the presence of metal salts.[68] Thus, the conjugate addition of butylmanganese chloride to 2-cyclohexenone, which does not occur without a catalyst, takes place in the presence of a catalytic amount of $NiCl_2$, $FeCl_3$, or CuCl, to provide satisfactory yields of 3-butylcyclohexanone (Scheme 123). As shown previously, excellent yield is especially obtained in the presence of copper salts. It should be noted that only 0.1% CuCl is sufficient to catalyze the reaction efficiently.[69]

The Cu-mediated 1,4-addition of organometallic reagents to conjugated enones is well-known to be very efficient.[17f,70] This reaction was extensively studied and is now a powerful tool in organic synthesis. In the light of the preliminary result described above, we thought that it would be interesting to

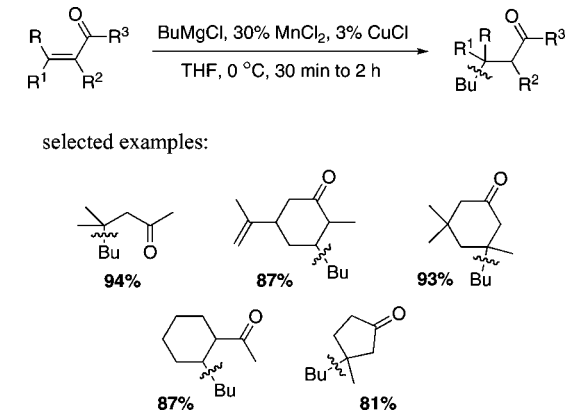
Scheme 124



Scheme 125



Scheme 126



study the copper-catalyzed addition of organomanganese reagents to enones, since the scope of the reaction could be different from the one of the classical copper-catalyzed procedures.

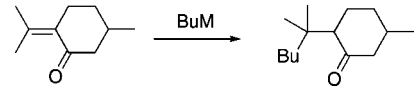
As expected, the presence of CuCl (5%) has a dramatic beneficial influence on the reaction.[69] Under very mild conditions, excellent yields of 1,4-addition product were obtained from a vast array of cyclic or acyclic conjugated enones (Scheme 124). The scope of the reaction is very large; thus, primary, secondary, or tertiary alkyl as well as alkenyl or arylmanganese chlorides lead to high yields of the expected product.

Functionalized organomanganese reagents also add to conjugated enones (Scheme 125).[15]

A few years later, we disclosed that excellent yields of conjugate addition product are obtained by adding a Grignard reagent to an α-enone in the presence of a catalytic amount of both manganese and copper chloride (Scheme 126).[69,71] As a rule, the use of 30% $MnCl_2$ and 1−3% CuCl gives the best results.

This manganese−copper-catalyzed procedure is as efficient as the copper-catalyzed reaction of organomanganese compounds described above. Both manganese-mediated conjugate addition reactions compare favorably with the classical copper-mediated procedures. The difference is especially marked when the starting α-enone is not very reactive, for instance, a β,β-disubstituted conjugated enone such as pulegone (Table 19).[71]

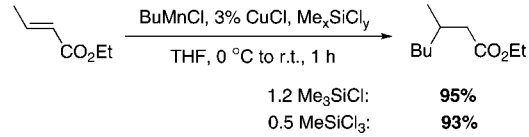
Table 19. Conjugate Addition to Pulegone: Comparison between Mn- and Cu-Mediated Procedures



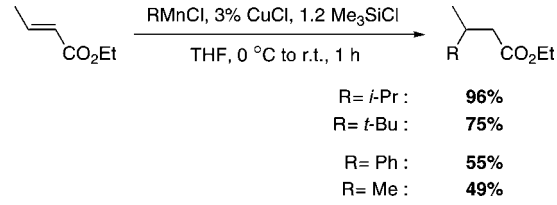
BuM	reaction conditions	yield[a] (%)
BuMgCl	30% $MnCl_2$, 3% CuCl THF, 0 °C, 2 h	94
BuMnCl	3% CuCl, THF, 0 °C, 1 h	95
BuMgCl	5% CuCl, THF, 0 °C	51
BuCu	ether−Me_2S, −50 to −10 °C	43[b]
BuCu	1.1 Me_3SiCl, ether, −10 °C	70[b]
BuCu(CN)Li	ether, −50 to −10 °C	13
0.6 Bu_2CuLi	ether, −78 to −30 °C	33
1.2 Bu_2CuLi	ether, −50 to −10 °C	85[c]
1.2 $Bu_2CuMgCl$	THF, −50 to −10 °C	47[c]
2 $Bu_2Cu(CN)Li_2$	ether, −78 °C, 5 h, then 0 °C	69[c,d]

[a] Yield of isolated product. All reactions were performed on a 30 mmol scale. [b] BuCu from CuBr·Me_2S. [c] 1,2-Addition partially occurs. [d] Yield based on the starting enone.

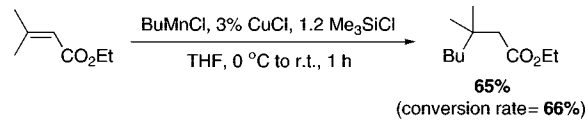
Scheme 127



Scheme 128



Scheme 129

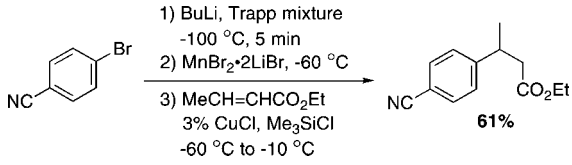


5.3. Copper-Catalyzed Conjugate Addition of Organomanganese Reagents to α,β-Ethylenic Esters

Organomanganese reagents also react with α,β-ethylenic esters in the presence of 3% CuCl and 1.2 equiv of Me_3SiCl to afford the 1,4-addition product in good yields (Scheme 127).[72] The reaction takes place under mild conditions (0 °C, 1 h). In the absence of Me_3SiCl, the enolate resulting from the conjugate addition reacts with the starting ester (Claisen condensation). Interestingly, Me_3SiCl can be successfully replaced by 0.5 equiv of $MeSiCl_3$, which is less expensive (Scheme 127).

Primary, secondary, and tertiary alkylmanganese reagents readily react with β-monosubstituted conjugated enoates to give good yields of 1,4-addition product. However, only

Scheme 130



Scheme 131

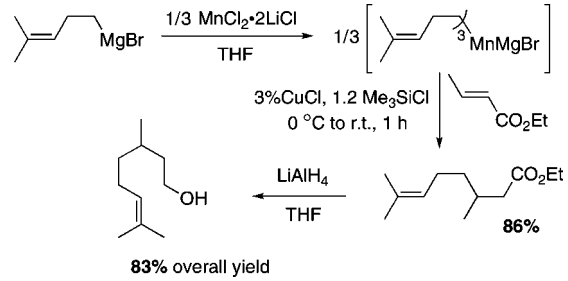
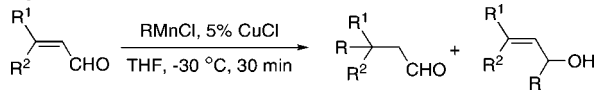
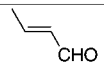
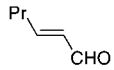
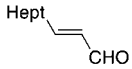


Table 20. Cu-Catalyzed Conjugate Addition of Various RMnCl to α,β-Ethylenic Aldehydes



α-enal	RMnCl	1,4-addition product (%)	1,2-addition product (%)
	HeptMnCl	72	10
	BuMnCl	72	7
	MeMnCl	80	5
	HeptMnCl	80	7
"	MeMnCl	83	3
"	PhMnCl	76	6
"		49	20

moderate yields were obtained with the less reactive methyl- and phenylmanganese chlorides (Scheme 128).

From the less reactive β,β-disubstituted enoates, the addition is very slow and the starting ester is partially recovered at the end of the reaction (Scheme 129).

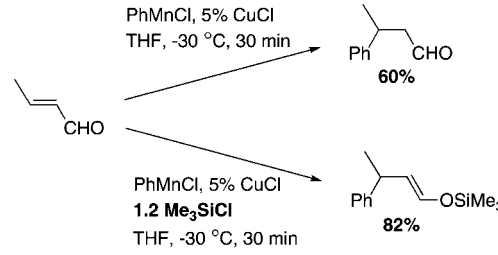
The conjugate addition to esters was also achieved with functionalized organomanganese reagents (Scheme 130).[15]

The efficiency of the 1,4-addition of organomanganese reagents to α,β-ethylenic esters was demonstrated by a short synthesis of citronellol (Scheme 131).[72] It should be noted that the conjugate addition is performed with a trialkylmanganate. Interestingly, the three alkyl groups bonded to manganese are transferred efficiently.

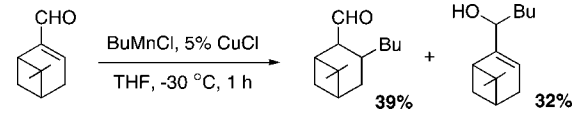
5.4. Copper-Catalyzed Conjugate Addition of Organomanganese Reagents to α,β-Ethylenic Aldehydes

Conjugate addition of organometallics to α,β-ethylenic aldehydes is very difficult to perform since the competitive 1,2-addition to the carbonyl group is a very fast reaction. Organomanganese reagents readily react with α,β-ethylenic aldehydes in the presence of CuCl to give the 1,4-addition

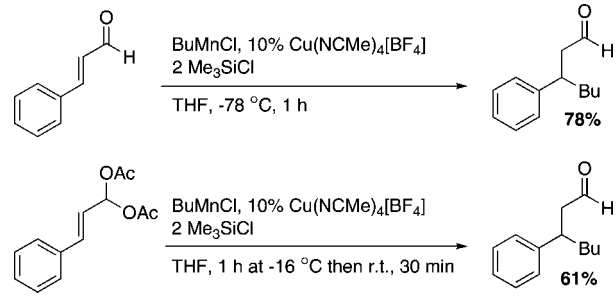
Scheme 132



Scheme 133



Scheme 134



products (Table 20).[73] Thus, β-mono- or β,β-bisubstituted conjugated enals give good yields of conjugate addition products.

Generally, the presence of Me_3SiCl has no significant influence on the course of the reaction. However, in some special cases, the yield was improved (Scheme 132).

With the α-substituted conjugated enals, the 1,2-addition competes seriously and the conjugate addition products are obtained in low yields (Scheme 133).

Recently, Deshmukh studied the copper-catalyzed 1,4-addition of BuMnCl to *trans*-cinnamaldehyde.[74] He showed that the nature of the copper salt has a dramatic influence on the reaction. The best result was obtained by using the complex $Cu(NCMe)_4[BF_4]$ in the presence of 2 equiv of Me_3SiCl. The acylal derived from cinnamaldehyde can also be employed (Scheme 134).

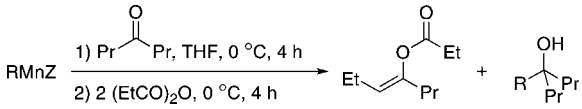
6. Preparation of Manganese Enolates and Applications in Organic Synthesis

6.1. Preparation by Deprotonation of Ketones with Manganese Amides

6.1.1. Manganese Amides: General Considerations

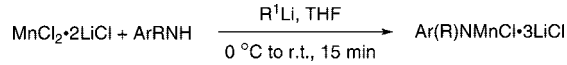
The chemistry of metal enolates and especially lithium enolates was extensively developed since the middle of the last century.[75] However, manganese enolates were almost ignored until our first results patented between 1988 and 1991.[76] We first remarked that organomanganese amides $RMnNR^1R^2$ were able to deprotonate ketones. However, when using *N*,*N*-dialkylamides, the reaction often competes with the 1,2-addition (Table 21). Then, we disclosed that this side reaction can be almost avoided by using *N*-arylmanganese amides Ar(R)NMnR′ or $(Ar)_2NMnR'$, prepared from mono- or diarylamines (Table 21). It is worthy

Table 21. Deprotonation of Ketones: Influence of the Nature of RMnZ

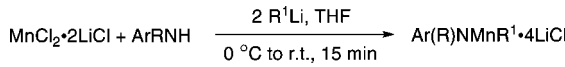


RMnZ	yield of enol ester (%)	yield of alcohol (%)
BuMnCl	20	75
(*i*-Pr)$_2$NMnPh	40	10
(Bu)$_2$NMnPh	46	6
Ph(Me)NMnPh	95	0
(Ph)$_2$NMnPh	92	0
Ph(CH$_2$CH(Et)$_2$)NMnPh	94	0

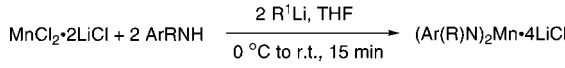
Scheme 135. Halogenomanganese Amides



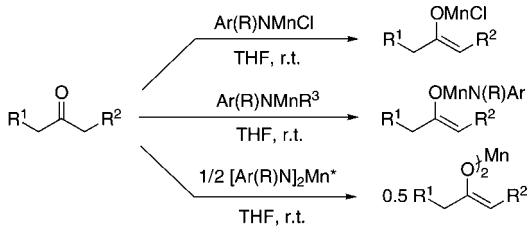
Scheme 136. Organomanganese Amides



Scheme 137. Manganese Diamides



Scheme 138



* The two amino groups of (Ar(R)N)$_2$Mn are used.

of note that the reaction can be performed efficiently from various aromatic amines. Thus, it is possible to change the size of the amino group, for example, to increase the regio- or the stereoselectivity of the reaction (see section 6.1.2). In practice, manganese enolates are prepared almost quantitatively by using manganese amides derived from *N*-methyl aniline.[76,77]

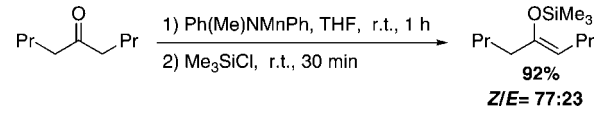
Organomanganese amides can be easily prepared in THF by adding an organolithium compound (generally BuLi or PhLi) to a mixture of the soluble ate-complex $MnCl_2 \cdot 2LiCl$ with 1 equiv of an aromatic amine ArRNH or Ar_2NH.[77] As shown in Schemes 135−137, three types of manganese amides can be formed, according to the ratio RLi/ArRNH.

All these manganese enolates can be employed efficiently to deprotonate a ketone (Scheme 138).

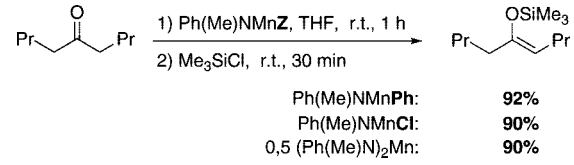
6.1.2. Preparation and Silylation of Manganese Enolates: Regio- and Stereoselectivity

Silyl enol ethers are versatile intermediates in organic synthesis; they are usually prepared by silylation of metal enolates.[78] It is interesting to note that this reaction allows one to highlight the stereo- and regioselectivity of the reaction of deprotonation. Indeed, it is generally conceded that metal enolates are trapped instantaneously by chlorotrimethylsilane with complete retention of the structure of the starting enolates.

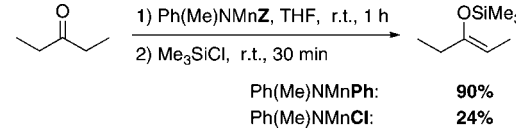
Scheme 139



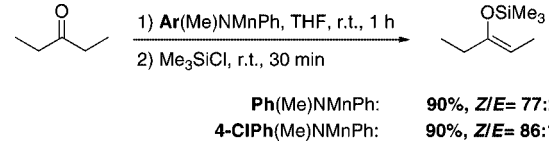
Scheme 140



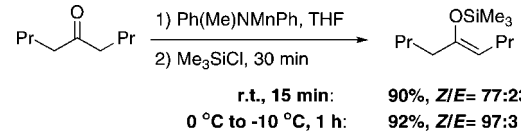
Scheme 141



Scheme 142



Scheme 143



As expected, manganese enolates readily react with Me_3SiCl in THF under mild conditions to afford the corresponding silyl enol ethers in high yields.[79] The (*Z*)-isomer is formed as the major product (Scheme 139).

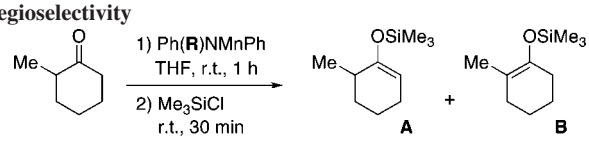
All types of manganese *N*-aryl amides described above (Scheme 140) can be used as a base. However, the deprotonation is clearly faster with organomanganese amides Ph(R)NMnR′.

This difference is only important in the case of very reactive ketones like diethylketone. Indeed, it is then necessary to form the enolate rapidly to prevent the competition with the aldol reaction. In such a case, organomanganese amides give better results than chloromanganese amides or manganese diamides (Scheme 141). Nevertheless, with cyclopentanone or methylketones, the aldol condensation cannot be avoided even by using organomanganese amides.

