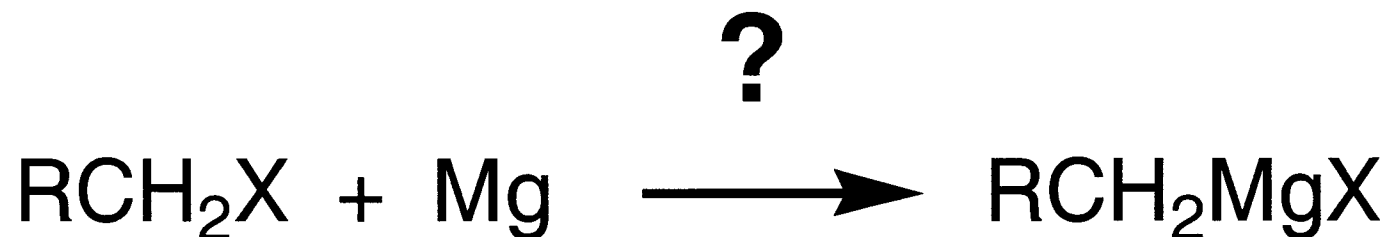


Mechanism of Grignard Reagent Formation

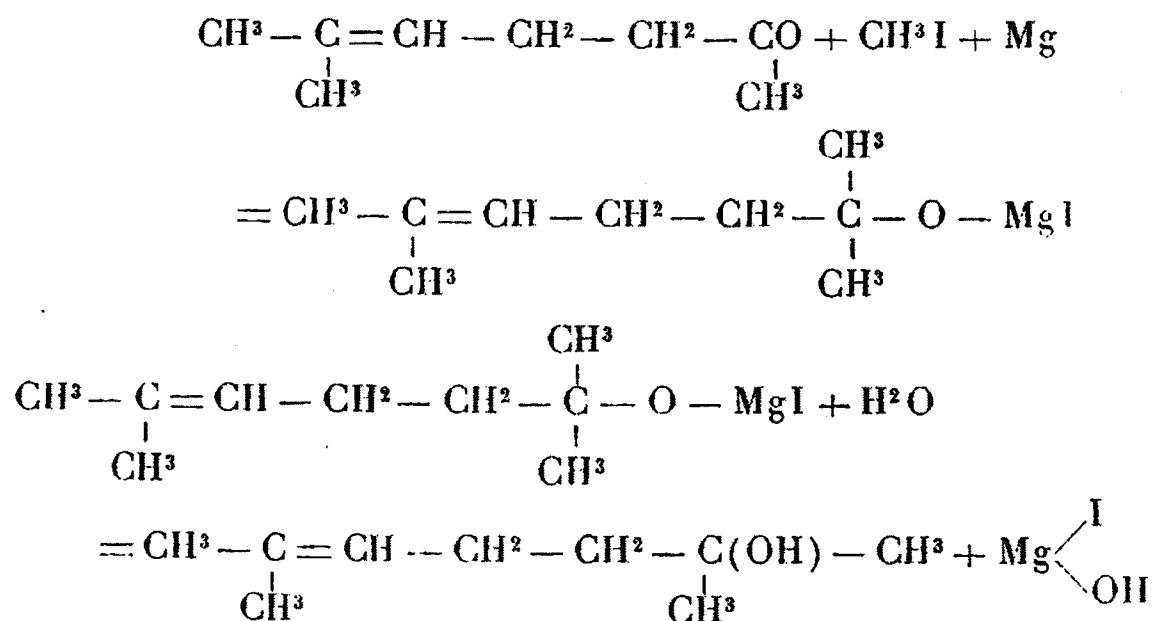


Justin Montgomery

8/31/4

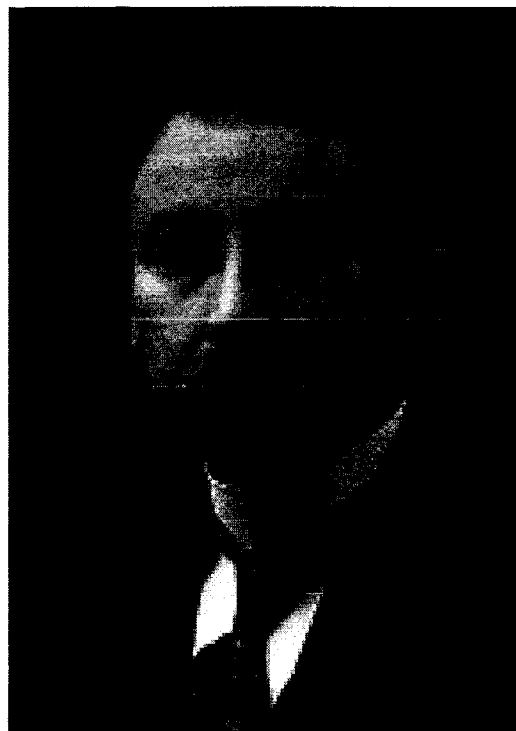
CHIMIE ORGANIQUE. — *Synthèse du diméthylhepténol.* Note de M. **PH. BARBIER**, présentée par M. Friedel.

» Les formules ci-dessous représentent la réaction qui lui a donné naissance :

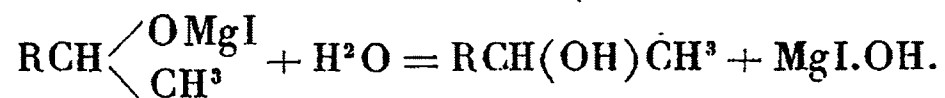
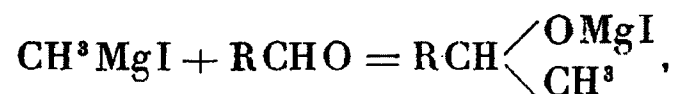
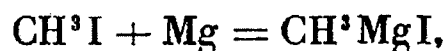


Barbier synthesis – was looking to improve the Wagner-Saytzeff synthesis (Zn) by using magnesium – worked in some cases but often gave irreproducible and bad results

Victor Grignard



CHIMIE ORGANIQUE. — *Sur quelques nouvelles combinaisons organométalliques du magnésium et leur application à des synthèses d'alcools et d'hydrocarbures* (1). Note de M. V. GRIGNARD, présentée par M. H. MOISSAN.



