

Grignard reagent

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1598 Organometallics 2009, 28, 1598–1605 CoVer Essay The Grignard Reagents Dietmar Seyferth Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139 Received February 4, 2009 During the past 100 years the Grignard reagents probably have been the most widely used organometallic reagents. Most of them are easily prepared in ethereal solution (usually diethyl ether or, since the early 1950s, THF) by the reaction of an organic halide with metallic magnesium (eq 1).

Table 1. Composition of Diethyl Ether Solutions of Various Grignard Reagents at Equilibrium (in mol %), $2\text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2$ a RX in RX + Mg reaction
 CH₃I C₂H₅I C₂H₅Br C₂H₅Cl n-C₃H₇I n-C₃H₇Br n-C₃H₇Cl C₆H₅I C₆H₅Br a
 RMgX 87.0 43.0 41.0 15.0 24.0 24.0 17.0 38.0 30.0 R₂Mg) MgX₂ 6.5
 28.5 29.5 42.5 38.0 38.0 41.5 31.0 35.0 RX + Mg f RMgX (X) Cl, Br, I)

(1) Most of them are stable in ethereal solution (although atmospheric moisture and oxygen should be excluded) and in general are quite reactive.

Discovered by Victor Grignard at the University of Lyon in France in 1900, 1 their ease of preparation and their broad applications in organic and organometallic synthesis made these new organomagnesium reagents an instant success. The importance of this contribution to synthetic chemistry was recognized very early, and for his discovery Grignard was awarded a Nobel Prize in Chemistry in 1912. Our cover molecule is the monomeric ethylmagnesium bromide bis(diethyl etherate) (1), whose solid-state molecular structure was determined by an X-ray diffraction study by Lloyd Guggenberger and Robert

Rundle in 1964 using crystals isolated from a diethyl ether solution of a C₂H₅Br/Mg reaction mixture by slow cooling with a stream of cold gaseous

<https://assignbuster.com/grignard-reagent/>

nitrogen. 2-4 Adapted from: Schlenk, W. , Jr. Ber. Dtsch. Chem. Ges. 1931, 64, 734. Wilhelm Schlenk and his son discovered 80 years ago, more than one magnesium-containing species exists in the diethyl ether solution of a Grignard reagent. 5 A redistribution of the substituents on magnesium takes place, and the RMgX species ends up in equilibrium with the two symmetrical species, the diorganomagnesium and the magnesium dihalide: the “ Schlenk Equilibrium” (eq 2). $2\text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2$ (2) Generally written as “ RMgX ” in textbooks, monographs and research papers, the Grignard reagents in ethereal solution are more complicated than this simple formula indicates. As (1) (a) Grignard, V. Compt. rend. Hebd. Seances Acad. Sci. 1900, 130, ? 1322. (b) Grignard, V. Dissertation “ Theses sur les combinaisons organo` magnesienes mixtes et leur application a des syntheses”, University of Lyon, ` ` Lyon, France, 1901. (2) (a) Guggenberger, L. J. ; Rundle, R. E. J. Am. Chem. Soc. 1964, 86, 5344. (b) Guggenberger, L. J. ; Rundle, R. E. J. Am. Chem. Soc. 1968, 90, 5375. 3) A crystalline solid, $\text{CH}_3\text{MgI} \cdot (\text{n-C}_5\text{H}_{11})_2\text{O}$, was isolated and identi? ed as such by elemental analysis (Mg and I) in 1908: Zerewitinoff, Th. Ber. Dtsch. Chem. Ges. 1908, 41, 2244. The oxonium structure The species that contain Mg-halogen bonds can be precipitated from Grignard reagent solutions in diethyl ether by the addition of 1, 4-dioxane. An insoluble, polymeric 1, 4-dioxane adduct is formed, leaving behind a solution of R_2Mg sa useful preparation of dialkyl- and diarylmagnesium reagents. 6 Wilhelm Schlenk, Jr. analyzed the 1, 4-dioxane precipitations from a number of Grignard reagent solutions. Assuming that the precipitation is essentially instantaneous, i. e. , that the calculated R_2Mg , MgX_2 , and RMgX percentages re? ect the actual composition of the Grignard

reagent solution at equilibrium, Schlenk reported the compositions collected in Table 1. Direct evidence (5) Schlenk, W. ; Schlenk, W. , Jr. Ber. Dtsch. Chem. Ges. 1929, 62, 920. (6) (a) Cope, A. C. J. Am. Chem. Soc. 1935, 57, 2238. (b) As Erwin Weiss found, evaporation of diethyl ether solutions of methyl- and ethylmagnesium bromide and chloride at reduced pressure followed by heating of the colorless solid residues at ca. 00 °C and 0. 001 mmHg for several hours gave a mixture of the respective pure, solvent-free, polymeric R₂Mg compounds and magnesium halides. The solid MgCl₂ thus obtained differed from a sample obtained from a MgCl₂ melt in that its lattice showed a strong stacking disorder. This form of MgCl₂ had an extremely high surface area: Weiss, E. Chem. Ber. 1965, 98, 2805. (7) Schlenk, W. , Jr. Ber. Dtsch. Chem. Ges. 1931, 64, 734 Further additions to the examples in Table 1 were soon thereafter reported by other workers: (a) Noller, C. R. ; Hilmer, F. B. J. Am. Chem. Soc. 1932, 54, 2503. (b) Johnson, G. O. Adkins, H. J. Am. Chem. Soc. 1932, 54, 1943. (c) Cope, A. C. J. Am. Chem. Soc. 1934, 56, 1578. was written for this compound. Earlier workers had isolated noncrystalline solid samples of etherates, e. g. , C₂H₅MgI · (C₂H₅)₂O and RMgI · 2(C₂H₅)₂O. (4) Other early Grignard reagent crystal structures: (a) Stucky, G. D. ; Rundle, R. E. J. Am. Chem. Soc. 1964, 86, 4825 (C₆H₅MgBr · 2Et₂O). (b) Vallino, M. J. Organomet. Chem. 1969, 20, 1 (CH₃MgBr · 3THF). . 10. 1021/om900088z CCC: \$40. 75 ? 2009 American Chemical Society Publication on Web 03/16/2009 Organometallics, Vol. 28, No. 6, 2009 1599 Figure 1.