As shown in Schemes 142 and 143, the preparation of manganese enolates by deprotonation of ketones with manganese amides is stereoselective since mainly the (*Z*)-isomer is formed. The selectivity can be increased by modifying the nature of the manganese amide (Scheme 142). However, the most impressive improvement was obtained by working at −10 °C instead of room temperature (Scheme 143).

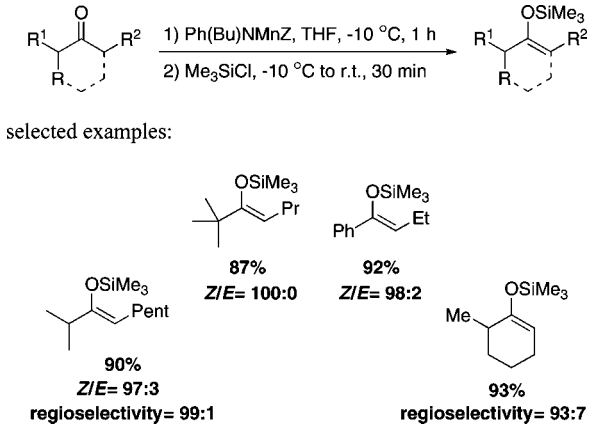
Manganese amides react with unsymmetrical ketones to give mainly the less substituted enolates (generally called kinetic isomer). Interestingly, the regioselectivity can be improved efficiently by slightly increasing the size of the alkyl group R in the manganese amide Ph(R)NMnPh (Table 22). However, it is necessary to optimize the results since the yield decreases when the steric hindrance is too

Table 22. Deprotonation of 2-Methylcyclohexanone by Mn-Amides Ph(R)NMnPh: Influence of the Nature of R on the Regioselectivity

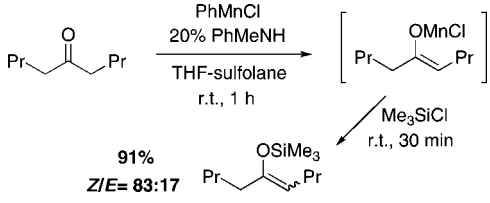


R from Ph(R)NMnPh	yield (%)	A/B
Me	90	84:16
i-Pr	75	98:2
Et_2CH	60	90:10
Bu	93	93:7
Me_2CHCH_2	81	95:5
Et_2CHCH_2	90	96:4

Scheme 144



Scheme 145



important. In most cases, a good compromise can be found between the selectivity and the yield. As a rule, good results are obtained at −10 °C with Mn-amides prepared from *N*-butyl aniline. In some cases, the regioselectivity is slightly improved by working with *N*-isobutyl or *N*-2-ethylbutylaniline (Table 22).

For preparative synthetic chemistry, this procedure is a very efficient and highly selective route to the less substituted (*Z*)-silyl enol ethers (Scheme 144).[79] It is interesting to note that it is currently the more simple and cheapest way to obtain these compounds. On the other hand, the formation of kinetic metal enolates usually requires the use of a low temperature, whereas the preparation of the less substituted manganese enolates can be performed under very mild conditions.

6.1.3. Preparation of Manganese Enolates by Using a Catalytic Amount of N-Alkylaniline

Further studies showed that the deprotonation can be performed by using both phenylmanganese chloride and a catalytic amount of *N*-methylaniline (20%) in the presence of *N*-methylpyrrolidone (NMP) or sulfolane as a cosolvent (Scheme 145).[80]

Interestingly, yields are very similar to those obtained with the stoichiometric procedure. The use of a catalytic amount

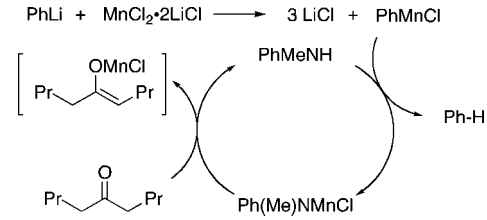
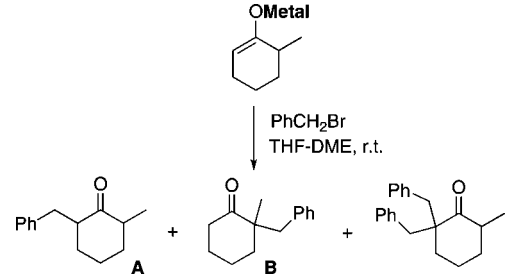


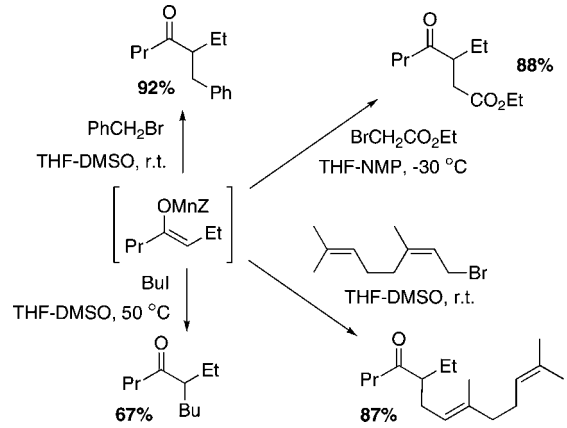
Figure 2. Amine-Catalyzed Deprotonation of Ketones by PhMnCl.

Table 23. Benzylation of 2-Methylcyclohexanone: Comparison between Li- and Mn-Enolates



metal	monoalkylated product (%)	A/B	polyalkylated product (%)
Li	45	76:24	18
Mn	90	95:5	<1

Scheme 146



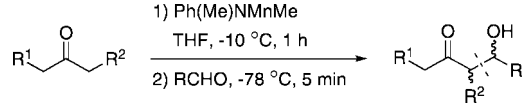
of *N*-methylaniline is very attractive from both economical and ecological points of view. Unfortunately, the selectivity of the reaction is slightly lower.

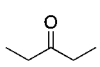
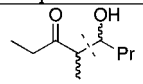
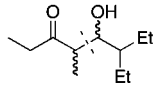
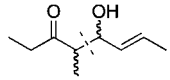
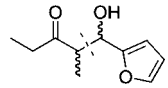
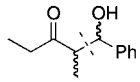
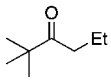
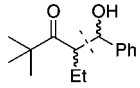
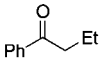
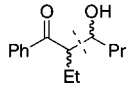
The catalytic cycle probably involves a chloromanganese amide Ph(Me)NMnCl as the effective base for the deprotonation (see Figure 2). The latter is easily regenerated by metalation of the amine by the phenylmanganese chloride used in a stoichiometric amount.

6.1.4. Alkylation of Manganese Enolates

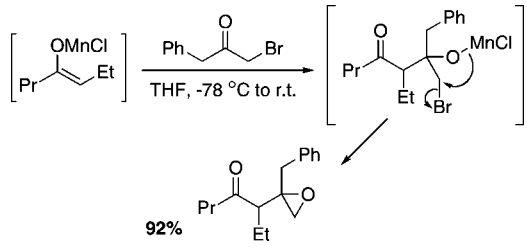
Numerous studies were devoted to the α-alkylation of ketones, especially via their lithium enolates prepared by deprotonation with LDA.[75] The main drawback is the formation of polyalkylation products (Table 23). Moreover, with unsymmetrical ketones, the regioselectivity is often unsatisfactory. In 1989, we showed that the use of manganese enolates allows one to obtain almost exclusively the monoalkylation product with an excellent regioselectivity.[77,81] The advantage of the manganese-mediated procedure is well-illustrated by the comparison of the results obtained for the benzylation of 2-methylcyclohexanone via the lithium and manganese enolates (Table 23).[81]

Table 24. Addition of Mn-Enolates to Aldehydes



ketone	product	yield (%)	*syn*/*anti*
		83	66:33
"		86	77:23
"		86	64:36
"		79	71:29
"		94	71:29
		81	99:1
		87	72:28

Scheme 147



With manganese enolates, the alkylation is performed at room temperature in the presence of a polar cosolvent such as NMP or DMSO. Under these conditions, ketones can be regioselectively monoalkylated in good yields (Scheme 146). It is important to underline that the formation of polyalkylation products is avoided in all cases (<1%).

6.1.5. Addition of Manganese Enolates to Carbonyl Compounds

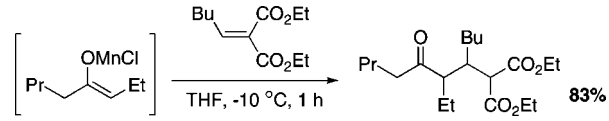
Manganese enolates readily react with aromatic, aliphatic, and even α,β-ethylenic aldehydes (Table 24).[76,81] As a rule, good-to-excellent yields are obtained at low temperature in THF. The reaction is stereoselective, and the *syn*-adduct is preferentially obtained.

Ketones also react with manganese enolates to give the 1,2-addition products. An interesting application is the efficient preparation of β-ketoepoxides from α-bromoketones (Scheme 147). After addition of the manganese enolate to the carbonyl group and then cyclization of the resulting bromoalcoholate, the β-ketoepoxide is formed in excellent yield.

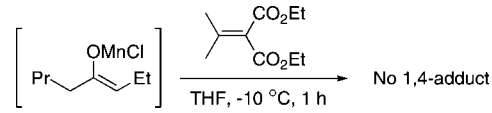
6.1.6. Conjugate Addition of Manganese Enolates to Various Michaël Acceptors

Manganese enolates readily add to β-monosubstituted alkylidene malonic esters to afford the conjugate addition products in good yields (Scheme 148).[81]

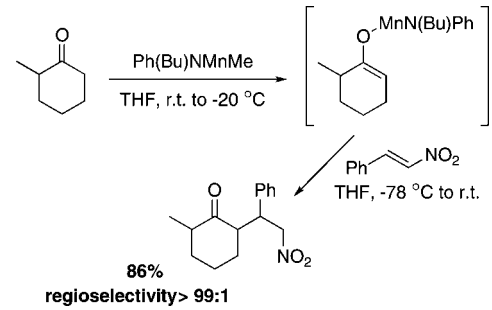
Scheme 148



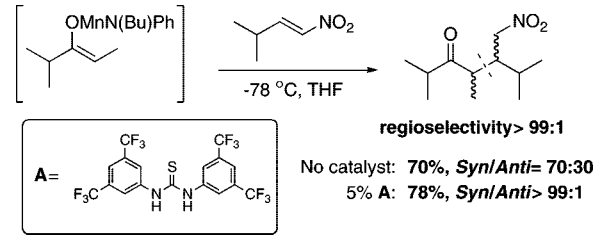
Scheme 149



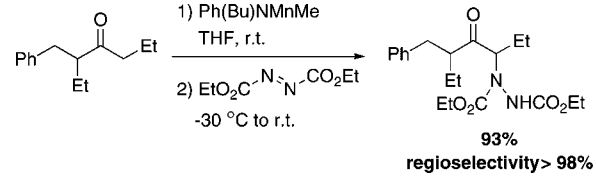
Scheme 150



Scheme 151



Scheme 152



The reaction is sensitive to steric hindrance; thus, the addition fails with the β,β-disubstituted alkylidene malonic esters (Scheme 149).

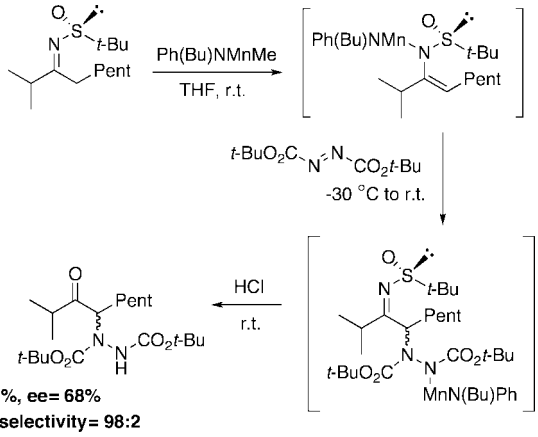
The reaction has recently been extended to conjugated nitroolefins by Cahiez and Ricci.[82] The high regioisomeric purity of the starting enolate (kinetic product) is preserved during the conjugate addition. Excellent yields of 1,4-addition products are obtained (Scheme 150).

Further investigations showed that the presence of a thiourea as an organocatalyst has a beneficial influence on the reaction. A typical example is given in Scheme 151. The yield is slightly better (78% instead of 70%), but, above all, the diastereoselectivity in favor of the *syn*-addition product jumps from 70:30 to 99:1.

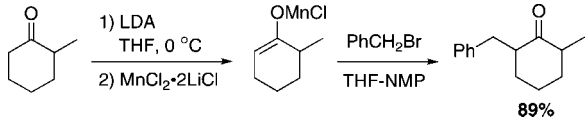
Cahiez and Ricci showed that the electrophilic amination of manganese enolates is an interesting method for introducing a nitrogen functionality in the α-position of a ketone.[83] By using DEAD in THF at −30 °C, the corresponding α-hydrazino ketones are thus obtained in high yields and with an excellent regioselectivity (Scheme 152).

As an alternative procedure, it is also possible to deprotonate chiral sulfinylimines with manganese amides (Scheme

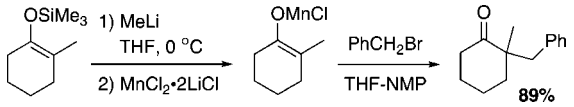
Scheme 153



Scheme 154



Scheme 155



153). The *N*-sulfinyl manganese enamidures thus obtained react with diethylazodicarboxylate (DEAD) or di-ter-butylazodicarboxylate (DTBAD) to give, after acidic hydrolysis, the expected α-hydrazino ketones with an excellent regioselectivity (kinetic product: 90−99%) and a significant enantiomeric excess (ee = 40−68%).

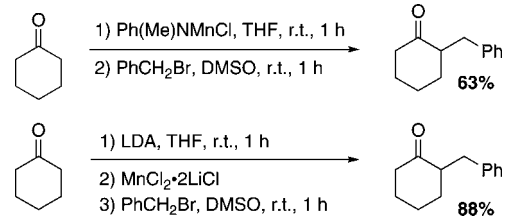
6.2. Preparation by Transmetalation from Li-Enolates

Mn-enolates can be readily prepared by transmetalation from the corresponding Li-, Mg-, K-, or Na-enolates.[76,84] In general, lithium enolates are the most suitable precursors, since they can be easily obtained from a large variety of carbonyl derivatives. Lithium−manganese transmetalation quantitatively takes place with the soluble ate-complexes $MnBr_2 \cdot 2LiBr$ (ether or THF) or $MnCl_2 \cdot 2LiCl$ (THF) at room temperature. It is thus possible to prepare kinetic and thermodynamic manganese enolates from the corresponding lithium enolates (Schemes 154 and 155).

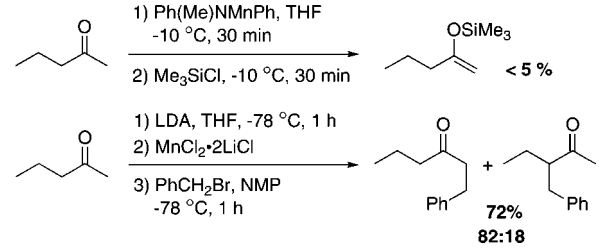
In the case of thermodynamic enolates, this procedure is complementary to the preparation of manganese enolates by deprotonation of ketones with manganese amides previously described. Thus, from unsymmetrical ketones, the more substituted manganese enolates are easily prepared via the thermodynamic lithium enolates (Scheme 155), whereas they cannot be obtained by direct deprotonation with manganese amides (see section 6.1).

As another example, manganese enolates derived from very reactive ketones are obtained in poor yields by using manganese amides, since the aldol reaction seriously competes with the deprotonation. On the other hand, they are efficiently prepared via the corresponding lithium enolates. The difference is significant with cyclohexanone (Scheme 156).

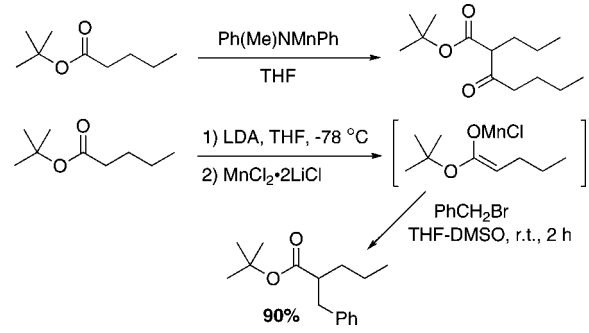
Scheme 156



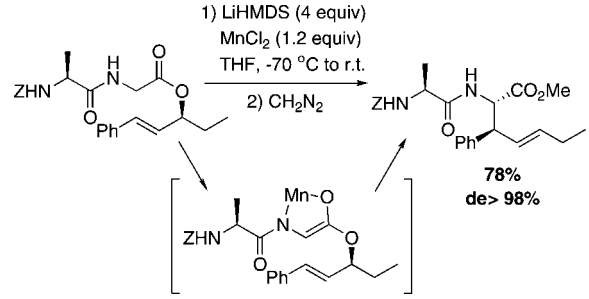
Scheme 157



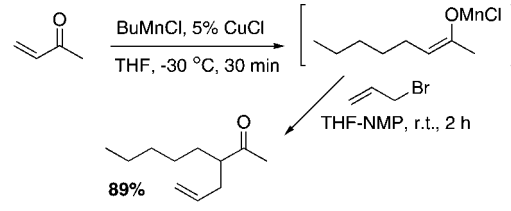
Scheme 158



Scheme 159



Scheme 160

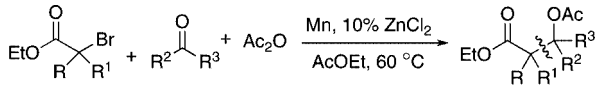


However, it is clearly more impressive in the case of a methylketone (Scheme 157).