- Born May 6, 1871

- Late 1890's – began working with Phillippe Barbier as a graduate student

- Continued study of the Barbier synthesis with continued problems

- Suggested to Barbier that RMgX was the effective intermediate and that perhaps it could be preformed and added to a carbonyl compound – Barbier didn't like the idea and it was abandoned temporarily

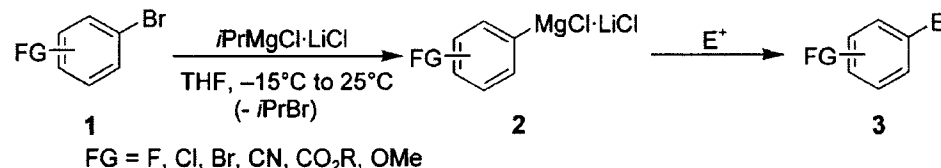
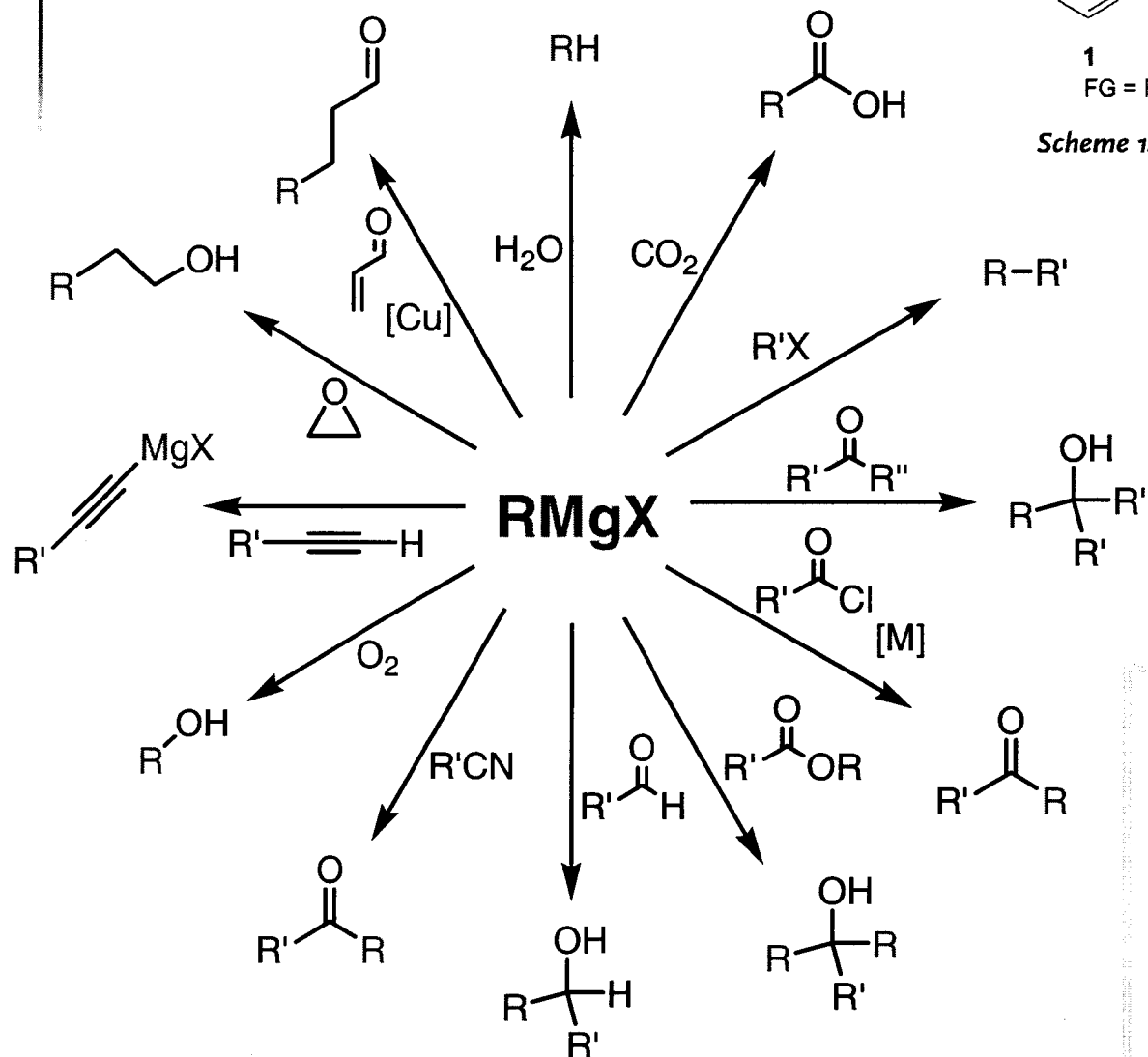
- Grignard was given more freedom with a change of appointment and he did the experiments to confirm his hypothesis

- Barbier congratulated him for making an important discovery and encouraged him to exploit it

- Nobel Prize 1912

- By his death in 1925 – over 6,000 references to Grignard reagents

<http://www.nobel.se/chemistry/laureates/1912/Grignard>, *Compt. Rend.*, **1900**, 130, 1322.



Scheme 1. Preparation of functionalized arylmagnesium reagents.

A. Krasovskiy, P. Knochel, *ACIE* **2004**, 3333.

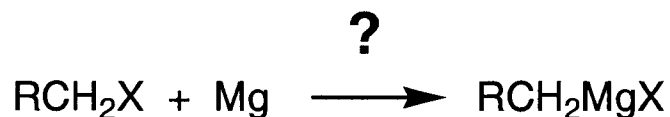
Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents Catalyzed by a Low-Valent Iron Complex**

Rubén Martín and Alois Fürstner*

ACIE **2004**, 3955.

“no method of organic synthesis superior to that of Grignard’s is known, and indeed there is scarcely any sphere of organic chemistry outside it’s scope.”

-Prof. H.G. Söderbaum, President of the Royal Swedish Academy of Sciences, on Dec. 10, 1912 during the Nobel Prize presentation speech



- 1904 – Tschelintzeff – Based on observations that organic halides are unreactive towards magnesium in benzene, and that reaction can be “catalyzed” by the addition of ether or tertiary amines – proposed that an oxonium or quaternary ammonium salt is the actual reactant with magnesium

- 1907 – Grignard – quaternary ammonium halides are inert towards magnesium

- 1921 – Meisenheimer and Casper – iodobenzene does not form quaternary ammonium salts

- 1954 – Kharasch and Reinmuth – Ethers/amines don’t “catalyze” the reaction, they just allow the reaction to continue by removing products from the surface of the magnesium, which would otherwise be inactivated

- 1939 – Brun – Placed electrodes in reaction media and monitored current during a Grignard reaction

- found <0.1 coulomb for 2.25 g of magnesium reacted

- 18,903 coulombs are expected for the dissolution of the same amount of magnesium in a normal electrical cell

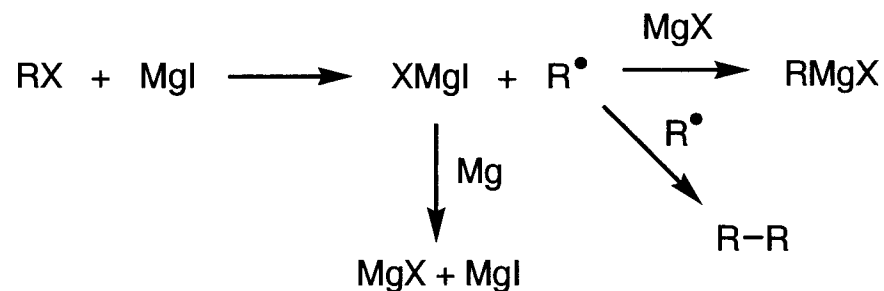
- suggests that Grignard reagent formation is a non-ionic process

Mechanism: Involvement of Radicals

6

Gomberg and Bachmann – to account for magnesium iodide activation of magnesium – “We consider that the magnesium first reacts with the magnesic iodide and gives magnesous iodide; then the latter, being soluble and much more reactive than the metal, is able to remove the halogen from the aryl halide; the aryl groups then partly double up, but largely unite with the MgX groups in the solution.”