Association of several Grignard compounds in tetrahydrofuran (J. Am. Chem. Soc. 1969, 91, 3847.). that solutions of “ CH₃MgBr” in diethyl ether contain

CH_3MgBr and $(\text{CH}_3)_2\text{Mg}$ was obtained by Ashby and co-workers by means of ^1H NMR spectroscopic measurements at -105°C . Solutions of "t-butylmagnesium chloride" in diethyl ether also were studied. ⁸ The tendency of the halide substituents in the RMgX and MgX_2 species present in ethereal solution at equilibrium to form bridges between magnesium atoms, Mg-X-Mg , in a Lewis base/Lewis acid type interaction further complicates the nature of the Grignard reagent in ethereal solvents.

In a very thorough study of the association factors of various Grignard reagents in diethyl ether and THF by careful ebullioscopic molecular weight measurements, Eugene Ashby and Frank Walker at the Georgia Institute of Technology found that monomeric, dimeric, and higher oligomeric species were present, depending on the solvent and the halogen and the organic substituents on the magnesium atom. ⁹ Included in this study along with data for the " RMgX " solutions were data for a few R_2Mg compounds and for the magnesium dihalides.

As Figure 1 shows, the observed association factor (the i value is the apparent molecular weight divided by the formula weight of the monoetherate) shows that the Grignard reagents and $(\text{C}_6\text{H}_5)_2\text{Mg}$ are close to monomeric in the relatively strong Lewis basic THF. The picture is quite different in diethyl ether solution (Figures 2 and 3), with association factors of 1 to nearly 4 for solute concentrations up to ca. 3 molal. It is not clear what these i values mean in terms of the actual species present in these solutions.

On the assumption that the Schlenk equilibrium is operative in all cases, in view of the presence of a significant concentration of MgX_2 , one cannot

expect only simple solvated species of type $i(R)Mg-X]_n$ [i (average n) i]. Toney and Stucky isolated crystals of a dimeric species, 2, from a solution of " C_2H_5MgBr " in di-n-butyl ether by addition of this solution to triethylamine. 10 The molecular Figure 2. Association of alkylmagnesium chlorides in diethyl ether. Demonstration of importance of halogen vs R group in determining the form of association in diethyl ether (J. Am. Chem. Soc. 1969, 91, 3848.).

Figure 3. Association of several alkyl- and arylmagnesium bromides and iodides and related magnesium compounds in diethyl ether (J. Am. Chem. Soc. 1969, 91, 3848.). structure, as determined by X-ray analysis, contained a double Br bridge with the ethyl groups in a trans arrangement. That (8) In " CH_3MgBr " solutions in diethyl ether: (a) Ashby, E. C. ; Parrish, G. ; Walker, F. Chem. Commun. 1969, 1464. (b) " $(CH_3)_3CMgCl$ " solutions in diethyl ether at -26 °C: Parris, G. ; Ashby, E. C. J. Am. Chem. Soc. 1971, 93, 1206. (9) (a) Walker, F. W. ; Ashby, E. C. J. Am. Chem. Soc. 1969, 91, 3845. (b) Ashby, E. C. Bull. Soc.

Chim. Fr. 1972, 2133 (review, in English). (c) Meisenheimer, J. ; Schlichenmaier. Ber. Dtsch. Chem. Ges. 1928, 61 (an earlier, similar, but more limited study in diethyl ether). more complicated structures can be present in an " $RMgX$ " solution in diethyl ether was demonstrated by the determination of the X-ray crystal structure of a crystalline compound obtained from a THF solution of " C_2H_5MgCl " of composition $C_2H_5Mg_2Cl_3$. This compound was not a simple Cl-bridged dimer, as the empirical formula might suggest. Actually, it was a tetramer (Figure 4) in which the Mg atoms have a coordination number greater than 4. 1 There is a caveat, however:

the species that crystallizes from a Grignard reagent solution does not necessarily directly reflect what species are swimming around in the solution. The crystalline solid shown in Figure 4 could well have self-assembled during the crystallization process by combination of two molecules of the $C_2H_5Mg_2Cl_3$ dimer and not been present in solution at all. Even in the case of monomeric "RMgX" in THF solution, the Schlenk equilibrium will be operative and the strongly Lewis basic THF apparently prevents halide bridging between Mg atoms.

Consequently, the (10) Toney, J. ; Stucky, G. D. Chem. Commun. 1967, 1168.
(11) Toney, J. ; Stucky, G. D. J. Organomet. Chem. 1971, 28, 5. 1600
Organometallics, Vol. 28, No. 6, 2009 Scheme 1 Figure 4. Molecular structure of $[C_2H_5Mg_2Cl_3(C_4H_8O)_3]_2$, a tetrameric Grignard reagent. Modified from Toney and Stucky (J. Organomet. Chem. 1971, 28, 15. (copyright 1971, with permission from Elsevier)). presence of monomeric RMgX, R_2Mg , and MgX_2 , all solvated, would result in the measurement of an association factor of 1, as Walker and Ashby observed.