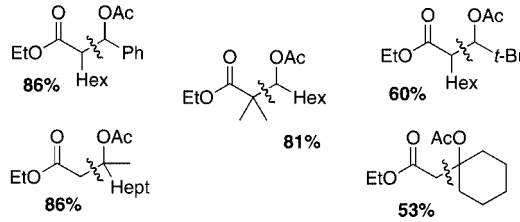
It is interesting to note that the lithium−manganese transmetalation procedure is the only way to prepare manganese enolates derived from esters (Scheme 158).[76] With manganese amides, only the formation of the Claisen condensation product is observed.

Kazmaier and Maier developed a new synthetic approach for the stereoselective synthesis of aminoacids.[85] The key step is the Claisen rearrangement of manganese enolates

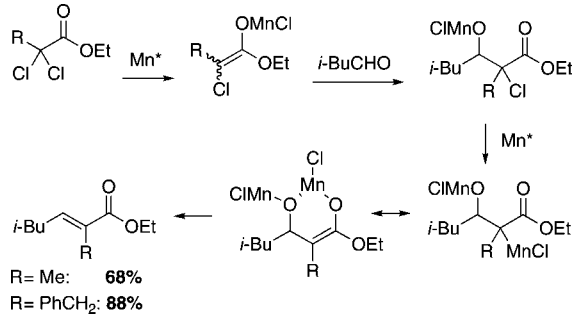
Scheme 161



selected examples:



Scheme 162



prepared from allylic esters of α-aminoacids via the corresponding lithium enolates (Scheme 159). The formation of the cyclic manganese enolate depicted in Scheme 159 only allows one to obtain one stereoisomer. Consequently, the Claisen rearrangement then occurs with an excellent diastereoselectivity (typically >95%) to give the expected α-aminoesters in good yields.

Finally, manganese enolates can also be prepared efficiently and regioselectively by 1,4-addition of organomanganese reagents (see section 5) to α,β-ethylenic ketones, esters, or aldehydes (Scheme 160).[86]

6.3. Manganese Enolates Prepared from α-Halogeno Carbonyl Compounds

6.3.1. Manganese-Mediated Reformatsky Reaction

As previously mentioned (see section 2.3.1), commercial coarse-ground manganese metal, activated by 10% zinc chloride, reacts with α-bromo esters to give manganese enolates in ethyl acetate at 60 °C.[22] When the reaction is performed in the presence of an aldehyde or a ketone, the manganese enolate immediately adds to the carbonyl compound. It is important to trap the alcoholate resulting from the reaction by working in the presence of acetic anhydride to obtain good yields of 1,2-addition products. Indeed, the 1,2-addition reaction is reversible. As a rule, good yields of β-acetoxyesters are obtained from aldehydes, whereas ketones give more moderate results (Scheme 161).

An interesting preparation of (*E*)-α,β-ethylenic esters according to a Mn-mediated sequential reaction was recently described by Concellón (Scheme 162).[87] Manganese enolates are obtained from the corresponding α,α-dichloroesters by oxidative addition to Rieke Mn* in THF. They react immediately with the aldehyde present in the reaction mixture to give, under reflux, the (*E*)-α,β-ethylenic esters in high yields and with an excellent stereoselectivity. The mechanism

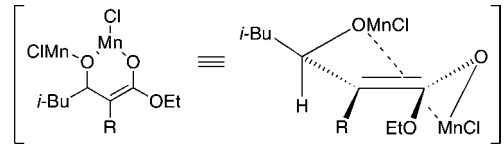
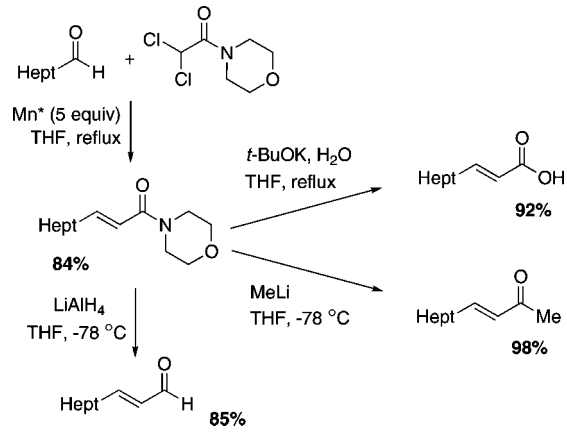
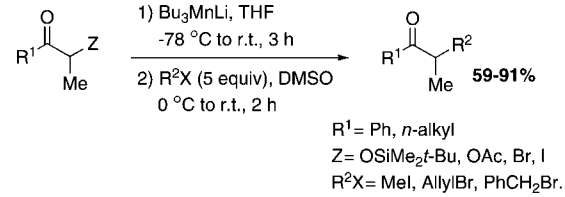


Figure 3. Mn-Mediated Reformatsky Reaction with α,α-Dichloroesters: Chelated Chair-Transition State.

Scheme 163



Scheme 164



proposed by the authors involves a second oxidative addition of the α-chloroester β-alcoholate to Mn*. The enolate−alcoholate thus obtained undergoes an elimination to give an (*E*)-α,β-ethylenic ester.

The stereoselectivity of the reaction would result from the geometry of the chelated chair-transition state (Figure 3).

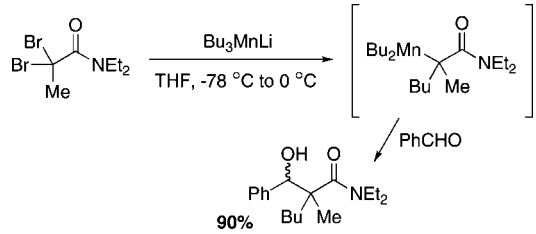
This method was successfully extended to the synthesis of (*E*)-α,β-unsatured amides.[88] Unfortunately, the use of ketones instead of aldehydes did not allow to obtain the corresponding tetrasubstituted α,β-ethylenic amides. It should be noted that various (*E*)-α,β-ethylenic ketones, aldehydes, or carboxylic acids were prepared via the α,β-unsatured amides derived from morpholine (Scheme 163).

6.3.2. Preparation of Manganese Enolates by Action of Trialkylmanganates on α-Halogeno Carbonyl Compounds or Related Derivatives

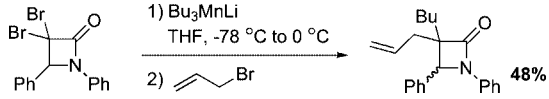
As previously shown (see section 2.4, Scheme 44), α-silyloxy-, acetoxy-, or halogenoketones react with lithium tributylmanganate in THF to give the corresponding manganese enolates.[36] These reagents can be hydroxyalkylated with aldehydes or alkylated with reactive electrophiles in the presence of DMSO (Scheme 164).

Oshima reported that α,α-dibromoesters and α,α-dibromoamides are readily converted to di- or trisubstituted esters or amides by treatment with an organomanganate (Scheme 165).[89] In a first stage, the reaction leads to an alkylated or arylated manganese enolate. The latter can be trapped with a reactive electrophile, such as an aldehyde or an allylic bromide, to produce various α-di- or trisubstituted esters or amides in high yields (70−95%).

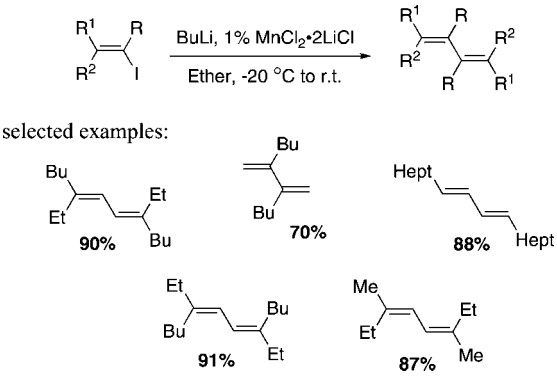
Scheme 165



Scheme 166



Scheme 167



Moderate yields were obtained from α,α-dibromo-β-lactames (Scheme 166).

It is noteworthy that Oshima showed that the manganate can be replaced by 3 equiv of Grignard reagent in the presence of a catalytic amount of manganese chloride.[89] However, the yields are lower than those obtained with the stoichiometric procedure.

7. Cross-Coupling Reactions of Organomanganese Compounds

7.1. Manganese-Catalyzed Homocoupling Reactions

In the past few decades, the homocoupling of organometallic compounds has been extensively studied.[1,90] In most cases, the reaction is achieved in the presence of a catalytic amount of a metal salt associated with an appropriate oxidant.

In 1976, Cahiez and Normant reported that alkenyl iodides react with butyllithium in the presence of a catalytic amount of $MnCl_2$, in ether, to give stereospecifically the corresponding conjugated diene in excellent yields (Scheme 167).[11] It is established that the reaction proceeds via an alkenyl lithium formed by iodine-lithium exchange from the starting alkenyl iodide.

The mechanism depicted in Figure 4 was proposed. In the presence of $MnCl_2$, the alkenyllithium **1** is converted to a trialkenylmanganate **2**. This one then reacts with butyl iodide to lead to an unstable Mn^{IV} derivative **3**, which decomposes to give a mixture of butane and butene (β-hydrogen elimination). The putative intermediate **4** then leads to diene **5** by reductive elimination. The trialkenylmanganate **2** is then regenerated from **6**. It should be noted that this mechanism is strongly supported by various experiments performed by using stoichiometric amounts of organomanganese reagent.[11]

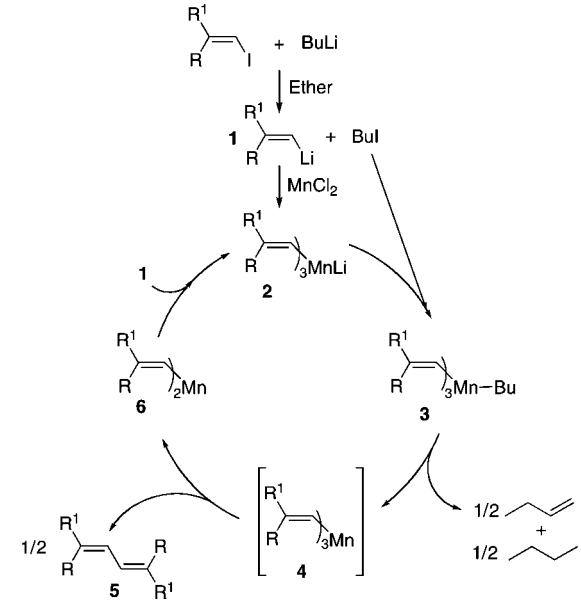
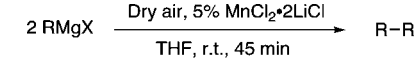
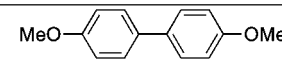
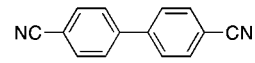
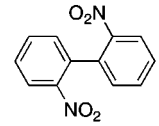
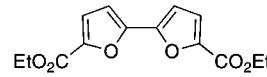
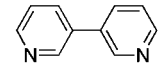
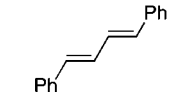
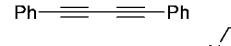
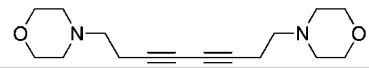


Figure 4. Mn-Catalyzed Homocoupling of Alkenyl Iodides by Action of BuLi.

Table 25. Mn-Catalyzed Homocoupling of RMgX with Atmospheric Oxygen as an Oxidant



R-R	yield (%)
	95
	78*
	75*
	88*
	80
	90*
	89
	85

*** The reaction was performed between -20 °C to 10 °C.**

Very recently, we have described a simple chimio- and stereoselective manganese-catalyzed procedure for the homocoupling of Grignard reagents (Table 25).[91] In most cases, the reaction can be performed at room temperature, to give various biaryls, 1,3-dienes, or 1,3-diynes with good-to-excellent yields. On the other hand, alkylmagnesium halides do not react efficiently. Noteworthy is the use of atmospheric oxygen as an inexpensive and environmentally benign oxidant.

The catalytic cycle proposed in Figure 5 starts with the formation of a stable symmetrical organomanganese(II) **1**. It reacts with oxygen to give the unstable manganese(IV) peroxo complex **2**. Then, the homocoupling product R−R is formed by reductive elimination, and the resulting Mn^{II}

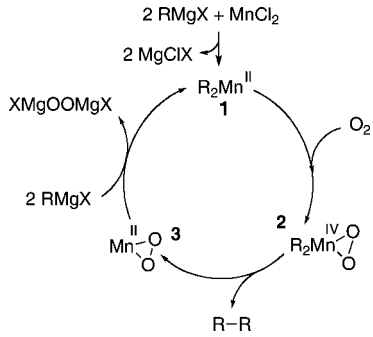
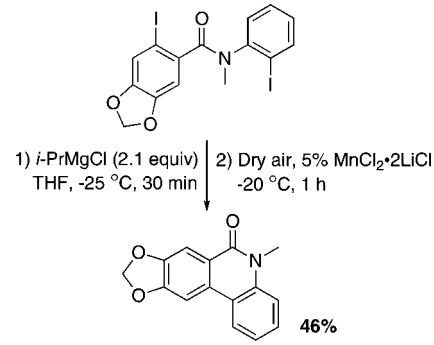
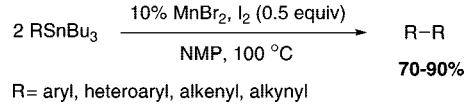


Figure 5. Mn-Catalyzed Homocoupling of RMgX by Action of Atmospheric Oxygen.

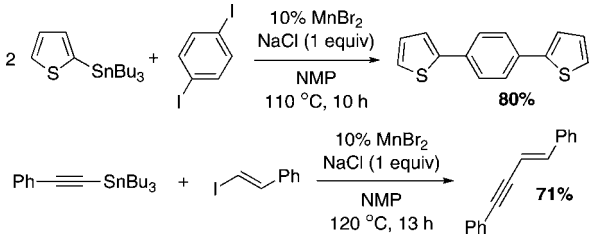
Scheme 168



Scheme 169



Scheme 170



peroxo complex **3** reacts with the Grignard reagent to afford the symmetrical organomanganese **1**.

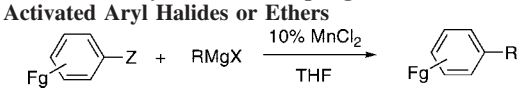
The method was successfully applied to the synthesis of *N*-methylcrinasiadine, a natural product extracted from *Lapiedra martinezzi* (Scheme 168).[91] The starting di-Grignard reagent is prepared by an iodine-magnesium exchange from 2,2′-diiodo-*N*-methyl-4,5-methylenedioxybenzanilide. Under the previous coupling conditions, the cyclization then takes place to give *N*-methylcrinasiadine in 46% global yield.

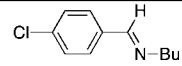
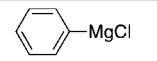
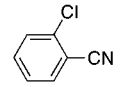
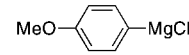
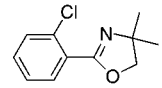
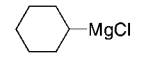
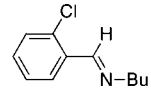
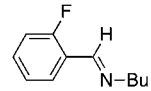
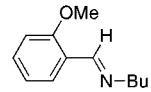
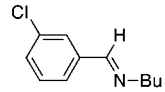
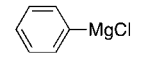
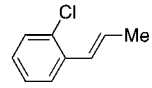
The manganese-catalyzed homocoupling of organostannanes was also reported.[92] The reaction occurs at 100 °C in DMF or NMP in the presence of 10% $MnBr_2$, and iodine is used as an oxidant. Various biaryls, dienes, or diynes were obtained in good yields (Scheme 169).

7.2. Manganese-Catalyzed Cross-Coupling Reactions

Manganese salts are cheap and non toxic; thus, it is tempting to try to use them as catalysts in place of the well-established palladium or nickel complexes.[90] In spite of several attempts in this field, the development of manganese-catalyzed cross-coupling reactions is still in its infancy.