J. Am. Chem. Soc. **1927**, *49*, 236.

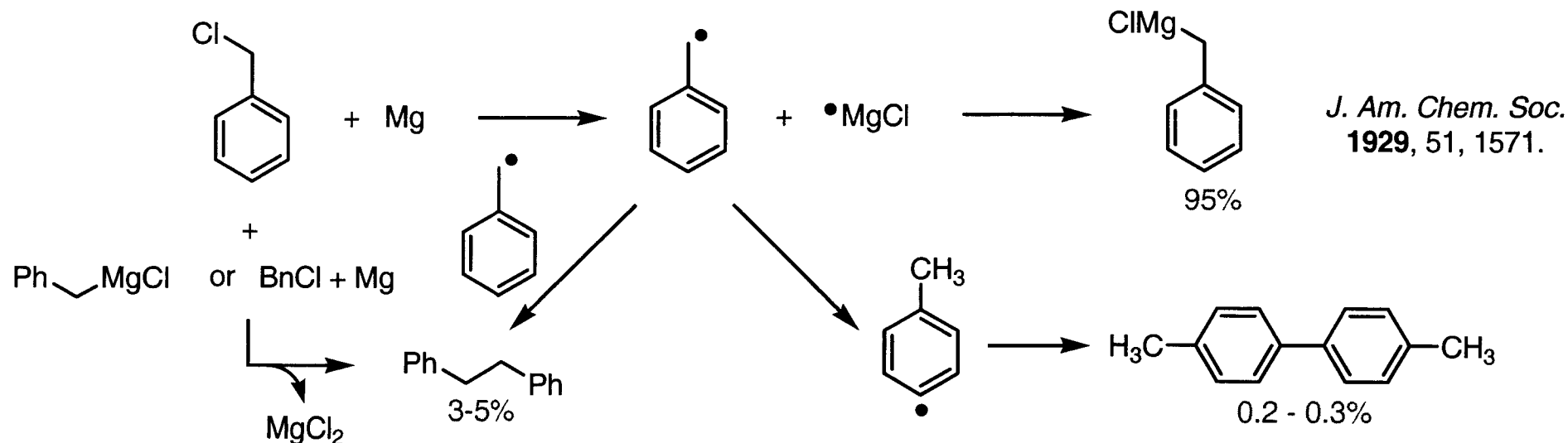


THE FORMATION OF DI-PARA-TOLYL INCIDENTAL TO THE PREPARATION OF BENZYL MAGNESIUM CHLORIDE. THE PROBABLE PRELIMINARY FORMATION OF FREE RADICALS IN THE PREPARATION OF GRIGNARD REAGENTS

BY HENRY GILMAN AND JAMES E. KIRBY

RECEIVED JANUARY 21, 1929

PUBLISHED MAY 6, 1929

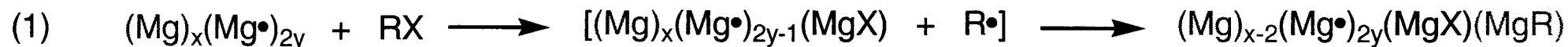


Mechanism: 1954 – Kharasch and Reinmuth

7

$(\text{Mg})_x$ - normal magnesium surface
 $(\text{Mg}\bullet)_{2y}$ - "centers of exceptional reactivity"
 $x \gg 2y$

(MgR) = surface bound $\text{R}\bullet$
 RMgX = Grignard Reagent

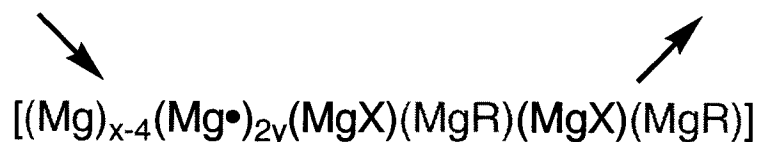
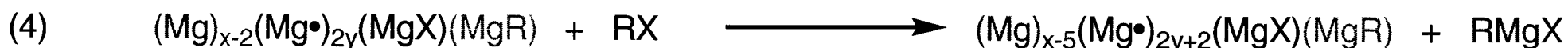
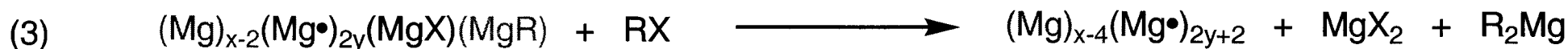


$\text{R}\bullet$ is generated from one $(\text{Mg}\bullet)$
 giving (MgX) and one less $(\text{Mg}\bullet)$;
 therefore, $2y-1$

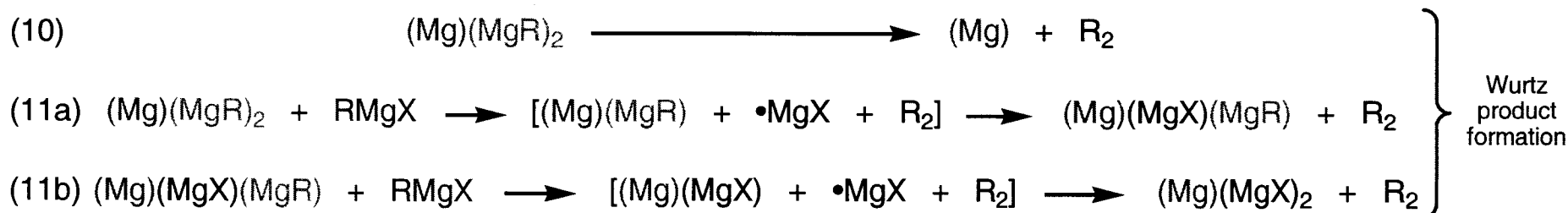
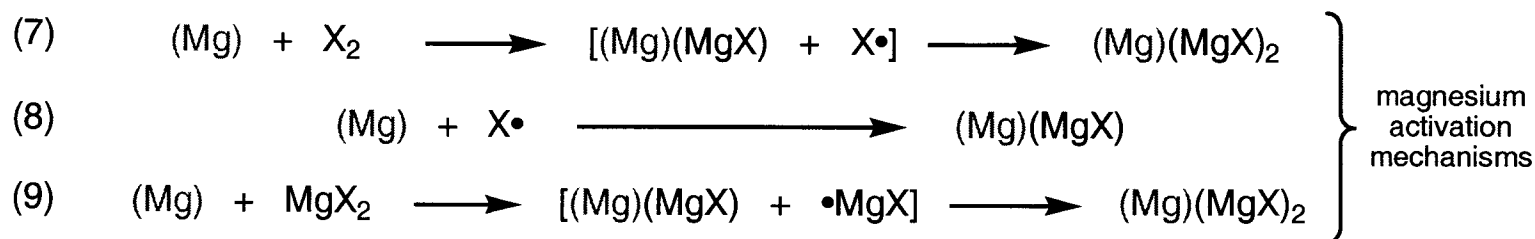
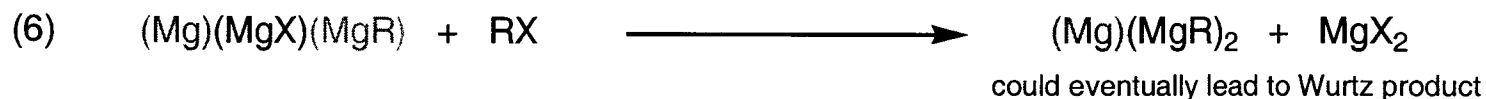
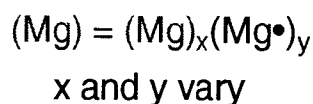
$\text{R}\bullet$ reacts with two (Mg) 's;
 one gives (MgR) , and a new
 $(\text{Mg}\bullet)$ is formed; therefore,
 $x-2$ and $(2y-1) + 1 = 2y$



two new $(\text{Mg}\bullet)$'s are left behind when
 (MgX) and (MgR) combine with RX ;
 therefore, $(x-2)-2 = x-4$ and $2y+2$