There are so many factors that bear on the question of the constitution of a given Grignard reagent in ethereal solution—the Lewis basicity and steric properties of the ether solvent, the electronegativity and size of the halogen atom in RMgX, the nature and steric properties of the organic substituent on the magnesium atom. These will affect the magnitude of the equilibrium constant of the Schlenk equilibrium and the extent of Mg-X-Mg bridging. For most applications in synthetic chemistry it will suffice to take the easy way out—to regard and to write the Grignard reagent as RMgX.

There is another interesting and useful property of ethereal Grignard reagent solutions. The magnesium species are weak electrolytes in such solvents of low dielectric constant, and "RMgX" solutions conduct an electric current. 12 The electrolysis of solutions of organomagnesium halides was studied in some detail by Kondyrew at the State Research Institute in Leningrad¹³ and by Ward Evans and his students at Northwestern University. 14 During the electrolysis, magnesium species migrate both to the cathode and to the anode. Scheme 1 shows the simplest picture based on RMgX. Metallic magnesium is formed at the cathode. 12) The earliest report appears to be a 1912 French paper: Jolibois, P. *Compt. rend. Hebd. Seances Acad. Sci.* 1912, 155, 213. See also: Nelson, J. M. ; Evans, W. V. *J. Am. Chem. Soc.* 1917, 39, 82. (13) (a) Kondyrew, N. W. *Ber. Dtsch. Chem. Ges.* 1925, 58, 459. (b) Kondyrew, N. W. ; Manojew, D. P. *Ber. Dtsch. Chem. Ges.* 1925, 58, 464. (c) Kondyrew, N. W. *Ber. Dtsch. Chem. Ges.* 1928, 61, 208. (d) Kondyrew, N. W. ; Ssusi, A. K. *Ber. Dtsch. Chem. Ges.* 1929, 62, 1856. (14) The Evans group published many papers in *J. Am. Chem. Soc.* during the 1933-1942 period. See, for example: (a) Evans, W. V. ; Lee, F.

H. J. Am. Chem. Soc. 1934, 56, 654. (b) Evans, W. V. ; Field, E. *J. Am. Chem. Soc.* 1936, 58, 720. (c) Evans, W. V. ; Braithwaite, D. *J. Am. Chem. Soc.* 1939, 61, 898. (d) Evans, W. V. ; Braithwaite, D. ; Field, E. *J. Am. Chem. Soc.* 1940, 62, 534. (e) Evans, W. V. ; Pearson, R. *J. Am. Chem. Soc.* 1942, 64, 2865. The alkyl radicals formed at the anode can undergo the usual alkyl radical processes of coupling (to R-R), disproportionation (to RH + R(-H)), or, if the anode is composed of a reactive metal such as zinc, aluminum, cadmium, or lead, they can attack the anode to form an organometallic compound.

A graduate student of Evans, David G. Braithwaite, joined the Nalco Chemical Co. after he graduated and developed an electrolytic process for the commercial-scale syntheses of tetramethyl- and tetraethyllead antiknock agents in which the respective alkyl Grignard reagents were electrolyzed in a mixed THF/diethylene glycol dimethyl ether solvent system using a lead anode and a steel cathode. 15 The reactions of the Grignard reagents with organic, organometallic, and inorganic substrates and their applications are too numerous and varied to be covered here.

Not only do they find extensive use on a small to moderate scale in research laboratories but they also have been prepared and utilized on a large scale in diverse industrial processes. For the most part they react as nucleophilic reagents, as would be expected, on the basis of the polarity of the carbon-magnesium bond, $C^{\delta-}-Mg^{\delta+}$. However, they also can undergo electron transfer reactions with appropriate electron-acceptor substrates. They are weak bases capable of deprotonating the stronger weak organic acids such as terminal acetylenes and cyclopentadiene.

Their basicity can be enhanced (as can be the basicity of organolithium reagents) by the addition to $RMgX$ solutions in ethers of additives such as hexamethylphosphoric triamide (HMPA) and N-methyl-2-pyrrolidinone (NMP) or alkali-metal alkoxides. All such information can be found in books devoted solely or in part to Grignard reagents. 16 Two special topics are of current interest and merit special mention. (1) The preparation of highly functionalized organomagnesium reagents by Paul Knochel and his co-workers at the University of Munich¹⁷ by means of halogen-magnesium exchange (e. . . , eq 3). The availability of reagents such as 3-8 (which must

be utilized at low temperature) has added a new and spectacular dimension to Grignard reagent chemistry. (2) The synthesis of olefins, styrenes, 1, 3-dienes and biaryl derivatives by the crosscoupling of Grignard reagents with organic halides. The crosscoupling of Grignard reagents with vinylic halides was discovered by Morris Kharasch and Charles Fuchs at the University of Chicago Organometallics, Vol. 28, No. 6, 2009 1601 Table 2.