Table 26. Mn-Catalyzed Cross-Coupling Reaction of RMgX with Activated Aryl Halides or Ethers



ArZ	RMgX	reaction conditions	yield (%)
		0 °C, 6 h	93
		0 °C, 2 h	85
		r.t., 2 h	64
	BuMgCl	0 °C, 30 min	93
	"	0 °C, 2 h	90
	"	r.t., 20 min	91
		r.t., 24 h	0
	"	r.t., 24 h	0

Manganese bromide was employed as a catalyst for the coupling of aryl or styryl iodides with aryl or alkynylstannanes (Scheme 170).[93] The reaction occurs in NMP at 100 °C, and the presence of 1 equiv of sodium chloride is essential to obtain the cross-coupling product in satisfying yields. Indeed, in the absence of this salt, the organostannane mainly gives the homocoupling product.

A manganese-catalyzed cross-coupling of activated aryl halides with Grignard reagents was reported (Table 26).[94] Thus, aryl halides (X = Cl, Br, or F) or ethers bearing an electron-withdrawing group in the *ortho*-(nitrile, imine, or oxazoline) or in the *para*-position (imine) readily react under mild conditions to afford the coupling product in good yields. On the other hand, the *meta*-substituted aromatic halides are inert.

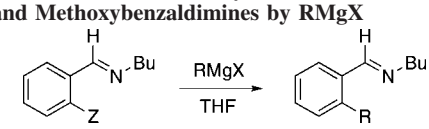
This reaction compares very favorably to the classical nucleophilic aromatic substitution (Table 27). Thus, the manganese-catalyzed procedure gives higher yields. In addition, the reaction is faster (X = OMe, F) and its scope is larger (X = Cl, Br).

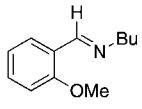
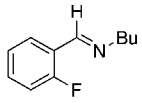
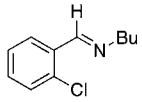
In some cases, the aromatic nucleophilic substitution and the manganese-catalyzed reaction can be complementary (Scheme 171).[94]

Aryl Grignard reagents also react with 2-chloroaryl ketones in the presence of manganese chloride to afford the corresponding *ortho*-substituted arylketones in good yields (Scheme 172).[95] It is interesting to note that the attack of the carbonyl group by the Grignard reagent is never observed.

On the contrary, with alkyl Grignard reagents, which are clearly more reactive, the 1,2-addition product is formed in large amounts (50−60%). Interestingly, it is possible to

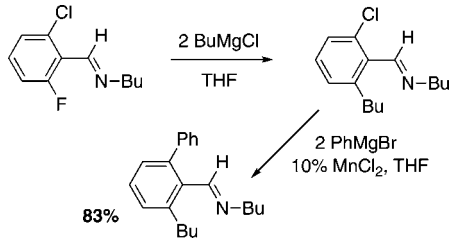
Table 27. S_NAr Versus Mn-Catalyzed Substitution of 2-Chloro-, Fluoro-, and Methoxybenzaldimines by RMgX



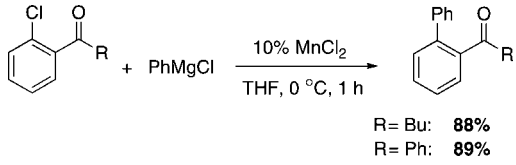
ArZ	RMgX	reaction conditions	yield (%)[a]
	BuMgCl	10% $MnCl_2$ r.t., 20 min	91
		r.t., 24 h	75
	BuMgCl	10% $MnCl_2$ 0 °C, 2 h	90
		r.t., 24 h	40
	PhMgBr	10% $MnCl_2$ r.t., 2 h	88[b]
		r.t., 24 h	0

[a] Quantitative yields of crude imine were obtained. The yield of isolated product is based on the corresponding aldehyde obtained after chromatography on silica gel. [b] The 2-bromobenzaldimine gives a similar yield.

Scheme 171



Scheme 172



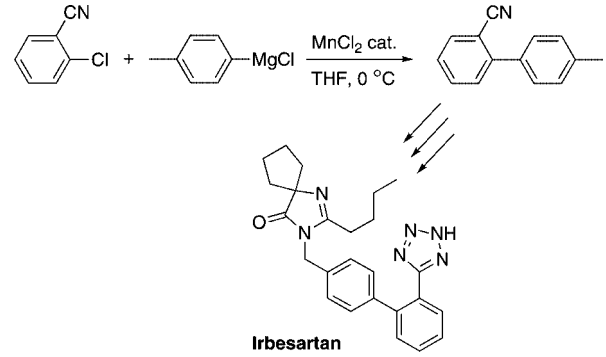
perform a chemoselective reaction by using an organomanganese compound (see section 7.7, Table 33).[95]

It is worthy of note that this coupling reaction is used, on a ton scale, for the industrial preparation of 2-cyano-4′-methylbiphenyl (Scheme 173). This compound is an important intermediate for the preparation of Irbesartan, an antihypertensive drug from Sanofi-Aventis.[96]

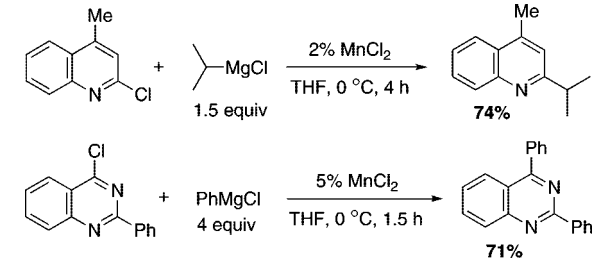
The reaction has been extended with success by Rueping to 2- and 3-chloroquinolines and to related heterocyclic chlorides (Scheme 174).[97] Thus, interesting polyheterocyclic products can be obtained in moderate-to-good yields (40−74%).

Chloroenynes and chlorodienes are much more reactive than simple alkenyl chlorides. Thus, they couple stereoselectively with alkylmagnesium reagents under manganese catalysis in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) as a cosolvent (Scheme 175).[98]

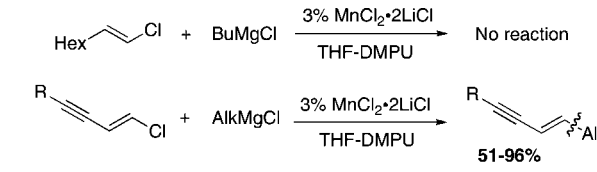
Scheme 173



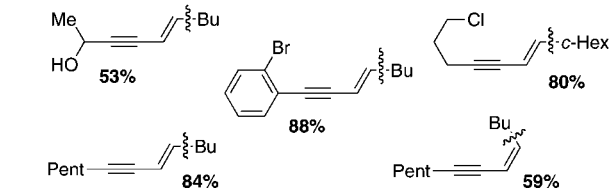
Scheme 174



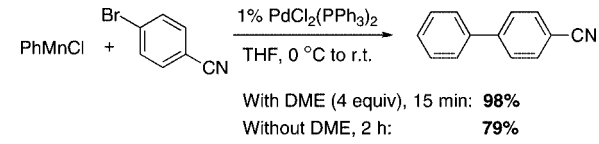
Scheme 175



selected examples:



Scheme 176

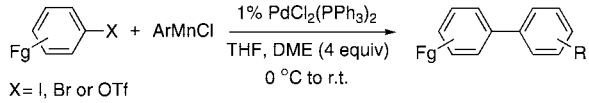


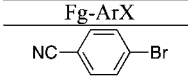
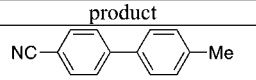
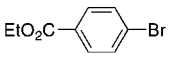
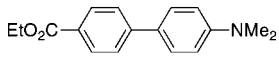
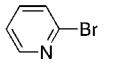
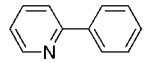
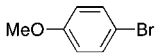
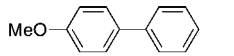
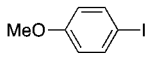
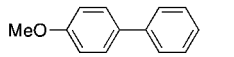
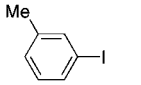
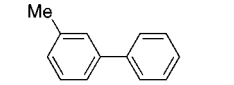
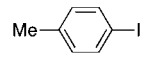
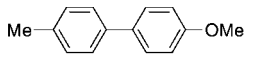
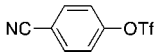
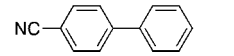
7.3. Palladium-Catalyzed Cross-Coupling of Organomanganese Compounds

Numerous organometallic compounds (Mg, Sn, Zn, Cu, B, etc.) have already been used to perform Pd-catalyzed cross-coupling reactions.[90] The use of organomanganese reagents is recent since we described the first palladium-catalyzed cross-coupling reaction in 1997.[99] In this report, we showed that arylmanganese compounds quickly react with aryl halides or triflates in the presence of 1% $PdCl_2(PPh_3)_2$. It is interesting to note that the addition of 1,2-dimethoxyethane (DME) as a cosolvent allows one to improve the yield and the reaction rate (Scheme 176).

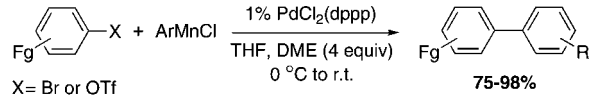
This procedure is very efficient; thus, various functionalized unsymmetrical biaryls can be prepared in high yields, from aryl iodides or activated aryl bromides bearing an electron-withdrawing group (Table 28).

Table 28. Pd-Catalyzed Cross-Coupling Reaction of Aryl Halides with ArMnCl



Fg-ArX	product	yield (%)
		91
		91
		96
		42
		91
		93
		93
		98

Scheme 177



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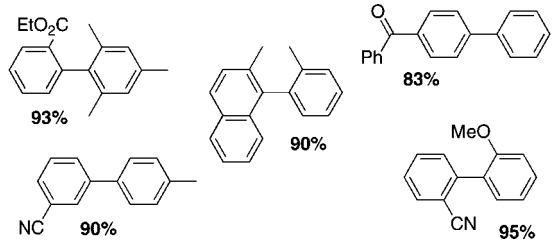
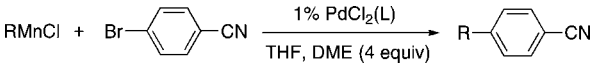
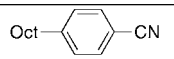
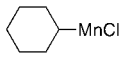
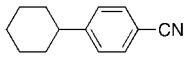
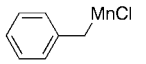
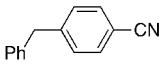
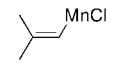
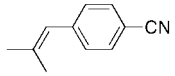
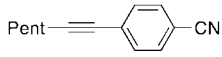


Table 29. Pd-Catalyzed Cross-Coupling Reaction from Various RMnCl



RMnCl	product	time (h)	yield (%)
OctMnCl		0.3	91[a]
		0.5	93[a]
		1	91[b]
		0.6	92[b]
		24	91[b]

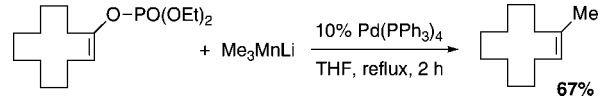
[a] $PdCl_2$(dppf). [b] $PdCl_2$(dppp).

However, the yield of heterocoupling product is lower with deactivated aryl bromides bearing an electron-donating group or with *ortho*-substituted aryl bromides. In this case, we found that the use of $PdCl_2$(dppp) as a catalyst allows one to perform the reaction successfully (Scheme 177).[100] A vast array of functionalized biaryl compounds, and even the challenging *o*,*o*′-disubstituted biaryls can be obtained with excellent yields.

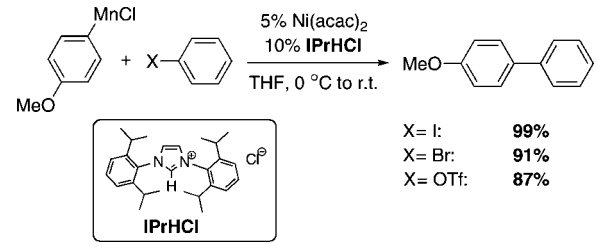
It should be noted that this procedure is not restricted to aromatic organomanganese reagents. Thus, benzyl-, alkenyl-, and alkynylmanganese chlorides react easily with aryl bromides. In the case of alkylmanganese chlorides having one or several eliminable β-hydrogen atoms, the use of $PdCl_2$(dppf) instead of $PdCl_2$(dppp) is necessary (Table 29).[100]

Finally, Oshima showed that enol phosphates react with organomanganates in the presence of 10% $Pd(PPh_3)_4$.[101] The reaction takes place in THF under reflux, and 2 equiv of organomanganate (6 equiv of RMgX or RLi) are required (Scheme 178).

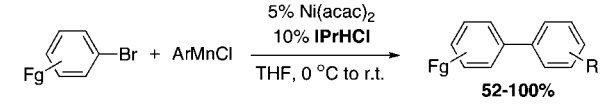
Scheme 178



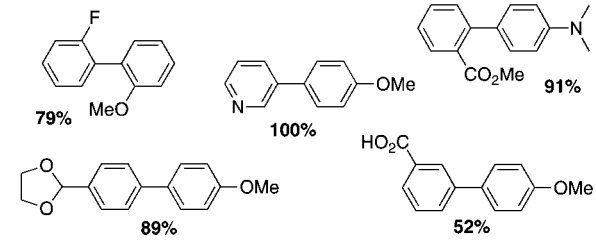
Scheme 179



Scheme 180



selected examples:



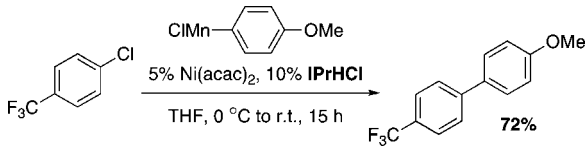
It is even possible to couple various aryl chlorides in spite of their low reactivity (Scheme 181).

7.4. Nickel-Catalyzed Cross-Coupling of Organomanganese Compounds

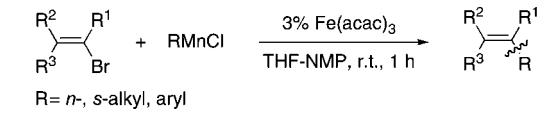
Like palladium complexes, those of nickel are known to be powerful catalysts for the cross-coupling between aryl halides and organometallic reagents.[90] Schneider has recently reported that nickel carbene complexes are efficient to catalyze the coupling of arylmanganese chlorides with aromatic halides.[102] The best results were obtained by using 10% *N*,*N*′-bis(2,6-diisopropylphenyl)imidazolium chloride (IPrHCl) associated with 5% $Ni(acac)_2$. In THF, under mild conditions, arylmanganese chlorides react with aryl iodides, bromides, and also triflates to afford the corresponding biaryls in high yields (Scheme 179).

Both electron-rich and electron-deficient aryl bromides can be used (Scheme 180).

Scheme 181

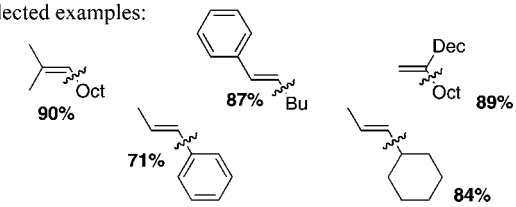


Scheme 182

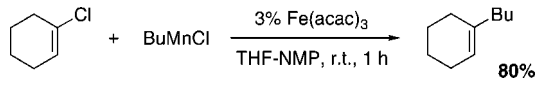


R= *n*-, *s*-alkyl, aryl

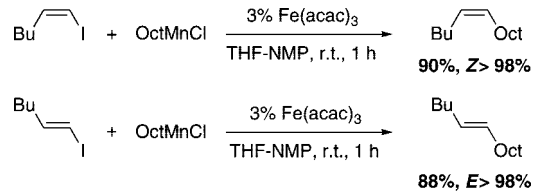
selected examples:



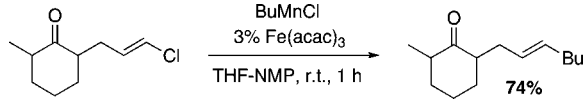
Scheme 183



Scheme 184



Scheme 185



7.5. Iron-Catalyzed Cross-Coupling of Organomanganese Compounds

The iron-catalyzed alkenylation of organomanganese reagents is efficiently performed in THF at room temperature (Scheme 182).[103,104]

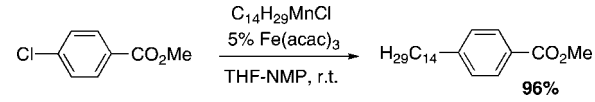
Excellent yields are obtained by using 5% $Fe(acac)_3$, a cheap and nonhygroscopic iron salt, and NMP as a cosolvent. Aryl as well as primary and secondary alkylmanganese chlorides couple efficiently with alkenyl iodides, bromides, and even chlorides (Scheme 183). This is worthy of note since alkenyl chlorides are not generally employed because of their low reactivity.

On the other hand, tertiary alkyl- as well as alkenylmanganese chlorides afford moderate yields. As shown in Scheme 184, the reaction is highly stereoselective (≥98%).