Kharasch and Reinmuth – Activation and Byproducts ⁸



Also:
disproportionation reactions - substitute $R_{(+H)} + R_{(-H)}$ for R_2 above
solvent reactions - $H\bullet$ abstraction *etc.*

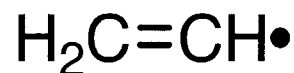
"There would appear to be no compelling reason to regard these radicals as "free" in the sense that they occur in significant numbers in the body of the solution. The processes described might very well take place at the solid liquid interface."

"In the cases of such highly reactive free radicals as the phenyl, or even methyl, the notion that they could survive long enough in the presence of any of the usual Grignard solvents to undergo the reaction $2R\bullet \rightarrow R_2$ to an appreciable extent is absurd."

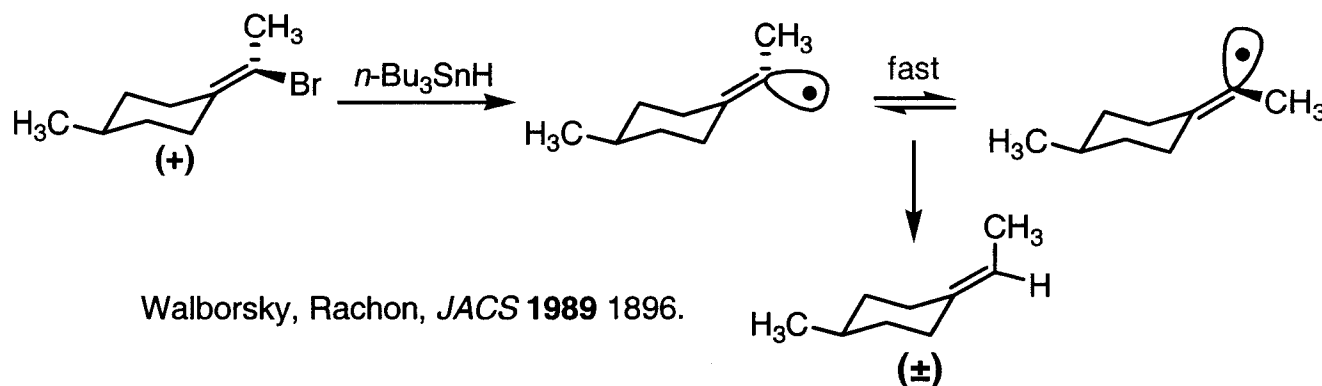
"Whether or not free radicals ever actually escape into the body of the solution in significant quantities is a question that can scarcely be answered with any assurance."

Background: Vinyl and Cyclopropyl Radicals

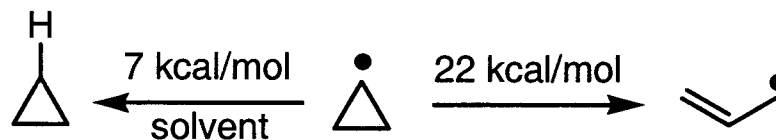
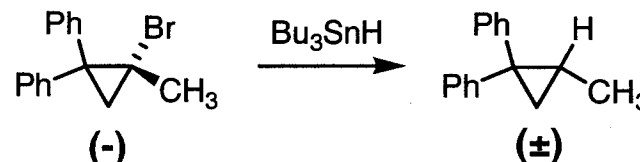
9



- nonlinear (σ -radical, ESR)
- inversion barrier of 2 kcal/mol
- rate of inversion at -170 °C estimated at 3×10^{-10} to 3×10^{-8} sec



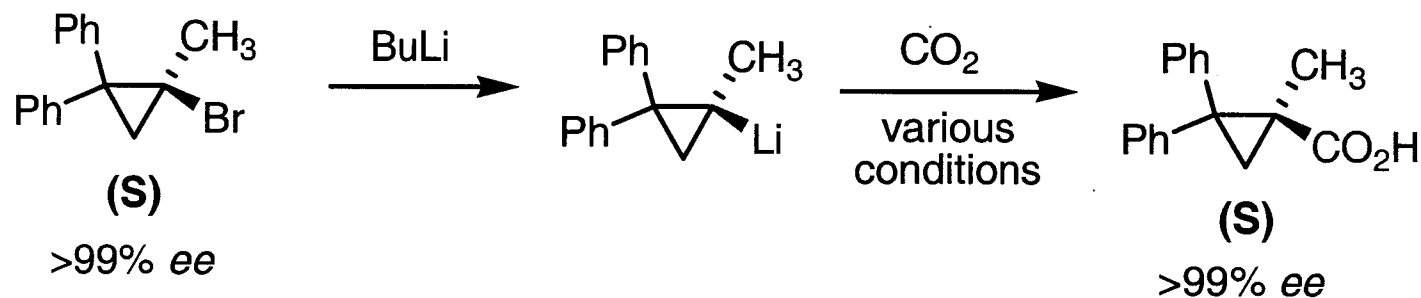
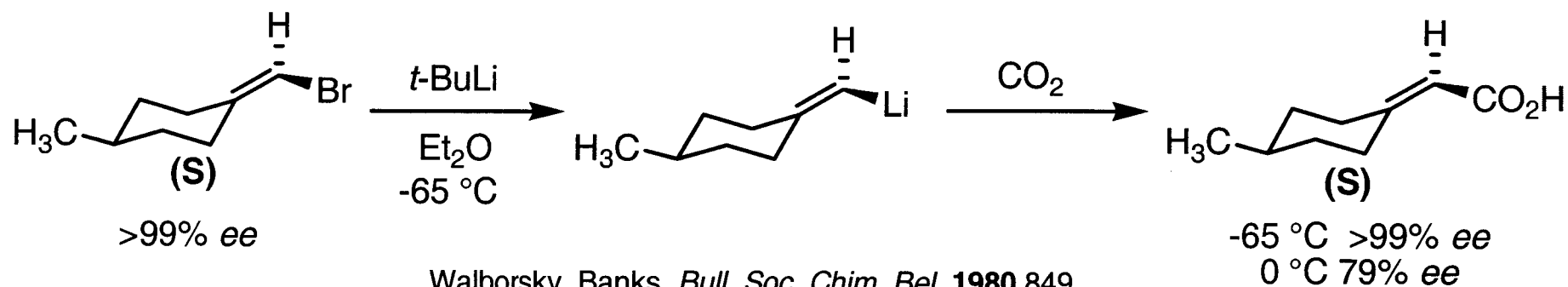
- nonlinear (σ -radical, EPR)
- inversion barrier of 3 kcal/mol
- rate of inversion at 71 °C estimated at 10^{-12} sec



Both vinyl and cyclopropyl radicals are σ (non-planar) radicals with inversion frequencies near diffusion control, that do not maintain configuration when generated in solution