Transition Metal Halide Catalyzed Homocoupling of Arylmagnesium Iodides

metal halide	FeCl ₂	CoBr ₂	NiBr ₂	RuCl ₃	RhCl ₃	PdCl ₂	OsCl ₃	IrCl ₃
amt, mol	0.01	0.01	0.03	0.0036	0.0036	0.00566	0.00275	0.003
amt of C ₆ H ₅ MgI, mol	0.03	0.03	0.095	0.0108	0.013	0.0163	0.007	0.01
yield of biphenyl, %	98	98	100	99	97.5	98	53	28

Taken from: J. Am. Chem. Soc. 1939, 61, 957. In 1943 during the classic studies of Kharasch on the chemistry of Grignard reagents in the presence of transition-metal halides. Kharasch and Fuchs found that arylmagnesium bromides in diethyl ether reacted readily with vinylic halides of type RCHdCHX and R₂CdCHX (but not CH₂dC(R)X) to give styrenes in 50-75% yield when the reactions were carried out in the presence of 5 mol % of CoCl₂ (eq 4). It was reported that other metal halides (of iron, nickel, and chromium) also were effective catalysts of this cross-coupling reaction. Benzylmagnesium chloride also reacted in this manner with vinyl bromide to give PhCH₂CHdCH₂ in 75% yield.

Alkylmagnesium halides such as cyclohexyl- and n-butylmagnesium bromide, on the other hand, gave only "small to negligible" yields of the expected coupling product. The ArMgBr-derived biaryl usually was obtained as a byproduct in these reactions. Such homocoupling of arylmagnesium halides

in the presence of a transition metal halide as well as copper and silver halides was a known reaction. It had been investigated in 1939 by Gilman and Lichtenwalter, who found that aryl Grignard reagents undergo homocoupling in the presence of ca. 0 mol % of various transition-metal halides in diethyl ether solution to give the respective biaryl in high yield in most cases (eq 5, Table 2).¹⁹ The metal halide, in addition to being the needed catalyst precursor, also served as an oxidizing agent and, in some cases (CoBr₂, NiCl₂, RhCl₃), formation of a black solid indicated complete reduction to the metal. This does not occur in the absence of the organic halide but in its presence was vigorously exothermic. The added organic halide was only partially consumed and did not show up in the biaryl product.

When p-bromotoluene was added to a phenylmagnesium bromide/CoCl₂ catalyst reaction mixture, only biphenyl was formed. A remarkable reaction! Most likely a free radical process, as Kharasch suggested. The organic halide was believed to function as an oxidizing agent. This interesting, simple, and potentially useful cross-coupling reaction, as exemplified in eq 4, was not adopted by the synthetic organic community right away. After a long dormancy it was rediscovered some 30 years later by a number of groups in the USA, Japan, and France, all of whom apparently were not aware of the 1943 Kharasch/Fuchs JACS paper.¹ Transition-metal catalysts other than CoCl₂ were used, but the concept and the basic reaction were the same. In 1971 Tamura and Kochi reported a thorough study of the cross-coupling of Grignard reagents with vinylic halides catalyzed by soluble iron species in concentrations of ca. 10⁻⁴ M in THF at 0-25 °C.^{26, 27} Various Fe(III) compounds could be used as Fe catalyst precursors; the best were

Fe(III) -diketonates such as $\text{Fe}(\text{RC}(\text{O})\text{CHC}(\text{O})\text{R})_3$ (R) Ph, CH₃, t-Bu). These exothermic reactions were not free radical processes. The reactions of cis- and trans-propenyl bromide proceeded with retention of geometric con? uration (eqs 6 and 7) and were not adversely affected by the presence of 0. 4 M styrene. A $\text{ArMgBr} + \text{RCHdCHX} \rightarrow \text{ArCHdCHR} + \text{MgBrX}$ 8 (X) Cl, Br) CoCl_2 5 mol % (4) $2\text{ArMgX} + \text{MX}_n \rightarrow \text{Ar-Ar} + \text{MgX}_2 + \text{MX}_{n-2}$ (5) A novel catalytic process for such ArMgX to Ar-Ar coupling was discovered by Kharasch and Fields when ethereal solutions of an aryl Grignard reagent that contained a catalytic amount (3 mol %) of CoCl_2 were heated at re? ux for 1 h and then treated with an equivalent amount of an organic halide (C₆H₅Br, C₂H₅Br, i-C₃H₇Cl). 20 The coupling reaction to give Ar-Ar did (15) (a) Bott, L.

L. Hydrocarbon Process. Petrol. Re? ner 1965, 44, 115. (b) Guccione, E. Chem. Eng. 1965, (June 21), 102. See also Part 2 of the tetraethyllead essay: (c) Seyferth, D. Organometallics 2003, 22, 5154 (pages 5172-5174). (16) (a) Krause, E. ; von Grosse, A. Die Chemie der metall-organischen Verbindungen; Gebruder Borntrager: Berlin, 1937; pp 14-61, 110-114. ? ? (b) Kharasch, M. S. ; Reinmuth, O. Grignard Reactions of Nonmetallic Substances; Prentice Hall: New York, 1954. (c) Handbook of Grignard Reagents; Silverman, G. S. , Rakita, P. E. , Eds. ; Dekker: New York, 1996. d) Grignard Reagents-New DeVelopments; Richey, H. G. , Ed. ; Wiley: Chichester, New York, 2000. (e) The Chemistry of Organomagnesium Compounds; Rappaport, Z. , Marek, L. , Eds. ; Wiley-VCH: Weinheim, Germany, 2008. (17) Knochel, P. ; Dohle, W. ; Gommermann, N. ; Kneisel, F. F. ; Kopp, F. ; Korn, T. ; Sapountzis, J. ; Vu, V. A. Angew. Chem. , Int. Ed. 2003, 42, 4302 (review). (18) Kharasch, M. S. ; Fuchs, C. F. J. Am. Chem. Soc.