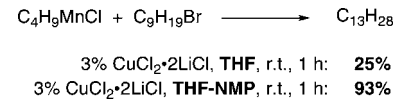
Moreover, it is also very chemoselective; thus, even a keto group is tolerated (Scheme 185).[103,104]

A few years later, Fürstner showed that alkylmanganese compounds react with activated aryl chlorides in the presence of iron salts.[105] Thus, 4-chloromethylbenzoate couples with tetradecylmanganese chloride, ditetradecylmanganese, and the corresponding lithium manganate, to afford the desired product in excellent yields (Scheme 186).

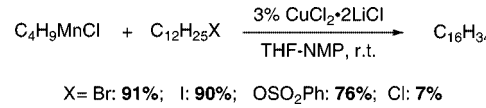
Scheme 186



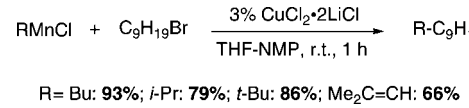
Scheme 187



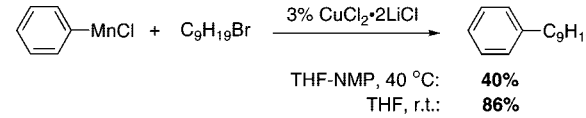
Scheme 188



Scheme 189



Scheme 190



7.6. Copper-Catalyzed Cross-Coupling of Organomanganese Compounds

Organomanganese chlorides react with alkyl bromides in the presence of copper chloride. It is important to note that the presence of a polar cosolvent such as DMF, DMSO, or NMP is required to obtain excellent yields (Scheme 187).[104,106]

Alkyl iodides or sulfonates can also be used successfully (Scheme 188). On the other hand, the less reactive alkyl chlorides lead to poor yields.

Alkenyl- as well as primary, secondary, and tertiary alkylmanganese chlorides afford the substitution product in good-to-excellent yields (Scheme 189).

Unexpectedly, with arylmanganese chlorides, the presence of NMP has a detrimental influence. Indeed, better results were obtained by working in THF alone (Scheme 190).

The high chemoselectivity of the reaction should be underlined. Thus, alkyl bromides bearing an ester, a ketone, or a sulfonate group react selectively (Scheme 191).[104,106]

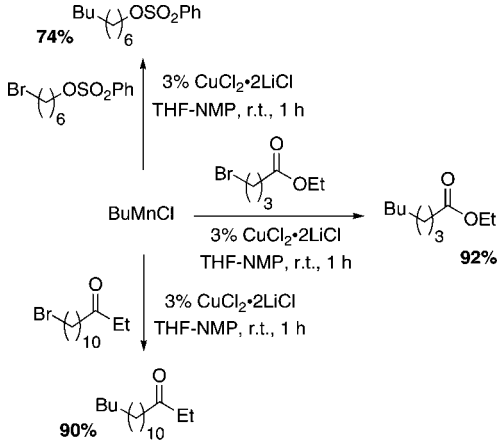
Moreover, hydroxy or carboxylic acid groups are deprotonated by the organomanganese compound (2 equiv of RMnX have to be used) but do not disturb the course of the coupling reaction (Scheme 192).

It is well-known that, with alkyl bromides bearing a leaving group in the β-position, the β-elimination often competes seriously with the desired substitution. Interestingly, the copper-catalyzed organomanganese procedure leads to excellent yields of alkylated product from various β-acyloxy alkyl bromides (Scheme 193).[104,106]

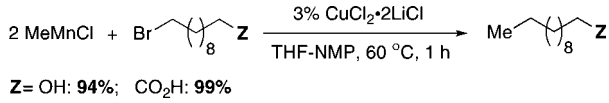
With 2-bromo-1-chloroethane, a very challenging example, the elimination cannot be avoided. Nevertheless, the substitution product is obtained in 38% yield (Scheme 194).

As shown in Scheme 195, Cahiez and Van Koten discovered that Grignard reagents readily react with alkyl bromides in the presence of the complex **A** (10%) and CuCl (5%).[107]

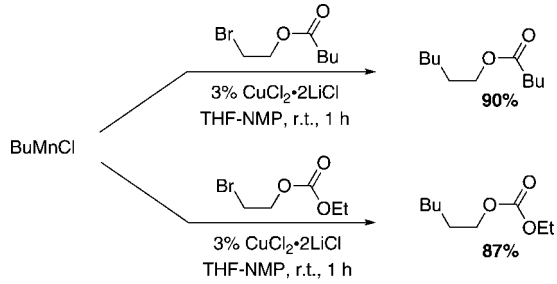
Scheme 191



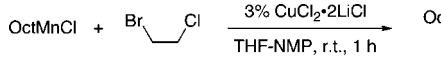
Scheme 192



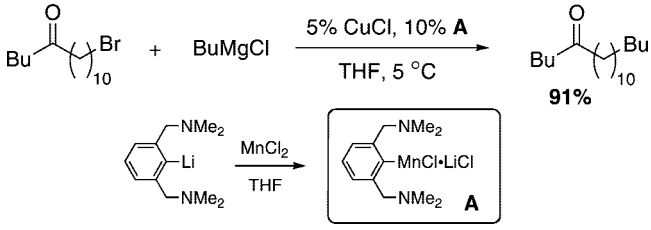
Scheme 193



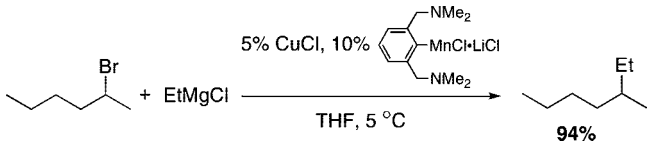
Scheme 194



Scheme 195



Scheme 196



It is worthy of note that this manganese−copper catalysis is very efficient, since secondary alkyl bromides can be used (Scheme 196).[107b]

Organomanganese reagents also react with epoxydes in the presence of copper salts.[106] Monosubstituted epoxydes lead selectively to the secondary alcohols in good yields. The reaction can be performed in THF with or without NMP. Unfortunately, only moderate yields are obtained with 1,2-disubstituted epoxydes (Scheme 197).

Scheme 197

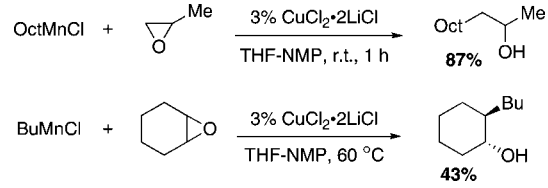
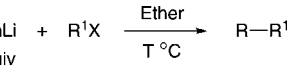
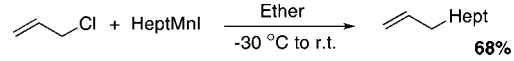


Table 30. Reaction of Me_3MnLi and Bu_3MnLi with Various Organic Halides



halide	R_3MnLi	reaction conditions	yield (%)
Ph–Br	Me_3MnLi	0 °C, 46 h	82
	Bu_3MnLi	0 °C, 1 h	65
Hept–I	Me_3MnLi	0 °C, 1 h	82
	Bu_3MnLi	-78 °C, 2 h	30
Br	Me_3MnLi	-20 °C, 1 h	75
	Bu_3MnLi	-20 °C, 1 h	10
I	Me_3MnLi	0 °C, 48 h	50
	Bu_3MnLi	0 °C, 48 h	30
DecI	Me_3MnLi	0 °C, 21 h	55
	Bu_3MnLi	0 °C, 20 h	0

Scheme 198



7.7. Cross-Coupling Reactions with Organomanganese Compounds

In 1970, Corey described the first application of lithium organomanganates in a cross-coupling reaction (Table 30).[5c] These organometallics, obtained by transmetalation from the corresponding organolithium compounds, are stable enough to be used at 0 °C. The author found that lithium trimethylmanganese can efficiently couple with vinylic or allylic halides (X = Br, I), whereas aryl and primary alkyl iodides slowly lead to the expected product in moderate yields. The reaction is clearly less effective by using lithium tributylmanganate in place of the trimethyl analogue. It should be noted that a huge excess of organometallic is used (15 equiv of BuLi or MeLi).

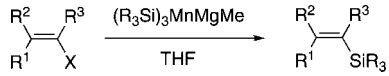
On the other hand, allylic halides react with a stoichiometric amount of organomanganese halide to give satisfactory yields (Scheme 198).[104]

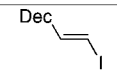
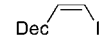
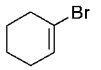
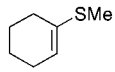
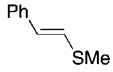
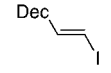
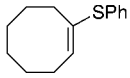
A few years later, Oshima described the cross-coupling of trisilylmanganates $(R_3Si)_3MnMgMe$ with alkenyl halides and sulfides (Table 31).[6g,108] The reaction generally occurs stereospecifically at 0 °C to furnish vinylsilanes in good yields. However, in some cases a lower temperature is necessary to obtain a better stereoselectivity.

Trisilylmanganates $(R_3Si)_3MnMgMe$ also react smoothly with allylic sulfides or ethers (Scheme 199).[6g,108a] The reaction is regiospecific, and high yields of S_N2 product were obtained.

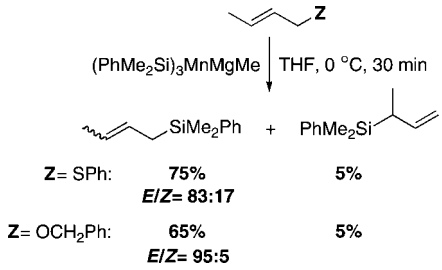
Interestingly, the substitution can also be carried out by using the silyl Grignard reagent $PhMe_2SiMgMe$ in the presence of a catalytic amount of $MnCl_2 \cdot 2LiCl$. The reaction was extended to enol phosphates and enol triflates. The latter lead to the vinylsilane in quantitative yields (Scheme 200).[101]

Table 31. Cross-Coupling between $(R_3Si)_3MnMgMe$ and Alkenyl Halides or Sulfides

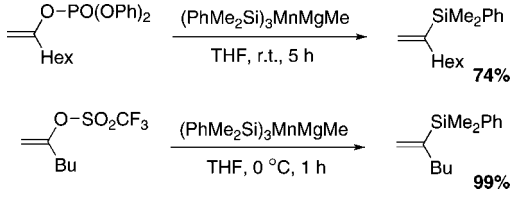


alkenyl halide	R_3Si from $(R_3Si)_3MnMgMe$	reaction conditions	yield (%)	ratio *E*/*Z*
	$PhMe_2Si$	0 °C, 30 min	72	100:0
	"	0 °C, 30 min	73	20:80
"	"	-95 °C, 1.3 h	40	0:100
	"	0 °C, 2 h	93	-
	"	0 °C, 1 h	75	-
	"	0 °C, 1 h	70	100:0
	Me_3Si	-95 °C, 2 h	100	30:70
	"	0 °C, 3 h	89	-

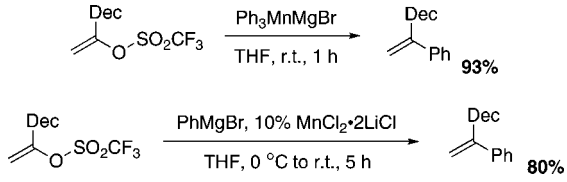
Scheme 199



Scheme 200



Scheme 201

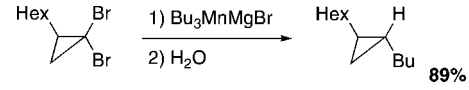


Magnesium triarylmanganates couple successfully with the very reactive enol triflates (Scheme 201). Moreover, aryl Grignard reagents in the presence of a catalytic amount of $MnCl_2 \cdot 2LiCl$ are also efficient. However, the yields are generally lower.

Oshima then studied the reaction of various organomanganates with *gem*-dibromocyclopropanes.[6h,109] After hydrolysis, a debromomonoalkylated product is obtained in satisfactory yields (Scheme 202).

If an electrophile is added before the final workup, a new compound is formed in 50−90% yield as a mixture of two

Scheme 202



Scheme 203

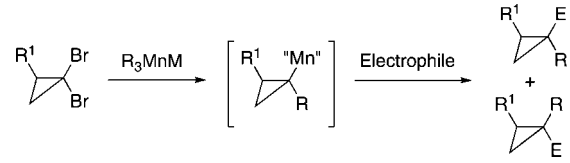
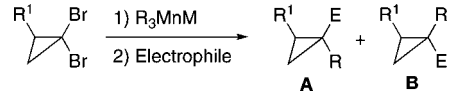


Table 32. Stereoselective Disubstitution of *Gem*-Dibromocyclopropanes



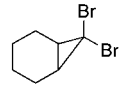
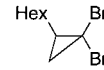
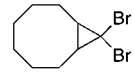
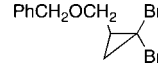
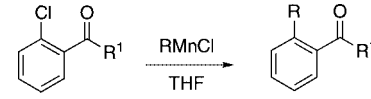
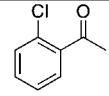
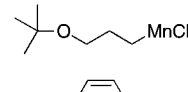
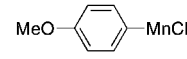
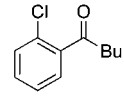
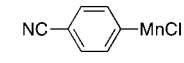
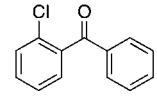
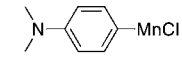
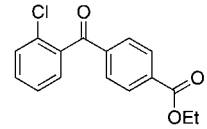
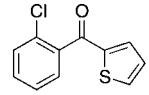
substrate	R_3MnM	electrophile	yield (%)	A/B
	Bu_3MnLi	H_2O	56	87:13
	$Bu_3MnMgBr$	H_2O	82	97:3
	"	MeI	65	94:6
	"	PhCOCl	72	83:17
	$(PhMe_2Si)_3MnLi$	H_2O	84	58:42
	$Allyl_3MnMgBr$	H_2O	64	83:17
	$Bu_3MnMgBr$		66	88:12

Table 33. Cross-Coupling of Various RMnX with 2-Chloroaryl Ketones

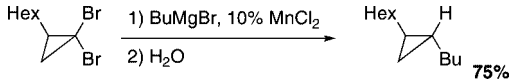


ArCl	RMnCl	reaction conditions	yield (%)
		0 °C, 30 min	73
"		0 °C, 30 min	92
		-10 °C to r.t., 1 h	75
		0 °C, 30 min	81
	BuMnCl	-40 °C, 1 h	97
	"	0 °C, 30 min	90

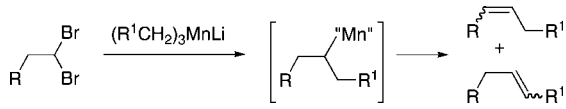
stereoisomers (Scheme 203). The formation of a cyclopropylmanganese as an intermediate seems reasonable.

Trialkyl-, triallyl-, and tri(dimethylphenylsilyl)manganates can be used (Table 32). As a rule, the yield and the stereoselectivity are better when magnesium organomanga-

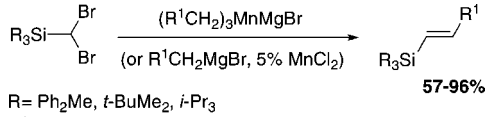
Scheme 204



Scheme 205

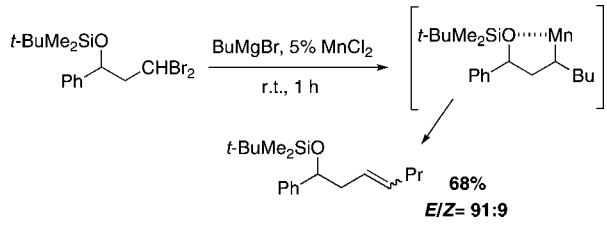


Scheme 206

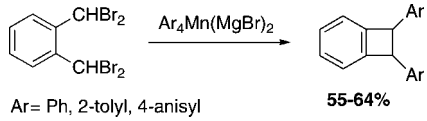


R= Ph_2Me, *t*-$BuMe_2$, *i*-Pr_3
R^1= H, Me, Pr, Me_3Si

Scheme 207



Scheme 208



Ar= Ph, 2-tolyl, 4-anisyl

nates are employed instead of the lithium analogues. On the other hand, triaryl-, trialkenyl-, or trialkynylmanganates afforded only poor yields.

It is also possible to use a Grignard reagent in the presence of a catalytic amount of $MnCl_2$, but the reaction generally gives a lower yield (Scheme 204).[6h,109]

From *gem*-dibromoalkanes, the reaction proceeds similarly via an organomanganese derivative (Scheme 205).[6h,110] After decomposition (β-hydrogen elimination), an (*E*,*Z*)-mixture of two olefins is obtained.

Therefore, the reaction is of little preparative interest except when the β-elimination can only occur on one side. An interesting application was described with dibromomethylsilanes (Scheme 206). In this case, the (*E*)-isomer is formed exclusively due to the presence of the bulky R_3Si group.