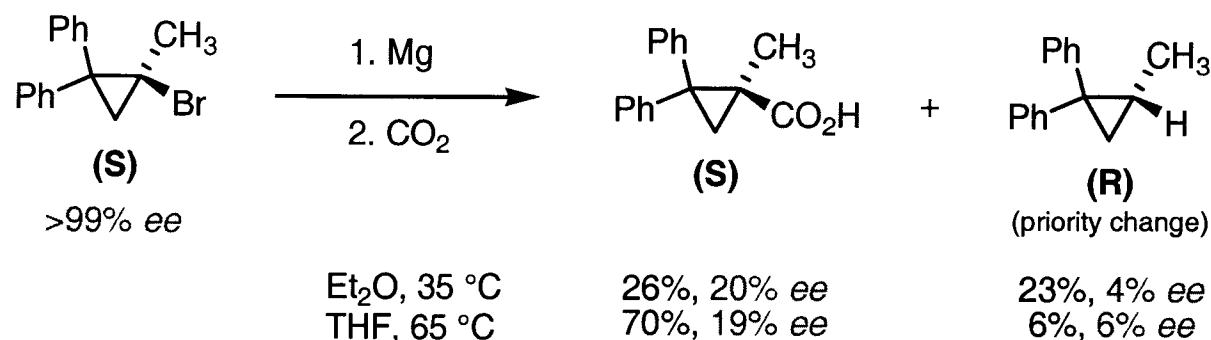
Background: Vinyl and Cyclopropyl Carbanions

10



Walborsky, Impasto, Young, *JACS* **1964** 3283.

While corresponding radicals lose their optical activity, both vinyl (low temp) and cyclopropyl organolithiums seem to be configurationally stable



Partial retention of configuration!

Solvent, temperature, reaction time, and particle size/purity of Mg showed no significant effect on stereochemical outcome and recovered SM was still >99% ee

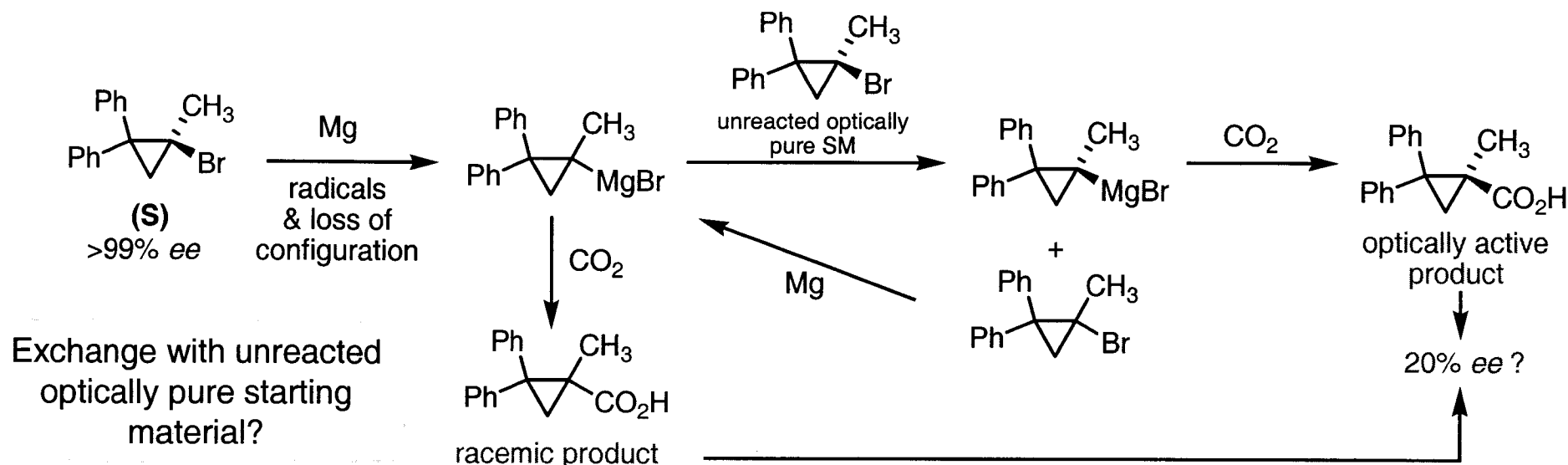
Where did racemization occur?

Racemization expected with cyclopropyl radical formation – what about the stability of the actual Grignard reagent?

Using what you've learned, design an experiment to show that racemization does not occur after the Grignard reagent is formed

Why Partial Retention? – First Hypothesis

12

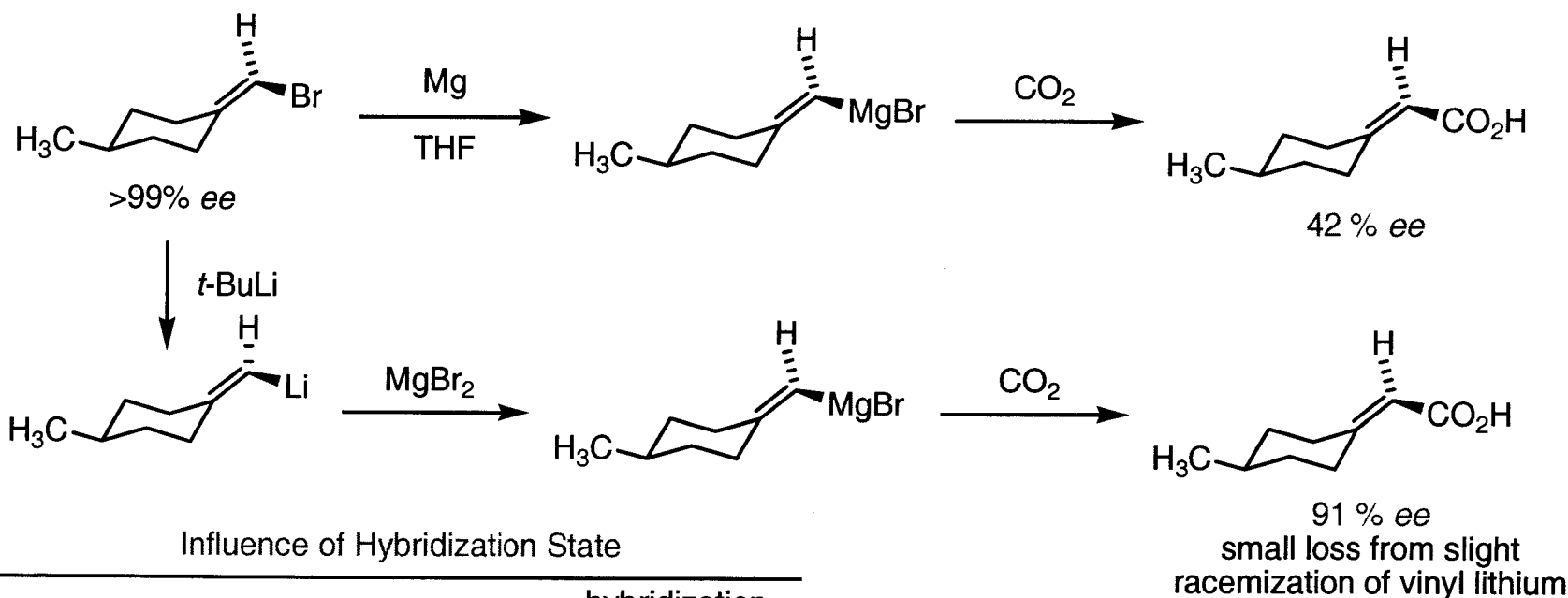


Exchange of Grignard reagents with ordinary alkyl halides:
(Zakharkin, *J. Organometallic Chem.* **1964**, 2, 309.)