1943, 65, 504. (19) Gilman, H. ; Lichtenwalter, M. J. Am. Chem. Soc. 1939, 61, 957. and earlier (back to 1914) references cited therein. 20) Kharasch, M. S. ; Fields, E. K. J. Am. Chem. Soc. 1941, 63, 2316. mechanism involving an organoiron(I) intermediate, obtained by reduction of the Fe(III) precursor by the Grignard reagent, was suggested. The results of a few experiments carried out on a 30-40 mmol scale (Table 3) showed that such iron-catalyzed reactions would be useful in the synthesis of olefins, but a broader study to optimize them and to broaden the scope of their application was not undertaken. The coupling of vinylic Grignard reagents with alkyl halides is catalyzed also by Ag(I) salts. 8 Thus, cis-propenylmagnesium (21) Two later “historical notes” 22, 23 and two book chapters 24, 25 that dealt with the cross-coupling reactions of Grignard reagents with vinylic halides also did not cite the Kharasch/Fuchs paper. (22) Tamao, K. J. Organomet. Chem. 2002, 653, 27. (23) Murahashi, S. -I. J. Organomet. Chem. 2002, 653, 27. (24) Kochi, J. K. Organometallic Mechanisms and Catalysis; Academic Press: New York, 1978; Chapter 14, Sections III and IV. (25) Hou, S. ; Negishi, E. -i. In Handbook of Organopalladium Chemistry; Negishi, E. -i. , Ed. , Wiley: New York, 2002; Vol. 1, Chapter III. 2. 6, pp 335-408.

As a historical note, the following quotation from this reference (p 335) is of interest: “ Although the reaction of Grignard reagents with organic halides was shown to be catalyzed by various late transition metal compounds (the Kharasch reaction) in the 1950s, it was not until the early 1970s that the applicability of this catalytic method was extended to the cross-coupling involving alkenyl and aryl halides catalyzed by Ag, Fe and other late transition metals. ” (26) (a) Kochi, J. ; Tamura, M. J. Am. Chem. Soc. 1971, 93,

1487. (b) Tamura, M. ; Kochi, J. *Synthesis*, 1971, 303. (27) Full papers: (a) Neumann, S.

M. ; Kochi, J. K. *J. Org. Chem.* 1975, 40, 599. (b) Smith, R. S. ; Kochi, J. K. *J. Org. Chem.* 1976, 41, 502. (c) Reviews: ref 24. (d) Kochi, J. K. *J. Organomet. Chem.* 2002, 653, 11 (historical note). (28) (a) Whitesides, G. M. ; Casey, C. P. *J. Am. Chem. Soc.* 1966, 88, 4541. (b) Tamura, M. ; Kochi, J. *J. Am. Chem. Soc.* 1971, 93, 1483. 1602 *Organometallics*, Vol. 28, No. 6, 2009 Table 3. Alkenylation of Grignard Reagents using FeCl₃ as Precatalyst (in THF)

R MgBr (amt, mmol)	n-C ₆ H ₁₃ MgBr (40)	CH ₂ dCH(CH ₂) ₄ MgBr (36)	n-C ₆ H ₁₃ MgBr (40)
a	1	R ₂ Br (amt, mmol)	CH ₂ dCHBr (204)
			CH ₂ dCHBr (102)
			CH ₃ CHdCHBr (355)

FeCl₃ (amt, mmol) 0. 05 0. 05 0. 10
 reacn temp, °C 0 25 25
 product (yield, %) n-C₆H₁₃CHdCH₂ (83) CH₂dCH(CH₂)₄CHdCH₂ (64) n-C₆H₁₃CHdCHCH₃ (67) (53/47 cis/trans mixture)
 Taken from: *Synthesis* 1971, 6, 303. Scheme 2
 bromide reacted with methyl bromide in THF in the presence of an Ag(I) catalyst to give cis-butene-2, but a similar reaction of trans-propenylmagnesium bromide gave a 7: 3 mixture of cis and trans-butene-2, respectively. 28b Apparently propenyl radicals were involved. A similar Grignard reagent based cross-coupling, olefin synthesis in which a copper(I) catalyst was used was published by French workers. 9 Normant et al. reported that their reactions (e. g. , n-Bu(Et)CdCHI + i-PrMgCl in THF at -20 °C with a Cu(I) catalyst) proceeded with retention of configuration. 29a For a reaction of CH₃CHdC(CH₃)MgCl with n-C₃H₇I in THF at 0 °C using CuI as catalyst, Linstremelle reported that the coupling product obtained in 97% yield was 88% cis and 12% trans, while a similar reaction of

$\text{CH}_2\text{dC}(\text{CH}_3)\text{MgBr}$ with $\text{trans-n-C}_6\text{H}_{13}\text{CHdCHI}$ gave a 4: 1 trans/cis product.