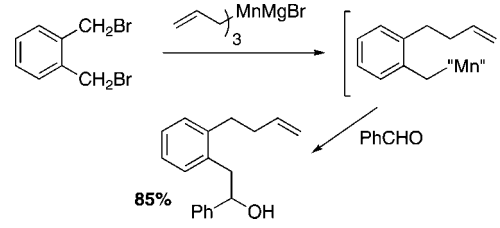
A regioselective β-hydrogen elimination occurs when the manganese atom is complexed by a silyloxy group in the γ-position (Scheme 207).[6h,110]

Treatment of bis(dibromomethyl)benzene with triaryl-, or better with tetraarylmanganates, results in satisfactory yields of *trans*-diaryl benzocyclobutanes (Scheme 208).[111]

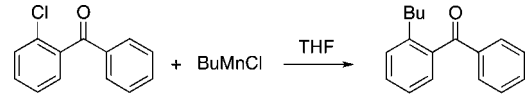
With triallylmanganate, the reaction leads to a benzylmanganese, which can be trapped with an electrophile in good yields (Scheme 209).

In 2004, we reported a very unexpected coupling reaction between organomanganese chlorides and various 2-chloroaryl ketones.[95] In spite of their apparent low reactivity, organomanganese compounds can be used at a low temperature. Thus, the reaction of butylmanganese chloride with 2-chlorobenzophenone is as efficient at −60 °C as at 0 °C (Scheme 210).

Scheme 209

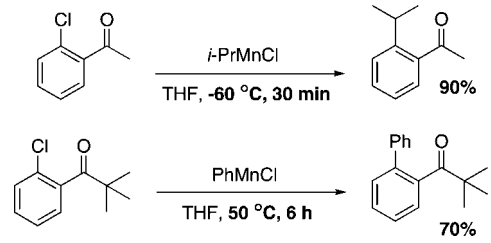


Scheme 210

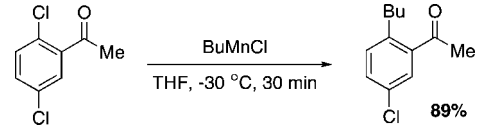


0 °C: **94%**
-60 °C: **98%**

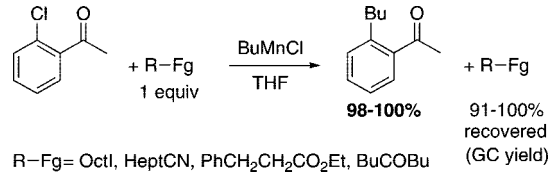
Scheme 211



Scheme 212

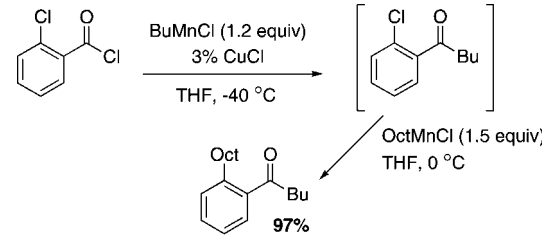


Scheme 213



R−Fg= OctI, HeptCN, $PhCH_2CH_2CO_2Et$, BuCOBu

Scheme 214



The reaction conditions closely depend on the nature of the reagents. Thus, with isopropylmanganese chloride and 2-chloroacetophenone, the reaction is completed in 30 min at −60 °C, whereas the coupling of phenylmanganese chloride with *tert*-butyl-2-chlorophenyl ketone requires 6 h at 60 °C (Scheme 211).

Various aromatic and heteroaromatic functionalized ketones were prepared in this way in excellent yields (Table 33).

A 2,5-dichloroarylketone is selectively alkylated in the *ortho*-position (Scheme 212).

Scheme 215

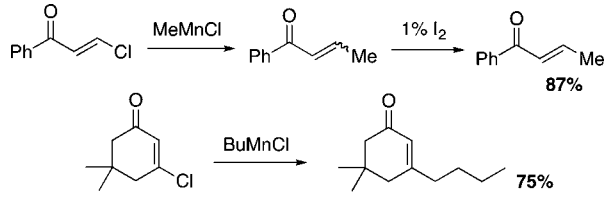
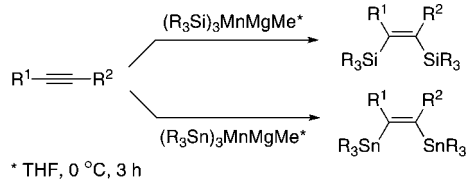
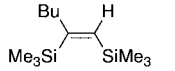
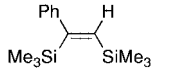
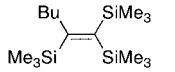
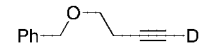
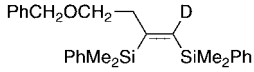
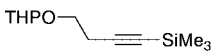
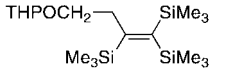
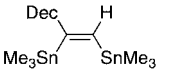
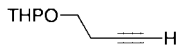
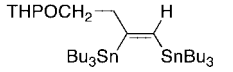
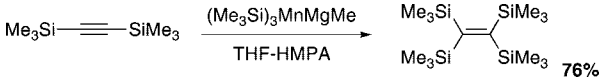


Table 34. Disilylation of Acetylenes with Si−Mn (or Sn−Mn) Reagents

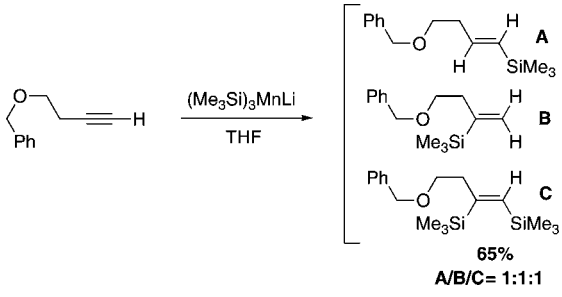


$R^1{\equiv}R^2$	product	yield (%)
Bu≡H		66
Ph≡H		65
Bu≡SiMe3		80
		55
		83
Dec≡H		56
		48

Scheme 216



Scheme 217



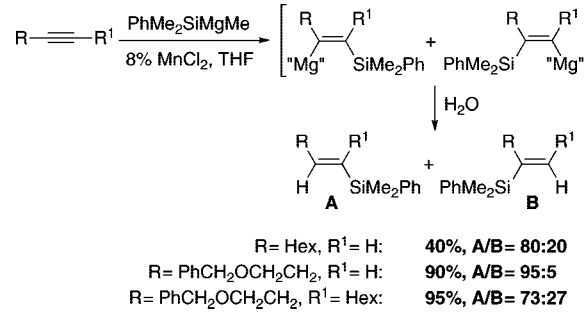
It is interesting to note that the coupling takes place chemoselectively in the presence of an ester, a nitrile, a ketone, or an alkyl iodide (Scheme 213).

The *ortho*-substituted aromatic ketones can be prepared according to a one-pot acylation-substitution procedure from 2-chlorobenzoyl chloride (Scheme 214). The acylation step is first performed by treating this latter, in THF, with an organomanganese chloride in the presence of 3% CuCl. Then, the addition of a second organomanganese compound allows one to obtain the desired coupling product in excellent yield.[95]

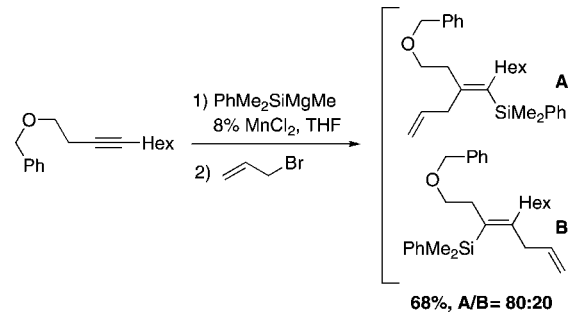
In 1991, Tolstikov reported that alkylmanganese derivatives readily react with β-chloroalkenyl ketones, in THF at −78 °C, to give β-alkylsubstituted enones (Scheme 215).[112]

It should be noted that, in our hand, all attempts to reproduce these results led to poor yields, except in the presence of iron salts.

Scheme 218



Scheme 219



8. Manganese-Catalyzed Carbometalation of Acetylenes, 1,3-Dienes, and Allenes

8.1. Manganese-Catalyzed Carbometalation of Acetylenic Compounds

In 1985, Oshima reported that terminal alkynes are converted to the corresponding disilylalkenes by treatment with silylmanganates $(R_3Si)_3MnMgMe$ (Table 34).[6g,h,113] The reaction was extended to stannylmanganate $(Bu_3Sn)_3MnMgMe$.

This procedure was applied to the synthesis of tetrakis(trimethylsilyl)ethylene (Scheme 216). It is the first efficient preparation of this compound.

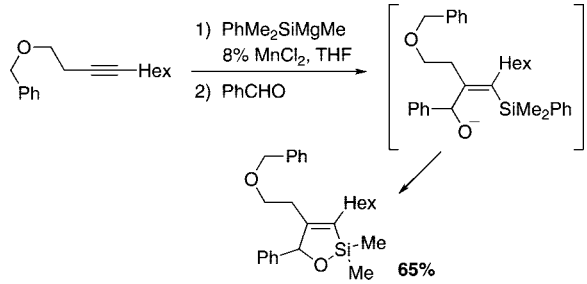
It is important to note that the use of the manganates $(R_3Si)_3MnLi$ instead of $(R_3Si)_3MnMgMe$ generally leads to a mixture of monosubstituted and disubstituted alkenes (Scheme 217).[6g,h,113]

The silyl Grignard reagent $PhMe_2SiMgMe$ can add to alkynes in the presence of 8% manganese chloride in THF (Scheme 218).[6h,114] The best yields are obtained with terminal or internal alkynes bearing an ether group in the β-position of the triple bond (90−95% instead of 40−50%). In addition, the regioselectivity is improved.

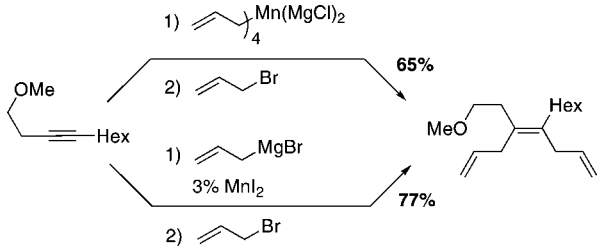
The resulting alkenylmagnesium derivatives can be trapped with various electrophiles such as allyl bromide (Scheme 219) or benzaldehyde (Scheme 220).

In the case of the reactive β-methoxyalkynes, the allylmetalation was also described.[6h,115,116] The reaction can be performed in THF by using a magnesium tetraallylmanga-

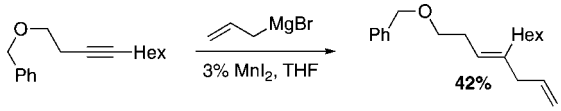
Scheme 220



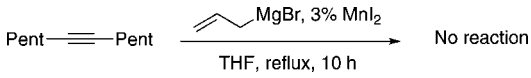
Scheme 221



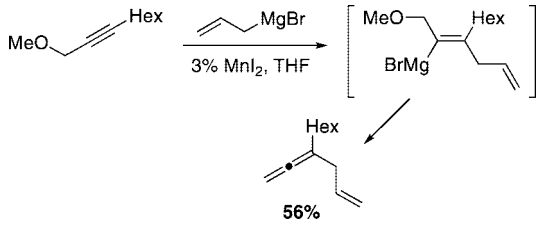
Scheme 222



Scheme 223



Scheme 224



nate, or an allylmagnesium halide, in the presence of manganese iodide (Scheme 221). In both cases, the resulting alkenylmanganese or magnesium compound reacts with allyl bromide to afford a tetrasubstituted alkene in good yields.

However, only moderate yields are obtained with bulkier alkoxy groups such as benzyl ethers (Scheme 222). These results underline the importance of the complexation with the oxygen atom in the β-position.

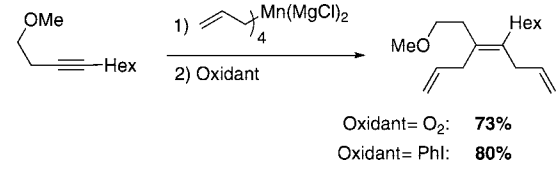
As expected, alkynes having no alkoxy group do not react, even after 10 h under reflux (Scheme 223).

With propargylic ethers, the Mn-catalyzed allylmagnesiation leads to an unstable β-alkoxyorganometallic that undergoes an elimination to give the corresponding allene (Scheme 224).[6h,115,116]

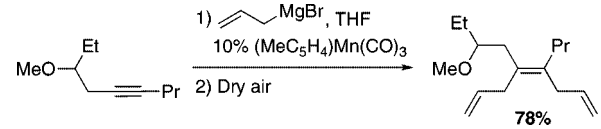
Interestingly, if the allylmetalation is performed with a tetraallylmanganate in the presence of an oxidant such as oxygen or iodobenzene, a diallylalkene is formed in good yield (Scheme 225).[6h,116]

A similar observation was reported when the allylmetalation is performed via the manganese-catalyzed procedure (Scheme 226).[6h,115,116] It should be noted that, in this case,

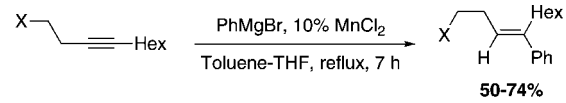
Scheme 225



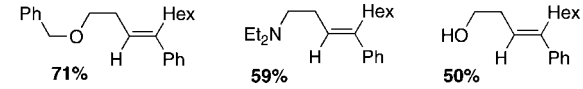
Scheme 226



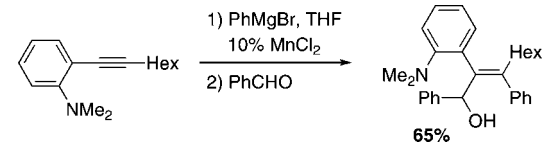
Scheme 227



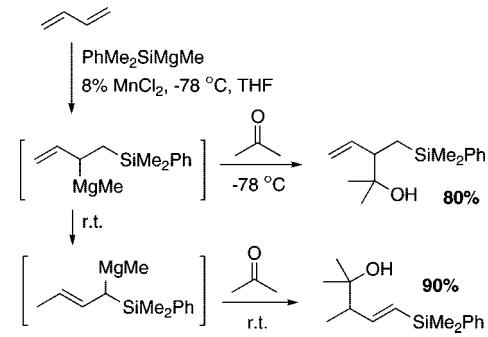
selected examples:



Scheme 228



Scheme 229



$(MeC_5H_4)Mn(CO)_3$ is a more efficient catalyst than manganese iodide.

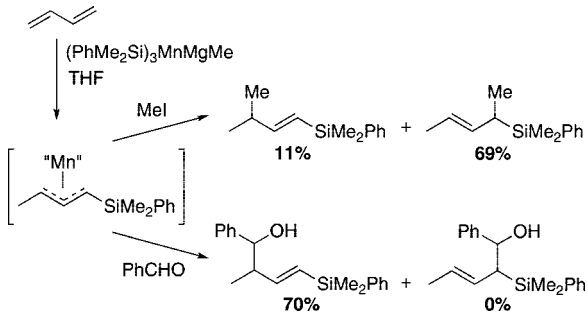
The manganese-catalyzed phenylmagnesiation of homopropargylic alcohols, ethers, and amines in a mixture of toluene−THF has also been reported (Scheme 227).[117a] This result is particularly interesting since only a few examples of arylmetalation were described.

Phenylacetylenes bearing an hydroxy or an amino group in the *ortho*-position also react with phenyl[117a] or alkylmagnesium bromide[117b] in the presence of manganese chloride (Scheme 228).

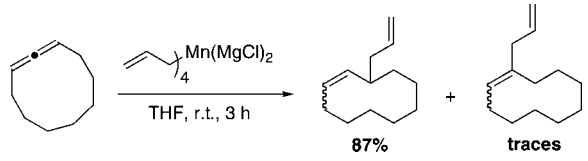
8.2. Manganese-Catalyzed Carbometalation of 1,3-Dienes

Oshima also studied the manganese-catalyzed silylmagnesiation[114] and the silylmanganation[6g,118] of conjugated dienes. As a rule, at −78 °C, the manganese-catalyzed procedure affords a β-silyl allylmagnesium compound.