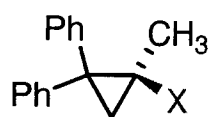


Given this fact, predict the outcome of changing the halogen in the above alkyl halide

Design an experiment to directly test for the proposed exchange



RX	ee of acid	hybridization of chiral C
vinyl above	42	sp^2
cyclopropyl	18	$\text{sp}^{2.28}$
(<i>c</i> -Hexyl)CHClCH ₃	0	sp^3

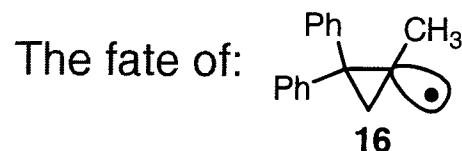


X	% ee product
Cl	26
Br	19
I	2

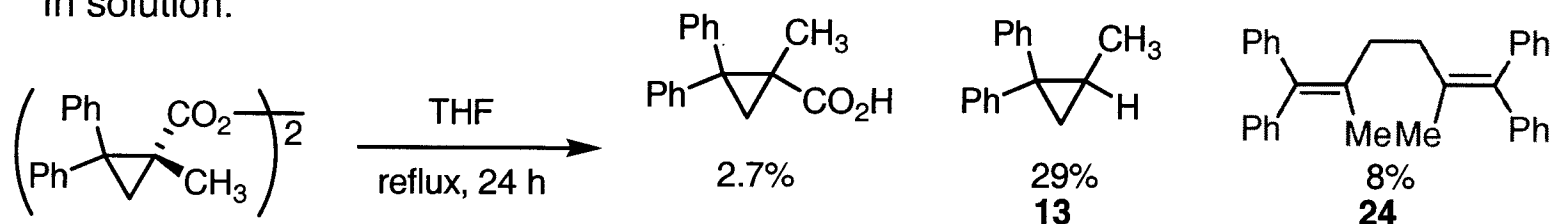
Energy of C-X decreases in the order $\text{Cl} > \text{Br} > \text{I}$

\therefore Cl should lead to more “tight” radical pairs explaining the trend observed

“At this point, it appeared that the radical intermediate was not entirely free...it was postulated that electron transfer occurs from the metal surface into the carbon-halogen bond to lead to a *tight anion radical – cation radical pair*, the collapse of which on the surface yielded Grignard reagent with complete retention of configuration.”

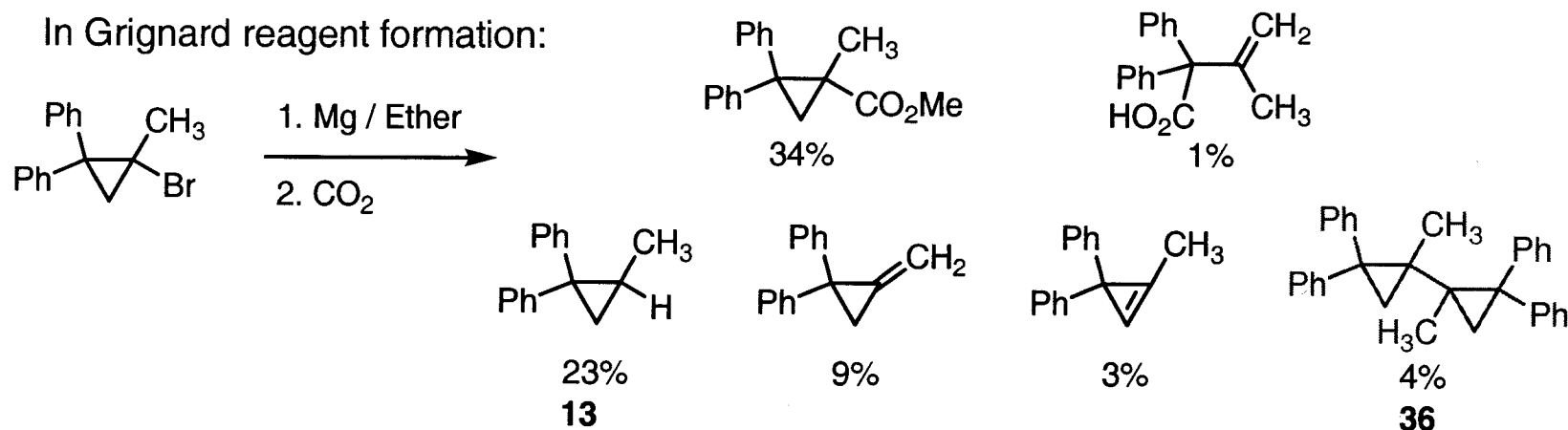


In solution:

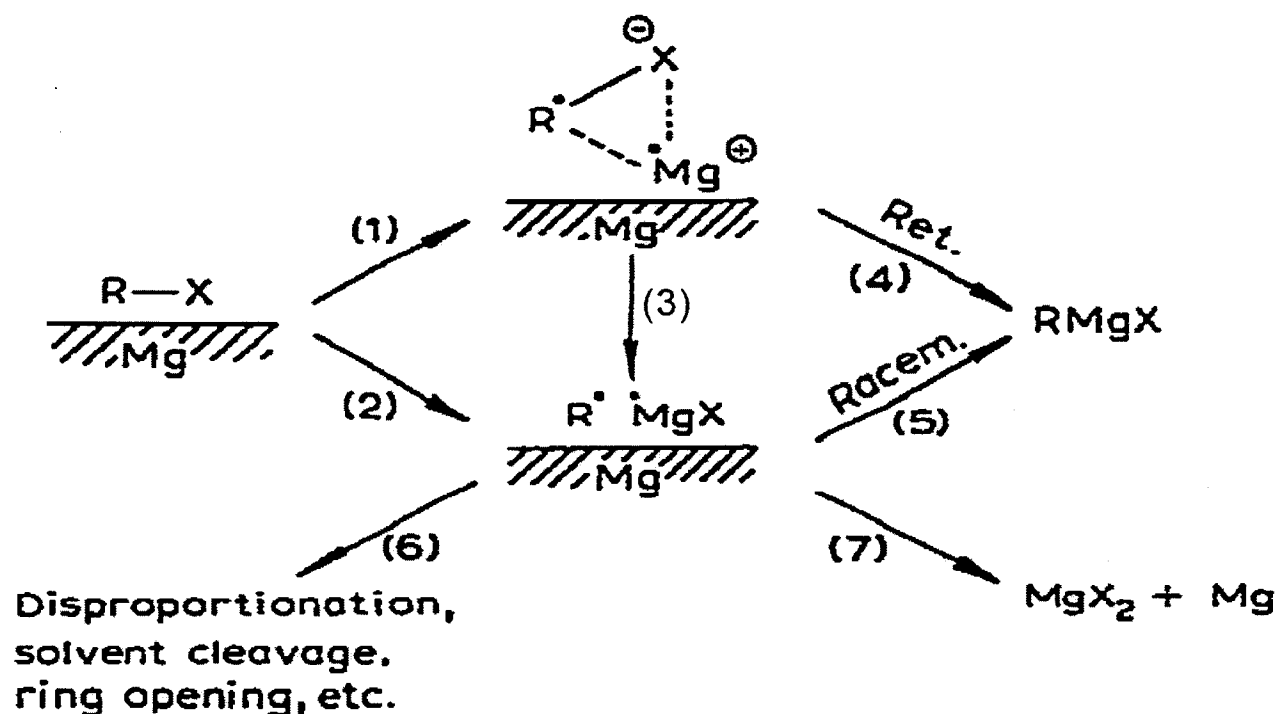


and "a complex mixture containing esters and lactones which we have not completely identified"