29b The use of Ni(II) catalyst precursors for Grignard reagent-vinyl halide cross-coupling was reported in 1972 by Corriu and Masse³⁰ and by Tamao, Sumitani, and Kumada.¹ The French group found Ni(II) acetylacetonate to be the most effective catalyst precursor, while the Japanese group favored a bis(tertiary phosphine)NiCl₂ catalyst precursor and, especially, chelating diphosphine complexes such as $(\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2)\text{NiCl}_2$. Reactions carried out in diethyl ether at reflux generally gave excellent yields. This procedure has been carried out commercially on an industrial scale in the preparation of *p*-chloro and *p*-tert-butylstyrene.³² Finally, the last to be discovered at that time and the most versatile procedure for the cross-coupling of Grignard reagents (29) (a) Normant, J. F. Commercon, A. ; Cahiez, G. ; Villieras, J. *Compt. Rend. Hebd. Seances Acad. Sci. , Ser. C* 1974, 278, 967. (b) Derguini ; Boumechal, F. ; Linstumelle, G. *Tetrahedron Lett.* 1976, 3225. (30) Corriu, R. J. P. ; Masse, J. P. *J. Chem. Soc. , Chem. Commun.* 1972, 144. (31) (a) Tamao, K. ; Sumitani, K. ; Kumada, M. *J. Am. Chem. Soc.* 1972, 94, 1375. (b) See also ref 22. Later work: (c) Tamao, K. ; Kiso, Y. ; Sumitani, K. ; Kumada, M. *J. Am. Chem. Soc.* 1972, 94, 9268. (d) Kiso, Y. ; Tamao, K. ; Kumada, M. *J. Organomet. Chem.* 1973, 50, C12. (e) Kiso, Y. ; Tamao, K. ; Miyake, N. ; Yamamoto, K. ; Kumada, M. *Tetrahedron Lett.* 1974, (No. 1), 3. (f) Tamao, K. ; Sumitani, K. ; Kiso, Y. ; Zembayashi, M. ; Fujioka, A. ; Kodama, S. ; Nakajima, I. ; Minato, A. ; Kumada, M. *Bull. Chem. Soc. Jpn.* 1976, 49, 1958. (g) Tamao, K. ; Kodama, S. ; Nakajima, I. ; Kumada, M. ; Minato, A. ; Suzuki, K. *Tetrahedron* 1982, 38, 3347. (32) Banno, T. ; Hayakawa ; Umeno, M. *J. Organomet. Chem.* 2002, 653, 288. (33) (a) Yamamura, M. ; Moritani, I. ;

Murahashi, S. -I. J. Organomet. Chem. 1975, 91, C39. Full paper: (b) Murahashi, S. -I. ; Yamamura, M. ; Yanagisawa, K. -i. ; Mita, N. ; Kondo, K. J. Org. Chem. 1979, 44, 2408. (c) Historical note: ref 23. Ith vinylic and aryl halides, that catalyzed by palladium complexes, was reported by Shun-Ichi Murahashi and coworkers in 1975. 33a The reactions were carried out in diethyl ether/benzene at room temperature using $(\text{Ph}_3\text{P})_4\text{Pd}$ as the catalyst precursor, and they proceeded stereospecifically in excellent yield (Scheme 2). Dang and Linstrumelle also used this procedure to prepare 1, 3-dienes stereospecifically by the reaction of vinylic iodides with vinylic Grignard reagents. 34 Palladium-catalyzed cross-coupling of Grignard reagents with organic halides has been a very active area in organic synthesis.

Reference 25 reviews (up to 2002) its application in (alkenyl) MgX-ArX , ArMgX-(alkenyl)X , and $(\text{alkenyl})\text{MgX-(alkenyl)X}$ coupling processes. A further chapter in this book deals with $\text{ArMgX-Ar}^? \text{X}$ coupling. 35 Another surge of research activity on cross-coupling of Grignard reagents with organic halides started around the turn of the century and still appears to be in progress at the present time (January 2009). Interest has revived in the use of iron complexes as precatalysts for the cross- and homocoupling of Grignard reagents, 36 since iron complexes are cheaper than those of palladium and are nontoxic.

The iron-catalyzed cross-coupling of organomagnesium bromides with vinylic bromides, although it produced olefins in good yield, was of interest to Jay Kochi, as noted above, primarily from the point of view of its reaction mechanism rather than of its potential for application in organic synthesis. After some 25 years several research groups carried out much experimental

work which has shown iron-catalyzed cross-coupling and homocoupling of Grignard reagents to be broadly applicable and very useful additions to the methods of organic synthesis.

In 1995 Gerard Cahiez, at the Universite Pierre et Marie Curie ?? in Paris, during the course of his extensive investigations of organomanganese chemistry, found that the cross-coupling of vinylic bromides with alkyl, vinylic, and phenylmanganese chlorides could be effected in good yield in the presence of 3 mol % of iron(III) acetylacetonate in a THF/N-methyl-2pyrrolidinone (NMP) mixed solvent at room temperature. 37 In a thorough study, this reaction was extended to the crosscoupling of vinylic halides with alkylmagnesium halides using 1 mol % of Fe(acac)₃ and the same solvent mixture. 8 High yields of ole? nic products were obtained. Successful crosscoupling of Grignard reagents with AcO(CH₂)₆CHdCHCl, CH₃C(O)(CH₂)₃CHdCHCl, Cl(CH₂)₄CBrdCH₂, 9, and 10 are noteworthy as examples of the selectivity and functional group tolerance of this reaction. The scope of this chemistry was extended further when some of Knochel's functionally substituted aryl Grignard reagents¹⁷ (vide supra) were reacted with vinylic bromides and iodides. 39 The cross-coupling reaction between aryl Grignard reagents and vinylic bromides and iodides also was found by Cahiez and co-workers to give ole? ic products in good yield with Organometallics, Vol. 28, No. 6, 2009 1603 Table 4. Iron-Catalyzed Biaryl Coupling Reactions a Table 5. Iron-Catalyzed Homocoupling of Grignard Reagents with Atmospheric Oxygen as Oxidanta a Taken from: J. Am. Chem. Soc. 2007, 129, 13788. palladium or nickel precatalysts. 42 Of these procedures, that of Cahiez et al.