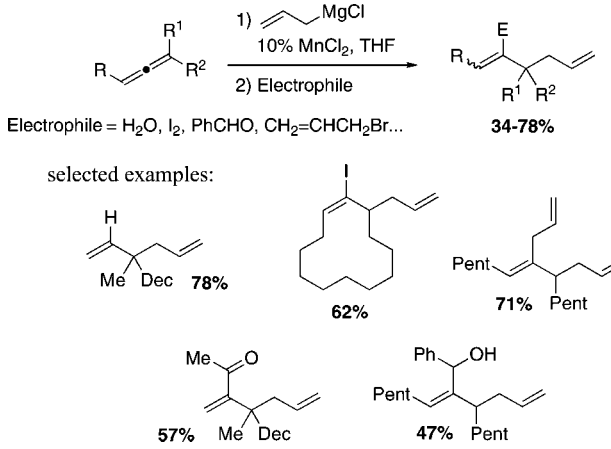
Scheme 230



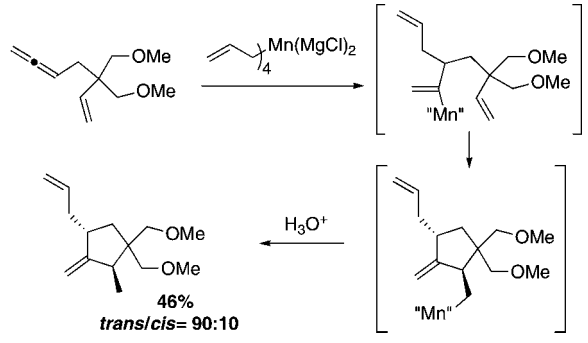
Scheme 231



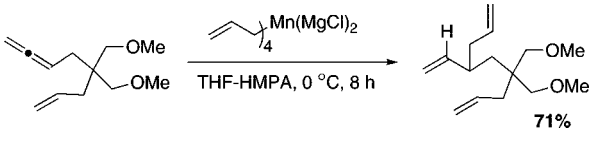
Scheme 232



Scheme 233



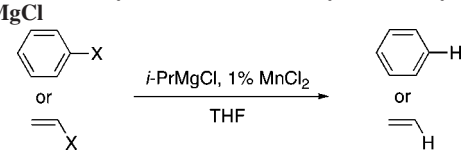
Scheme 234

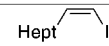
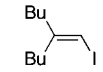
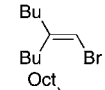
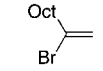
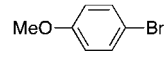
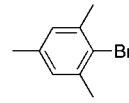
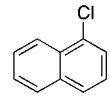


However, at room temperature, a rapid and quantitative isomerization leads to the corresponding α-silyl allylmagnesium reagent (Scheme 229).

With the silylmanganate $(PhMe_2Si)_3MnMgMe$, the isomerization is more rapid and the reaction only gives the α-silyl allylmanganate (Scheme 230).[6g,118] According to the nature of the electrophile used to trap the organometallic, it is possible to obtain selectively a vinyl or an allylsilane. It should be noted that, from 2-substituted butadienes, the addition takes place on the less hindered side of the dienic system.[6g,114,118]

Table 35. Mn-Catalyzed Reduction of Aryl or Alkenyl Halides by *i*-PrMgCl



organic halide	equivalents of *i*-PrMgCl	reaction conditions	yield (%)
	1.5	3 h, r.t.	93
	1.5	3 h, r.t.	90
	2	4 h, r.t.	88
	2	4 h, r.t.	92
	2	4 h, 45 °C	84
	2	10 h, 45 °C	65
	2	4 h, 45 °C	94

8.3. Manganese-Catalyzed Carbometalation of Allenes

Allenes also react under the conditions previously reported to give various alkenes.[119] Thus, the addition of magnesium tetraallylmanganate proceeds smoothly in THF at room temperature (Scheme 231). The addition is highly regioselective, since the allyl group is mainly introduced on the terminal carbon atom of the allenic system.

Allylmagnesium chloride also reacts regioselectively in the presence of 10% manganese chloride to afford an alkenylmagnesium reagent (Scheme 232). By addition of an electrophile, it is then possible to prepare various 1,5-dienes in good-to-moderate yields.

An application to the stereoselective synthesis of a cyclopentane from 1,2,6-heptatriene was reported (Scheme 233). The allylmanganation is followed by a cyclization of the organometallic intermediate.[119]

However, the attempts to prepare a cyclohexane from a 1,2,7-heptatriene resulted in failure since the cyclization does not occur after the allylmanganation (Scheme 234).

9. Miscellaneous Manganese-Mediated Reactions

9.1. Manganese-Catalyzed Reduction of Aryl or Alkenyl Halides by Grignard Reagents

In 1976, we disclosed that alkenyl bromides or iodides, as well as aryl chlorides or bromides, are efficiently reduced in THF by isopropylmagnesium chloride in the presence of 1% manganese chloride (Table 35).[120] The reaction takes place under mild conditions and generally gives excellent yields of dehalogenated product.

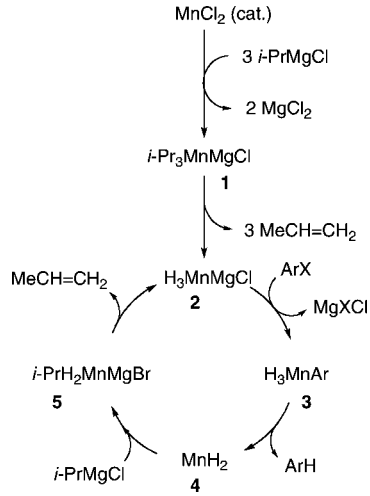
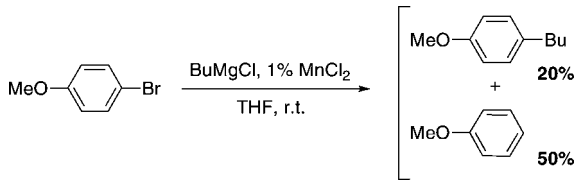
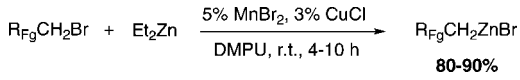


Figure 6. Mn-Catalyzed reduction of aryl and alkenyl halides by action of *i*-PrMgCl.

Scheme 235



Scheme 236



The catalytic cycle presented in Figure 6 was proposed. The triisopropylmanganate **1** resulting from the reaction of isopropylmagnesium chloride with manganese chloride is not stable at room temperature. It decomposes by β-elimination to give a hydridomanganate $H_3MnMgCl$ **2**. This one reacts with the aryl halide to afford an unstable Mn^{IV} intermediate H_3MnAr **3**. The reduction product is then obtained by reductive elimination from **3**. The manganese hydride **4** then reacts with the starting Grignard reagent to regenerate the manganate $H_3MnMgCl$ **2** via **5**.

A similar mechanism is proposed when an alkenyl halide is used instead of an aryl halide. Of course, the decomposition of the triisopropylmanganate **1** could give a hydridomanganese derivative such as *i*-$Pr_xH_yMnMgCl$ ($x + y = 3$) rather than the trihydridomanganate **2**. However, when butylmagnesium chloride is used in place of isopropylmagnesium chloride, the reaction leads to a mixture of reduction and coupling products (Scheme 235).

It is well-known that the tributylmanganate **6** is more stable than the triisopropyl analogue **1** (Figure 7). This result seems to indicate that the alkyl group can be transferred by reductive elimination if the formation of **2** is not rapid enough to avoid the formation of **8** from **7**.

9.2. Preparation of Dialkylzincs by a Mn/Cu-Catalysis: Applications in Organic Synthesis

Organozinc reagents are versatile and useful tools in modern organic synthesis, since they tolerate numerous functional groups.[121] In 1994, Cahiez and Knochel developed an efficient preparation of alkylzinc bromides from alkyl bromides.[122] The bromide−zinc exchange is performed by

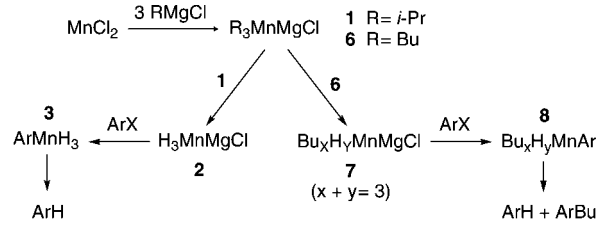


Figure 7. Mn-Catalyzed reaction of RMgCl with ArX: Reduction versus alkylation.

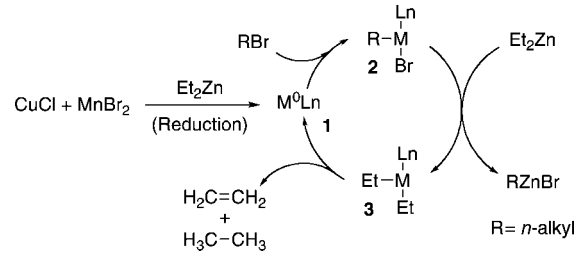
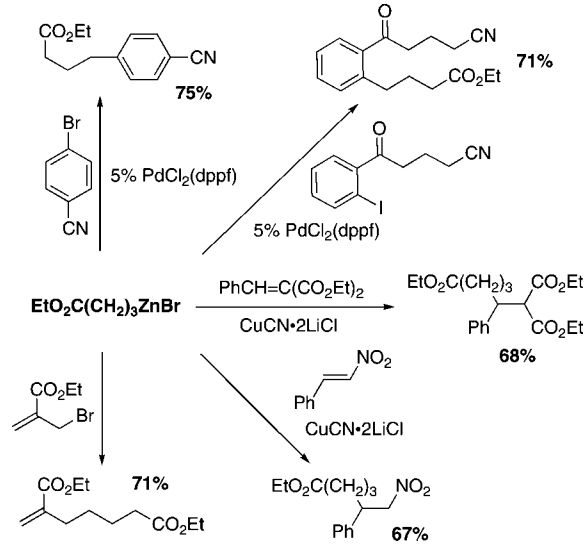


Figure 8. Mn/Cu-Catalyzed bromide−zinc exchange reaction.

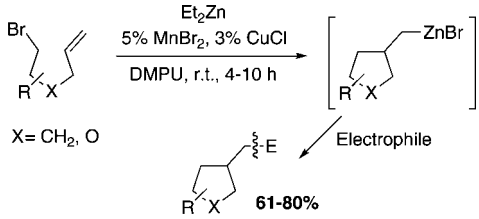
Scheme 237



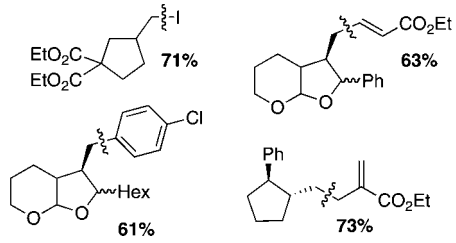
using diethylzinc under a new Mn/Cu-catalysis (Scheme 236). This preparative procedure is interesting since primary alkyl bromides are generally not reactive enough to react with zinc dust to give the corresponding alkylzinc bromides efficiently. The reaction allows one to prepare easily various functionalized alkylzincs in high yields under mild conditions.

A putative catalytic cycle is proposed in Figure 8. At first, it is important to note that the halogen−zinc exchange can be performed in the presence of copper salts alone from alkyl iodides but not from alkyl bromides. With the latter, the presence of manganese bromide is determinant. Thus, the intermediate **1**, which reacts with alkyl bromide to give **2**, is probably a Mn^0 rather than a Cu^0 species since the oxidative addition is easier with manganese. Then, alkylzinc bromide is formed by transmetalation from diethylzinc and **2**. The resulting organometallic **3** decomposes by β-elimination to give a mixture of ethane/ethylene and the catalytic intermediate **1**. It is reasonable to think that copper is probably involved in the decomposition of **3** to **1** since ethylcopper is less stable than its manganese analogue. In fact, the nature of M in the catalytic cycle is not clear, and the cocatalysis Mn/Cu probably involves at least two transmetalation reactions.

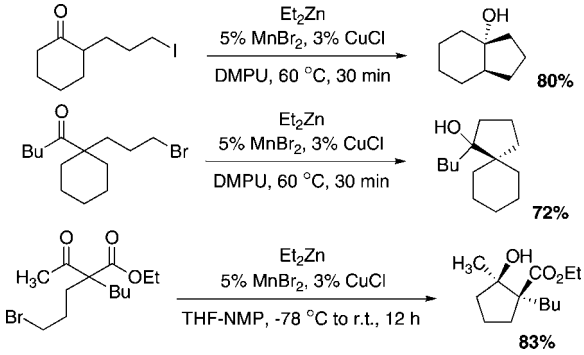
Scheme 238



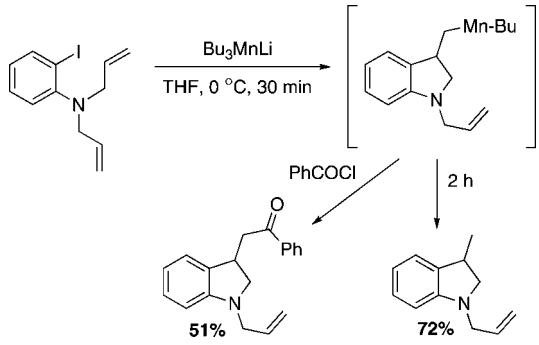
selected examples:



Scheme 239



Scheme 240

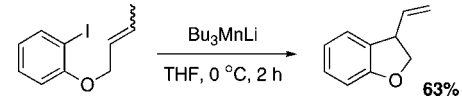


Functionalized alkylzinc reagents prepared by this method can be used to achieve various reactions (Scheme 237).[122] They are coupled with aryl iodides or bromides in the presence of 5% $PdCl_2$(dppf) to give polyfunctionalized aromatic compounds in good yields. After transmetalation to copper, conjugate additions to reactive Michaël acceptors can also be performed. Moreover, alkylzinc compounds easily react with allylic bromides. Various applications are presented in Scheme 237.

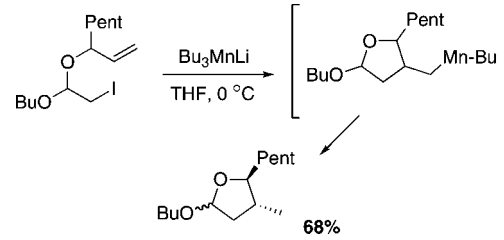
Interestingly, radical cyclizations were achieved by using this Mn/Cu-catalyzed bromide−zinc exchange.[123,124] Thus, substituted 5-membered rings are smoothly and stereospecifically obtained in good yields from δ-halogenoalkenes (Scheme 238).[123] The resulting organometallics can then be trapped with various electrophiles.

Polysubstituted cyclopentenols were prepared in good yields and with an excellent diastereoselectivity by intramolecular Barbier-type cyclizations from δ-bromo- or iodoaldehydes and ketones (Scheme 239).[123,124]

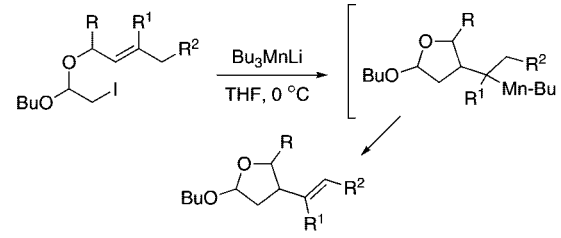
Scheme 241



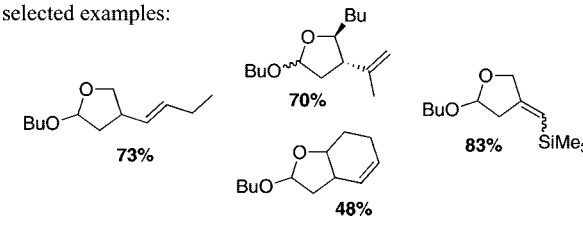
Scheme 242



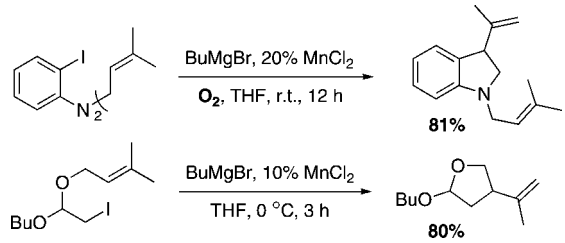
Scheme 243



selected examples:



Scheme 244



9.3. Radical Cyclizations Promoted by Trialkylmanganate Reagents

In 1997, Oshima showed that 2-iodophenyl allyl ethers and *N*,*N*-diallyl 2-iodoanilines react with lithium or magnesium tributylmanganates, under mild conditions, to give indolyl- or benzofuranylmanganese species (Schemes 240 and 241).[6h,38] The cyclization occurs during the halogen−manganese exchange. The organomanganese reagents thus prepared are not very stable, and they generally lead to the reduction or the β-elimination product. However, it is sometimes possible to trap the organometallic with a good electrophile such as benzoyl chloride.

The reaction can also be applied to δ-halogenoalkenes. Thus, various α-alkoxyfurans were synthesized from the iodoacetals depicted in Schemes 242 and 243.[6h,38]

Similar results are obtained by using butylmagnesium bromide in the presence of a catalytic amount of manganese

chloride. It should be noted that, in the case of aryl iodides, the presence of oxygen is required to achieve the reaction (Scheme 244).

10. Conclusion

As shown in this review, in spite of the recent and practical development of organomanganese(II) reagents in organic synthesis, numerous synthetic procedures competitive (i.e., especially with respect to chemoselectivity) with those using traditional organometallic reagents have been developed. Organomanganese compounds can be used as soft Grignard reagents, for instance, to perform chemoselective 1,2-addition, copper-catalyzed conjugated addition, acylation, and carbonation reaction. On the other hand, these reagents can also behave like transition metal derivatives, highlighted by the mild and efficient manganese-catalyzed homo- and heterocoupling reactions described previously.