In Grignard reagent formation:



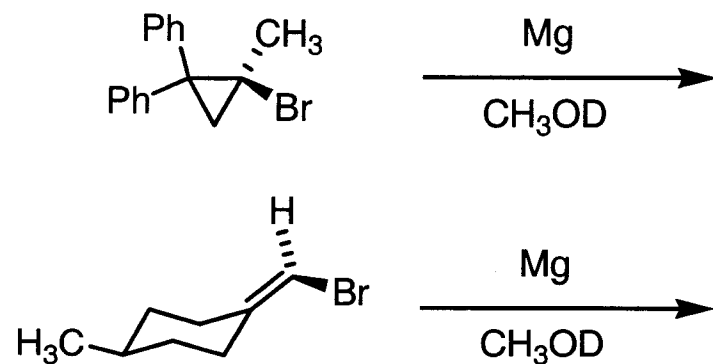
"Formation of dimer **36** provides strong evidence for the involvement of radical intermediates that are not free in solution... There is little doubt that if... radical **16** were generated in solution, it would either cleave the solvent to form cyclopropane **13**, or undergo ring opening to the more stable allyl radical, which would dimerize to yield **24**."



- (1) – electron transfer from Mg surface to σ^* antibonding orbital of carbon-halogen bond to produce a tight radical anion-radical cation pair as a transition state or intermediate.
- (2) – free radicals (on Mg surface) generated through concerted electron transfer bond breaking from Mg surface
- (3) – free radicals (on Mg surface) generated through dissociation of tight pair to produce a surface bound loose pair
- (4) – collapse of tight anion radical-cation pair leads to Grignard reagent formation with complete retention
- (5) – loose pair leads to “mainly” racemic reagent by a 180° rotation of the carbon radical relative to the surface and combination with Mg halide radical
- (6) – other reactions at the surface leading to byproducts (including dimerization) and a few radicals will escape and react with solvent
- (7) – pathway for destruction of magnesiumous halide – extra left over when dimerization occurs at surface

Ret. vs. Rac. depends on carbon-halogen bond strength – more retention for $\text{Cl} > \text{Br} > \text{I}$ and $\text{sp}^2 > \text{sp}^{2.28} > \text{sp}^3$

- Many examples of Grignard radicals giving very different product distributions as compared to solution analogs generated in an alternate way:
 - radicals that can rearrange
 - radical traps
 - radicals derived from optically active starting materials
 - alkyl, allenyl, vinyl, benzyl examples
- Kinetic studies – late 70's/early 80's – Volger and Whitesides Groups
 - RDS involves electron transfer from the metal surface
 - whether it's pathway 1 or 2 was never answered
- Spectroscopic studies
 - CIDNP – radicals are involved in Grignard reagent formation
 - EPR – radicals are involved in Grignard reagent formation
 - As to the surface nature of the generated radicals – Walborsky draws many conclusions but none are very convincing
- Reactions in CH_3OD ($\text{RX} + \text{Mg}$ in the presence of CH_3OD)

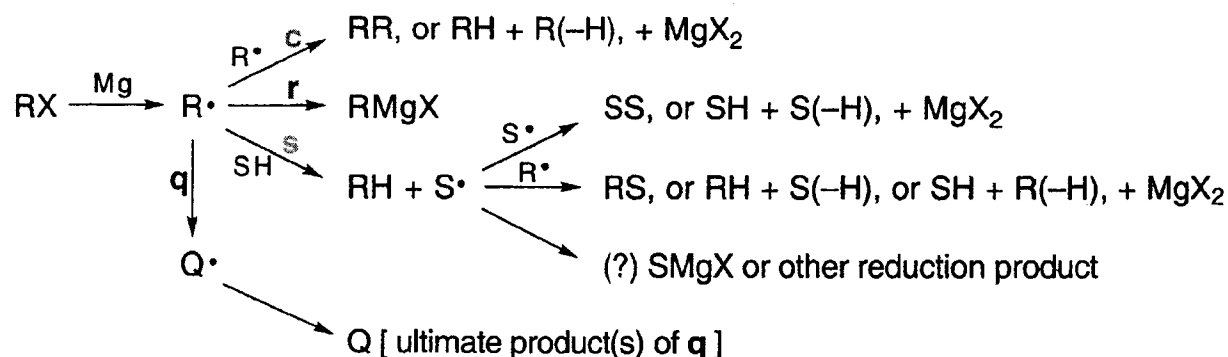


Predict the outcome and significance of these experiments

Pathway R and Adsorption vs. Diffusion

17

Pathway R

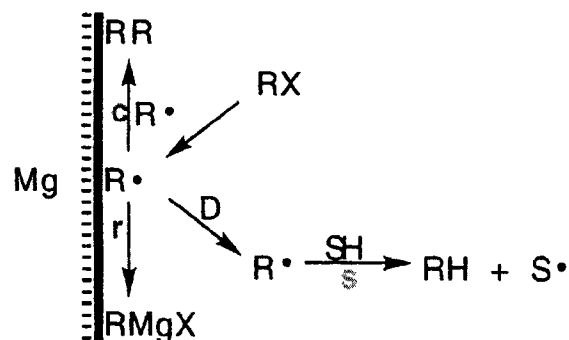


r = reduction – G. reagent formation

c = coupling/disproportionation

s = solvent attack

q = isomerization/trapping



AAD

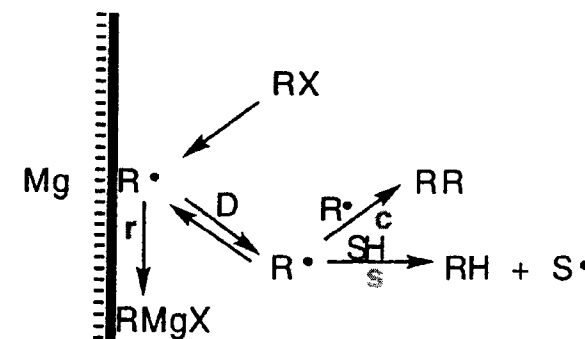
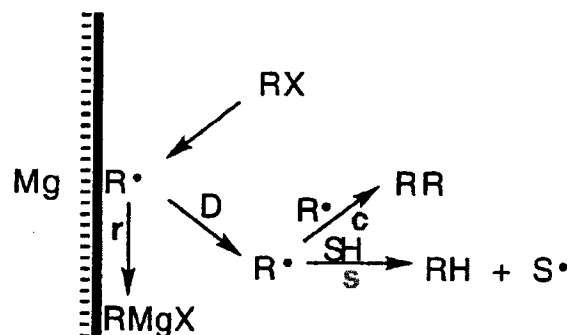
KRW Mechanism