41f appears to be the most useful. Alkyl halide/ alkylmagnesium halide cross-coupling is not a practical process. $3 \text{ RMgX} + \text{R}'\text{X} \rightarrow \text{R-R}' + \text{MgX}_2$ (8)

Iron-catalyzed reactions of aryl Grignard reagents with aryl halides to give biaryls generally are not synthetically useful. The desired cross-coupling products are obtained in only poor yield, the main product being the homocoupled biaryl derived from the aryl Grignard reagent (eq 9) (recall the Gilman/ Lichtenwalter and Kharasch/Fields reactions, vide supra). $\text{ArMgX} + \text{Ar}'\text{X} \rightarrow \text{Ar-Ar}' + (\text{low yield})$ (major Ar-Ar product) (9) a Taken from: J. Am. Chem. Soc. 2007, 129, 9844.

retention of geometric configuration when carried out in THF solution in the presence of 10 mol % of MnCl_2 . 0 As noted above, Kharasch and Fuchs had found that attempts to cross-couple aryl Grignard reagents with alkyl halides in the presence of catalytic amounts of CoCl_2 were unsuccessful. On the other hand, such reactions do occur in the presence of an iron precatalyst and various additives (eq 8, $\text{R}' = \text{alkyl}$), as summarized in ref 36. A number of other groups have reported the results of their research directed toward development of an effective procedure for the process shown in eq 8, all using an iron precatalyst of one kind or another, various additives such as TMEDA, NMP, etc. and generally diethyl ether (but sometimes THF) as solvent. 41 It is noteworthy that primary and secondary alkyl halides, i. e. , ones that contain hydrogen substituents on the carbon atom, can be cross-coupled with aryl Grignard reagents, a process that cannot be realized using (34) Dang, H. P. ; Linstremelle, G. Tetrahedron Lett. 1978, 191. (35) Anastasia, L. ; Negishi, E. -i. Chapter II. 2. 5, pp 311-344, in ref 25. (To date palladium and nickel catalysts have been widely used to effect aryl-aryl cross-coupling reactions. However, arylmagnesium halides

were found to undergo cross-coupling with aryl halides that contain electron-withdrawing activating substituents ortho or para with respect to the halogen substituent in the presence of 10 mol % of manganese(II) chloride (eq 10). 44 Cyclohexyl and 2-methylpropenyl Grignard reagents reacted with such substituted halobenzenes in a similar manner. Very (36) (a) Cahiez, G. ; Duplais, C. " Iron-Catalyzed Reactions of Grignard Reagents", Chapter 13, pp 594-630 in ref 16e. (b) Furstner, A. ; Leitner, A. ; Mendez, M. ; Kraus, H. J. Am.

Chem. Soc. 2002, 124, 13856 (a long ? paper that brings an excellent discussion of the literature, of questions concerning mechanism, and original results). (c) Sherry, B. D. ; Furstner, A. Acc. Chem. Res. 2008, 41, 1500. (37) Cahiez, G. ; Marquis, S. Tetrahedron Lett. 1996, 37, 1773. (38) Cahiez, G. ; Avedissian, H. Synthesis 1998, 1199. (39) Dohle, W. ; Kopp, F. ; Cahiez, G. ; Knochel, P. Synlett 2001, 1901. 1604 Organometallics, Vol. 28, No. 6, 2009 Table 6. Manganese-Catalyzed Homocoupling of Grignard Reagents with Atmospheric Oxygen as Oxidant Scheme 4

THF to a mixture of 3 mol % of $\text{FeF}_3 \cdot 3\text{H}_2\text{O}$ and 9 mol % of an N-heterocyclic carbene ($\text{SIPr} \cdot \text{HCl}$). In one example, chlorobenzene (1.0 equiv) and $p\text{-CH}_3\text{C}_6\text{H}_4\text{MgBr}$ (1.2 equiv) were added to this catalyst system and the reaction mixture was stirred at 60 °C for 1 day. The desired product, $p\text{-CH}_3\text{C}_6\text{H}_4\text{-C}_6\text{H}_5$, was obtained in 98% yield. The homocoupling product, biphenyl, was present only in trace amount, while $\text{CH}_3\text{C}_6\text{H}_4\text{C}_6\text{H}_4\text{CH}_3$ was formed in 3% yield. Some examples of the application of this remarkable reaction are shown in Table 4. Good results were obtained only with aryl chlorides.