Organomanganese compounds are amenable to large-scale applications, generally due to their chemoselectivity, affordability, and reduced environmental impact. To date, only a few manganese-catalyzed cross-coupling reactions have been reported, most likely due to the stability of organomanganese(II) species, which makes the reductive elimination step more difficult. Recently, however, in a report on the manganese-catalyzed homocoupling of Grignard reagents by action of atmospheric oxygen, a proposed manganese(IV) intermediate facilitates the reductive elimination. In fact, in many metal-catalyzed cross-coupling reactions, it is necessary to reduce the metal to favor the oxidative addition (for instance, a couple Pd^0/Pd^{II}), whereas with manganese, it would be necessary to oxidize the metal to favor the reductive elimination, which is the limiting step (a couple Mn^{II}/Mn^{IV}). With this concept, it will perhaps be possible to extend the scope of the manganese-catalyzed cross-coupling reactions. Finally, efforts to prepare organomanganese halides directly from massive commercial manganese metal have been met with limited success to date. No convenient method has been disclosed, and therefore, it remains a challenging area for future investigations, especially regarding the preparation of functionalized organomanganese reagents.

11. Acknowledgments

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12. References

(1) *Comprehensive Organometallic Chemistry III*; Mingos, M. P., Crabtree, R. H., Eds.; Elsevier Ltd.: Oxford, U.K., 2007; Vol. 10 and 11.
(2) *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 20, p 497.
(3) (a) Gilman, H.; Bailie, J. C. *J. Org. Chem.* **1937**, *2*, 84. (b) Gilman, H.; Kirby, R. *J. Am. Chem. Soc.* **1941**, *63*, 2046.
(4) (a) Beermann, C.; Clauss, K. *Angew. Chem., Int. Ed.* **1959**, *71*, 627. (b) Riemschneider, R.; Kassahn, H. G.; Schneider, W. *Z. Naturforsch.* **1960**, *15b*, 547. (c) Drevs, H. *Z. Chem.* **1975**, *15*, 451. (d) Nast, R.; Griesshammer, H. *Chem. Ber.* **1957**, *90*, 1315. (e) Andersen, R. A.; Carmona-Guzman, E.; Gibson, J. F.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1976**, 2204.
(5) (a) Tsutsui, M.; Zeiss, H. *J. Am. Chem. Soc.* **1961**, *83*, 825. (b) Fischer, E. O.; Schmidt, M. W. *Chem. Ber.* **1967**, *100*, 3782. (c) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, *4*, 315.
(6) For previous reviews, see: (a) Normant, J. F.; Cahiez, G. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley and Sons, Inc.: Chichester, U.K., 1983; Vol. 3, p 173. (b) Cahiez, G. *Actual. Chim.* **1984**, *7*, 24. (c) Cahiez, G. *An. Quim.* **1995**, *91*, 561. (d) Cahiez, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, U.K., 1995; Vol. 2, p 925. (e) Cahiez, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, U.K., 1995; Vol. 5, p 3227. (f) Cahiez, G.; Mahuteau-Betzer, F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 2, p 541. (g) Fugami, K.; Hibino, J.-I.; Nakatsukasa, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1988**, *44*, 4277. (h) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1.
(7) For various procedures concerning the preparation of organomanganese reagents, see: (a) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1977**, 130. (b) Friour, G.; Cahiez, G.; Normant, J. F. *Synthesis* **1984**, 37. (c) Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163. (d) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 3545. (e) Cahiez, G.; Razafintsalama, L.; Laboue, B.; Chau, F. *Tetrahedron Lett.* **1998**, *39*, 849. (f) Cahiez, G.; Laboue, B.; Tozzolino, P. Eur. Patent 283359, 1988. (g) *Chem. Abstr.* 1989, *110*, 114306. (h) Cahiez, G.; Laboue, B.; Tozzolino, P. Eur. Patent 374015, 1990. (i) *Chem. Abstr.* 1990, *113*, 191644.
(8) Cahiez, G.; Laboue, B.; Chavant, P.-Y. Unpublished results.
(9) Ducelliez, F. *Bull. Soc. Chim. Fr.* **1913**, 815.
(10) Cahiez, G.; Métais, E. Unpublished results.
(11) Cahiez, G.; Bernard, D.; Normant, J. F. *J. Organomet. Chem.* **1976**, *113*, 99.
(12) Fürstner, A.; Weidmann, H. *J. Organomet. Chem.* **1988**, *354*, 15.
(13) Cahiez, G.; Laboue, B. Unpublished results.
(14) (a) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (b) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.
(15) Klement, I.; Stadtmüller, H.; Knochel, P.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 1927.
(16) Kiefl, C.; Mannschreck, A. *Synthesis* **1995**, 1033.
(17) (a) Davidson, P. J.; Lappert, F.; Pearce, R. *Chem. Rev.* **1976**, *76*, 219. (b) Kochi, J. K. In *Organometallic Mechanisms and Catalysis*; Academic Press, Inc.: New York, 1978; Chapter 19, p 229. (c) Cotton, A. *Chem. Rev.* **1955**, *55*, 551. (d) Posner, G. H. *Org. React.* **1975**, *22*, 253. (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (f) Krause, N.; Morita, N. In *Comprehensive Organometallic Chemistry III*; Mingos, M. P., Crabtree, R. H., Eds.; Elsevier Ltd.: Oxford, U.K., 2007; Vol. 9, p 501.
(18) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *29*, 111.
(19) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369.
(20) Friour, G.; Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron* **1984**, *40*, 683.
(21) Hiyama, T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, *8*, 1237.
(22) (a) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373. (b) Cahiez, G.; Chavant, P.-Y.; Tozzolino, P. Eur. Patent 323332, 1989. (c) *Chem. Abstr.* 1990, *112*, 38679. (d) Cahiez, G.; Chavant, P.-Y.; Tozzolino, P. Fr. Patent 2625500, 1989. (e) *Chem. Abstr.* 1990, *112*, 35281.
(23) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049.
(24) Cintas, P. In *Activated Metals in Organic Synthesis*; CRC Press Inc.: Boca Raton, FL, 1993; p 256.
(25) (a) Rieke, R. D. *Top. Curr. Chem.* **1975**, *59*, 1. (b) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (c) Rieke, R. D. *Science* **1989**, *246*, 1260.
(26) Hiyama, T.; Obayashi, M.; Nakamura, A. *Organometallics* **1982**, *1*, 1249.
(27) Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009.
(28) Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197.
(29) Kim, S.-H.; Rieke, R. D. *Synth. Commun.* **1998**, *28*, 1065.
(30) (a) Rieke, R. D.; Kim, S.-H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921. (b) Rieke, R. D.; Suh, Y. S.; Kim, S.-H. *Tetrahedron Lett.* **2005**, *46*, 5961.
(31) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **1999**, *40*, 4931.
(32) Cahiez, G.; Martin, A.; Delacroix, T. *Tetrahedron Lett.* **1999**, *40*, 6407.
(33) (a) Tang, J.; Shinokubo, H.; Oshima, K. *Synlett* **1998**, 1075. (b) Tang, J.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1999**, *55*, 1893.
(34) Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807.
(35) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *Chem. Commun.* **1997**, *21*, 2077.
(36) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459.
(37) Hojo, M.; Sakuragi, R.; Murakami, Y.; Baba, Y.; Hosomi, A. *Organometallics* **2000**, *19*, 4941.

(38) (a) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910. (b) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039.
(39) (a) Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1977**, *38*, 3383. (b) Friour, G.; Cahiez, G.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1979**, 515.
(40) Cahiez, G.; Figadère, B. Unpublished results.
(41) Ahn, Y.; Doubleday, W. W.; Cohen, T. *Synth. Commun.* **1995**, *25*, 33.
(42) (a) Cahiez, G.; Figadère, B. *Tetrahedron Lett.* **1986**, *27*, 4445. For a few related experiments with $ClMnCH_2CN$ and $Mn(CMe_2CN)_2$, see: (b) Kauffmann, T.; Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, *125*, 899. (c) Kauffmann, T.; Kieper, H. *Chem. Ber.* **1992**, *125*, 907.
(43) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.
(44) Kauffmann, T. *Synthesis* **1995**, 745.
(45) (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992**, *33*, 4353. (b) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2514.
(46) Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969.
(47) Boucley, C.; Cahiez, G.; Carini, S.; Cerè, V.; Comes-Franchini, M.; Knochel, P.; Pollicino, S.; Ricci, A. *J. Organomet. Chem.* **2001**, *624*, 223.
(48) Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **1992**, *33*, 6963.
(49) Cahiez, G.; Boucley, C. Unpublished results.
(50) Cahiez, G.; Masuda, A.; Bernard, D.; Normant, J. F. *Tetrahedron Lett.* **1976**, *36*, 3155.
(51) Friour, G.; Cahiez, G.; Normant, J. F. *Synthesis* **1985**, 50.
(52) (a) Ritter, K.; Hanack, M. *Tetrahedron Lett.* **1985**, *26*, 1285. (b) Boche, G.; Eiben, R. *Tetrahedron Lett.* **1985**, *26*, 1289.
(53) Cahiez, G.; Rivas-Enterrios, J.; Granger-Veyron, H. *Tetrahedron Lett.* **1986**, *27*, 4441.
(54) Cahiez, G.; Alexakis, A.; Normant, J. F. *Synth. Commun.* **1979**, *9*, 639.
(55) Cahiez, G.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1977**, 570.
(56) (a) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1992**, *33*, 4439. (b) Cahiez, G.; Tozzolino, P. Eur. Patent 283359, 1988. (c) *Chem. Abstr.* 1989, *110*, 114306.
(57) Cahiez, G.; Venegas, P. Unpublished results.
(58) Cahiez, G. *Tetrahedron Lett.* **1981**, *22*, 1239.
(59) Cahiez, G.; Chavant, P.-Y.; Métais, E. *Tetrahedron Lett.* **1992**, *33*, 5245.
(60) Cahiez, G.; Rivas-Enterrios, J.; Cléry, P. *Tetrahedron Lett.* **1988**, *29*, 3659.
(61) Cahiez, G.; Métais, E. *Tetrahedron Lett.* **1995**, *36*, 6449.
(62) Cahiez, G.; Métais, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1373.
(63) Leznoff, C. C.; Yedidia, V. *Can. J. Chem.* **1980**, *58*, 287.
(64) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1986**, *27*, 569.
(65) Yorimitsu, H.; Hayashi, Y.; Tang, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2297.
(66) Kauffman, T.; Bisling, M. *Tetrahedron Lett.* **1984**, *25*, 293.
(67) Namboothiri, I. N. N.; Hassner, A. *J. Organomet. Chem.* **1996**, *518*, 69.
(68) Cahiez, G.; Alami, M. *J. Organomet. Chem.* **1990**, *397*, 291.
(69) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541.
(70) Posner, G. H. *Org. React.* **1972**, *19*, 1.
(71) Marquais, S.; Alami, M.; Cahiez, G. *Org. Synth.* **1995**, *72*, 135.
(72) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1990**, *31*, 7423.
(73) Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 7365.
(74) Deshmukh, M. B.; Jadhav, S. D.; Mali, A. R.; Suryawanshi, A. W.; Anbhule, P. V.; Jagtap, S. S.; Deshmukh, S. A. *Synth. Commun.* **2005**, *35*, 2967.
(75) (a) Jackman, L.; Lange, B. *Tetrahedron* **1977**, *33*, 2737. (b) Stork, G. *Pure Appl. Chem.* **1975**, *43*, 553. (c) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624. (d) D'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.
(76) (a) Cahiez, G.; Figadère, B.; Tozzolino, P. Eur. Patent 373993, 1990. (b) *Chem. Abstr.* 1991, *114*, 61550. (c) Cahiez, G.; Cléry, P.; Laffitte, J. A. Fr. Patent 2671085, 1992. (d) *Chem. Abstr.* 1993, *118*, 169340. (e) Cahiez, G.; Cléry, P.; Laffitte, J. A. Int. Patent 9306071, 1993. (f) *Chem. Abstr.* 1993, *119*, 116519.
(77) Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3065.
(78) (a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. (b) Rasmussen, J. K. *Synthesis* **1977**, 91. (c) Brownbridge, P. *Synthesis* **1983**, 1. (d) Brownbridge, P. *Synthesis* **1983**, 85.
(79) Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 6295.
(80) Cahiez, G.; Kanaan, M.; Cléry, P. *Synlett* **1995**, 191.
(81) Cahiez, G.; Chau, K.; Blanchot, B. *Org. Synth.* **1999**, *76*, 239.
(82) Micheletti, G.; Pollicino, S.; Ricci, A.; Berionni, G.; Cahiez, G. *Synlett* **2007**, 2829.
(83) Dessole, G.; Bernardi, L.; Bonini, B. F.; Capitò, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem.* **2004**, *69*, 8525.
(84) (a) Reetz, M. T.; Haning, H. *Tetrahedron Lett.* **1993**, *34*, 7395. (b) Cahiez, G.; Chau, K.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 3069.
(85) Maier, S.; Kazmaier, U. *Eur. J. Org. Chem.* **2000**, *7*, 1241.
(86) Cahiez, G.; Plantefève, H. Unpublished results.
(87) Concellón, J. M.; Rodríguez-Solla, H.; Díaz, P.; Llavona, R. *J. Org. Chem.* **2007**, *72*, 4396.
(88) Concellón, J. M.; Rodríguez-Solla, H.; Díaz, P. *J. Org. Chem.* **2007**, *72*, 7974.
(89) Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 910.
(90) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Transition Metals for Organic Chemistry*, 2nd ed.; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
(91) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.
(92) Kang, S.-K.; Baik, T.-G.; Jiao, X. H.; Lee, Y.-T. *Tetrahedron Lett.* **1999**, *40*, 2383.
(93) Kang, S.-K.; Kim, J.-S.; Choi, S.-C. *J. Org. Chem.* **1997**, *62*, 4208.
(94) Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138.
(95) Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, *6*, 4395.
(96) (a) Casas, A.; Merlos, M.; Castaner, J. *Drugs Future* **1997**, *22*, 481. (b) Bouisset, M.; Boudin, A. Eur. Patent 566468, 1993. (c) *Chem. Abstr.* 1993, *119*, 270816.
(97) Rueping, M.; Ieawsuwan, W. *Synlett* **2007**, 247.
(98) Alami, M.; Ramiandrasoa, P.; Cahiez, G. *Synlett* **1998**, 325.
(99) Riguet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 4397.
(100) Riguet, E.; Alami, M.; Cahiez, G. *J. Organomet. Chem.* **2001**, *624*, 376.
(101) Fugami, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, *16*, 2203.
(102) Leleu, A.; Fort, Y.; Schneider, R. *Adv. Synth. Catal.* **2006**, *348*, 1086.
(103) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773.
(104) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53.
(105) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.
(106) Cahiez, G.; Marquais, S. *Synlett* **1993**, 45.
(107) (a) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; Van Koten, G. *Recl. Trav. Chim. Pays−Bas Belg.* **1996**, *115*, 547. (b) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; Van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61.
(108) (a) Fugami, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2161. For other results on the coupling of alkenyl halides with organomanganates, see: (b) Kauffmann, T.; Stach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1684. (c) Kauffmann, T.; Laarmann, B.; Menges, D.; Neiteler, G. *Chem. Ber.* **1992**, *125*, 163. (d) Kauffmann, T.; Stach, D. *Chem. Ber.* **1992**, *125*, 913.
(109) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377.
(110) Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 3275.
(111) Kakiya, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2139.
(112) Kasatkin, A. N.; Tsypyshev, O. Y.; Romanova, T. Y.; Tolstikov, G. A. *Mendeleev Commun.* **1991**, *2*, 62.
(113) Hibino, J.-I.; Nakatsukasa, S.; Fugami, K.; Matsubara, S.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1985**, *107*, 6416.
(114) Tang, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 245.
(115) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076.
(116) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061.
(117) For Mn-catalyzed phenylmagnesiation, see: (a) Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **1998**, *27*, 11. (b) For Mn-catalyzed alkylmagnesiation of 2-alkynylphenols, see: Nishimae, S.; Inoue, R.; Shinokubo, H.; Oshima, K. *Chem. Lett.* 1998, 785.
(118) Fugami, K.; Nakatsukasa, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1986**, *15*, 869.
(119) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 4623.
(120) Cahiez, G.; Bernard, D.; Normant, J. F. *J. Organomet. Chem.* **1976**, *113*, 107.
(121) (a) *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley, J. and Sons, Inc.: Chichester, U.K., 2006. (b) Knochel, P.; Perrone, S.; Grenouillat, N. In *Comprehensive Organometallic Chemistry III*; Mingos, M. P., Crabtree, R. H., Eds.; Elsevier Ltd.: Oxford, U.K., 2007; Vol. 9, p 81.
(122) Klement, I.; Knochel, P.; Chau, K.; Cahiez, G. *Tetrahedron Lett.* **1994**, *35*, 1177.
(123) Riguet, E.; Klement, I.; Reddy, C. K.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 5865.
(124) Stüdemann, T.; Ibrahim-Ouali, M.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 143.

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