Aryl bromides and iodides gave low biaryl yields. A German group reported similar MnCl_2 -catalyzed cross-coupling between various heterocyclic chlorides and aryl as well as alkyl Grignard reagents: e. g. , eq 11. 46 a Taken from: *J. Am. Chem. Soc.* 2007, 129, 13788. The homocoupling reaction of aryl Grignard reagents, mentioned earlier, also has received renewed attention recently, and synthetically useful procedures have resulted. Nagano and Hayashi developed a procedure in which the reaction is carried out in refluxing diethyl ether in the presence of 1-5 mol % of FeCl_3 , NMP and 1. molar equiv of 1, 2-dichloroethane (which serves as the oxidant). 47 Cahiez and co-workers have improved this procedure by using THF as solvent, in which arylmagnesium halides, including the chlorides, are more easily prepared. 48 This procedure works well with Knochel's functional arylmagnesium halides (Scheme 3). Of interest also is the clever construction of the tricyclic system 11 by intramolecular homocoupling (Scheme 4). (40) (a) Cahiez, G. ; Gager, O. ; Lecomte, F. *Org. Lett.* 2008, 10, 5255. (b) Alami, M. ; Ramiandrasoa, P. ; Cahiez, G. *Synlett* 1998, 325. 41) A selection: (a) Martin, R. ; Furstner, A. *Angew. Chem. , Int. Ed. ?* 2004, 43, 3955 (see also ref 36b and references cited therein). (b) Nagano, T. ; Hayashi, T. *Org. Lett.* 2004, 6, 1297. (c) Bedford, R. B. ; Bruce, D. W. ; Frost, R. M. ; Goodby, J. W. ; Hird, M. *Chem. Commun.* 2004, 2822. (d) Nakamura, N. ; Matsuo, K. ; Ito, S. ; Nakamura, E. *J. Am. Chem. Soc.* 2004, 126, 3686. (e) Bedford, R. B. ; Bruce, D. W. ; Frost, R. M. ; Hird, M. *Chem. Commun.* 2005, 4161. (f) Cahiez, G. ; Habiak, V. ; Duplais, C. ; Moyeux, A. *Angew. Chem. , Int. Ed.* 2007, 46, 4364. g) Cahiez, G. ; Duplais, C. ; Moyeux, A. *Org. Lett.* 2007, 9, 3253. (h) Guerinot, A. ; Reymond, S. ; Cossy, J. *Angew. ? Chem. , Int. Ed.*

2007, 46, 6521. (42) However, Terao and Kambe have recently developed new Pd- and Ni-based precatalyst systems which avoid the problem of - elimination of primary and secondary alkyl groups: Terao, J. ; Kambe, M. *Acc. Chem. Res.* 2008, 41, 1545. (43) (a) Tamura, M. ; Kochi, J. *J. Organomet. Chem.* 1971, 31, 289. (b) Rollick, K. L. ; Nugent, W. A. ; Kochi, J. K. *J. Organomet. Chem.* 1982, 225, 279. (44) Cahiez, G. ; Lepifre, F. Ramiandrasoa, P. *Synthesis* 1999, 2138. (45) Hatakeyama, T. ; Nakamura, M. *J. Am. Chem. Soc.* 2007, 129, 9844. (46) Rueping, M. ; leawsuwan, W. *Synlett* 2007, 247. (47) Nagano, T. ; Hiyama, T. *Org. Lett.* 2005, 7, 491. (48) Cahiez, G. ; Chaboche, C. ; Mahuteau-Betzer, F. *Org. Lett.* 2005, 7, 1943. Scheme 3 special, but generally applicable, reaction conditions developed by Japanese workers⁴⁵ have generally provided the possibility of clean aryl-aryl cross-coupling reactions in which competitive homocoupling of the aryl Grignard reagent has been almost completely suppressed.

In this procedure an active catalyst system was prepared by addition of 18 mol % of C₂H₅MgBr in *Organometallics*, Vol. 28, No. 6, 2009 1605 A further improvement resulted when it was found that atmospheric oxygen could replace the 1, 2-dihaloethane as oxidant in the homocoupling of aryl, vinylic, and alkynyl Grignard reagents using either Fe or Mn catalyst precursors. 49 As Tables 5 and 6 show, this procedure gave excellent results. The most recent contribution to iron-catalyzed cross-coupling, which appeared during the preparation of the final draft of this paper, involves application of the old one-pot Barbier procedure in which FeCl₃ served as precatalyst and stoichiometric amounts of magnesium turnings and TMEDA additive were used. A mixture of an alkyl and an aryl bromide was added to the mixture of

precatalyst, TMEDA, magnesium, and solvent at 0 °C. Good yields of cross-coupled products were obtained. 50 There has been a great deal of activity in the areas of Grignard reagent/organic halide cross-coupling and aryl Grignard reagent homocoupling, and the coverage in this essay, whose focus is on the historical aspects, is far from exhaustive.

Attention is called to the 2005 review by Frisch and Beller⁵¹ and especially (49) Cahiez, G. ; Moyeux, A. ; Buendia, J. ; Duplais, C. J. *Am. Chem. Soc.* 2007, 129, 13789. (50) Czaplik, W. M. ; Mayer, M. ; von Wangelin, A. J. *Angew. Chem. , Int. Ed.* 2009, 48, 607. (51) Frisch, A. C. ; Beller, M. *Angew. Chem. , Int. Ed.* 2005, 44, 674. to the recent *Accounts of Chemical Research* special issue on cross-coupling. 52 Since it was first reported in 1943, the cross-coupling of Grignard reagents with organic halides, thanks to further development by many later workers, has become a broadly applicable, very useful reaction in organic synthesis. There is much more about Grignard reagents that I have not covered: the various procedures used in their preparation, the mechanism of their formation (which is still controversial), the more complex organomagnesium compounds such as bis(cyclopentadienyl)magnesium, magnesium butadiene, and magnesium anthracene, and the many kinds of reactions that Grignard reagents have been reported to undergo.

But this is only a short essay, and so I have been able to cover only a few selected topics, ones which I hope will be of interest to the reader. More information can be found in the books that I have cited earlier. 16 Acknowledgment. My thanks, as always, to Professor Arnold L. Rheingold for the cover figure. OM900088Z (52) *Acc. Chem. Res.* 2008, 41, No. 11, 1439-

1564, special issue. A collection of 11 reviews, many of them relevant to the subject matter of the present essay, with useful, up-to-date references.