(Adsorbed, Adsorbed,
Diffused for r, c, s)

-R• remains on Mg for r, c

-None of the R• that escape
count towards RR

ADD
(Adsorbed, Diffused,
Diffused for r, c, s)
-Adsorbed R• only undergo
r or diffuse



DDD

Garst Mechanism

(Difused for r, c, s)

-Difused R• account for all
reactions

Analytic Solution of the Equations of the Simplified D Model. Mathematical Specification. We treat the steady state in the limit as s approaches zero. The equations to be satisfied are A1–A8.

$$D \frac{d^2[R]}{dx^2} = (k_1 + k_5)[R] + 2k_c([R]^2 + [R][Q] + [R][S]) \quad x \neq s \quad (A1)$$

$$D \frac{d^2[Q]}{dx^2} = -k_1[R] + k_5[Q] + 2k_c([R][Q] + [Q]^2 + [Q][S]) \quad (A2)$$

$$D \frac{d^2[S]}{dx^2} = -k_5([R] + [Q]) + 2k_c([R][S] + [Q][S] + [S]^2) \quad (A3)$$

$$D \frac{d([R]/dx)}{dx} - (d[R]/dx)_{x=0} = v \quad (A4)$$

$$(d[R]/dx)_0 = \delta[R]_0 = (d[R]/dx)_s = \delta[R]_s \quad s \rightarrow 0 \quad (A5)$$

$$(d[Q]/dx)_0 = \delta[Q]_0 = \delta[Q]_s \quad s \rightarrow 0 \quad (A6)$$

$$(d[S]/dx)_0 = \delta[S]_0 = \delta[S]_s \quad s \rightarrow 0 \quad (A7)$$

$$\lim_{x \rightarrow 0} [R] = \lim_{x \rightarrow 0} [Q] = \lim_{x \rightarrow 0} [S] = \lim_{x \rightarrow 0} (d[R]/dx) = \lim_{x \rightarrow 0} (d[Q]/dx) = \lim_{x \rightarrow 0} (d[S]/dx) = 0 \quad (A8)$$

Equations A1–A3 describe the steady state. The left side of each equation is the rate of increase of $[R]$, $[Q]$, or $[S]$ at x due to diffusion, while the right side is the rate of decrease due to chemical reaction. Equation A4 replaces eq A1 when $x = s$; it equates the net flux of R out of the plane $x = s$ in both directions (Fick's first law) to the production flux v of R in that plane. Equations A5–A7 express the radiation boundary condition,⁶ which is appropriate for a surface that is partially absorbing (reacting) and partially reflecting toward species R , Q , and S . Equation A8 specifies boundary conditions at infinity.

The radiation boundary condition is equivalent to the assumption that the flux of an surface reaction is proportional to the concentration of the reactive intermediate at the surface. For example, the flux of RZ formation can be expressed as $b[R]_0$, where b is a constant of proportionality. By Fick's first law, the flux is also given by $D(d[R]/dx)_0$. Equating these two rate expressions gives $(d[R]/dx)_0 = (b/D)[R]_0$. The surface reactivity parameter δ is thereby identified as b/D .

Equalities involving $(d[R]/dx)_s$ and $[R]_s$ appear in eq A5 because we treat the limit in which $s \rightarrow 0$. The derivative $d[R]/dx$ is discontinuous at $x = s$, where $[R]$ has its maximum value.

Scaling to dimensionless parameters according to eq 1–8, gives eq A9–A16 from A1–A8.

$$d^2R/dx^2 = G^2R + (1/2)(R^2 + RQ + RS) \quad x \neq s \quad (A9)$$

$$d^2Q/dx^2 = (1 - G^2)R + Q + (1/2)(RQ + Q^2 + QS) \quad (A10)$$

$$d^2S/dx^2 = -(R + Q) + (1/2)(RS + QS + S^2) \quad (A11)$$

$$(dR/dx)_0 - (dR/dx)_{x=s} = V \quad (A12)$$

$$(dR/dx)_0 = \Delta R_0 = (dR/dx)_s = \Delta R_s \quad s \rightarrow 0 \quad (A13)$$

$$(dQ/dx)_0 = \Delta Q_0 = \Delta Q_s \quad s \rightarrow 0 \quad (A14)$$

$$(dS/dx)_0 = \Delta S_0 = \Delta S_s \quad s \rightarrow 0 \quad (A15)$$

$$\lim_{x \rightarrow 0} R = \lim_{x \rightarrow 0} Q = \lim_{x \rightarrow 0} S = \lim_{x \rightarrow 0} (dR/dx) = \lim_{x \rightarrow 0} (dQ/dx) = \lim_{x \rightarrow 0} (dS/dx) = 0 \quad (A16)$$

Since we treat the limit in which s approaches 0, we solve eq A9–A11 for concentration profiles only in the region $x \geq s$. In the following, R , Q , S , and related symbols represent scaled concentrations in this region of space only. Symbols such as R_0 represent the limit of R_s as s approaches zero.

Solution for T. Using $T = R + Q + S$, we obtain eq A17 as the sum of eq A9–A11. It is also the equation for the steady

$$d^2T/dx^2 = (1/2)T^2 \quad (A17)$$

state for the mechanism of Figure 3. Letting Z be dT/dx allows eq A17 to be replaced by A18 and A19, the quotient of which

$$dZ/dx = (1/2)T^2 \quad (A18)$$

$$dT/dx = Z \quad (A19)$$

is eq A20, which integrates to eq A21. The constant of integration

$$dZ/dT = (1/2)(T^2/Z) \quad (A20)$$

$$dT/dx = -T^{3/2} \quad (A21)$$

is zero because Z and T approach zero as x approaches infinity. Since dT/dx must be negative for $x > s$, the negative square root of T^3 is required.

Integration of eq A21 gives eq 9. The constant C is evaluated at $x = s$ in the limit as s approaches zero. Here T_0 is yet to be determined.

$$T = 4/(X + C)^2 \quad C = 2/T_0^{1/2} \quad (9)$$

Defining Y_{TZ} (yield of TZ) as the fraction of the intermediates R (Figure 1) or T (Figure 3) that are converted to TZ, we express Y_{TZ} in terms of Δ and T_0 . Equation A22 follows from eq A12

$$(dT/dx)_0 - (dT/dx)_{x=s} = V \quad (A22)$$

and the facts that dQ/dx and dS/dx , but not dR/dx , are continuous at $x = s$. In the limit as s approaches zero, $(dT/dx)_s$ approaches $(dT/dx)_0$, the scaled flux of formation of TZ, which can also be written as ΔT_0 (sum of eq A13–A15). Substituting ΔT_0 for $(dT/dx)_s$ and $-T_0^{3/2}$ for $(dT/dx)_0$ (eq A21) gives eq 10. Since ΔT_0 and V are the fluxes of formation of TZ and R ,

$$\Delta T_0 + T_0^{3/2} = V \quad (10)$$

respectively, Y_{TZ} is given by eq A23. Eliminating T_0 from eq

$$Y_{TZ} = \Delta T_0/V = (V - T_0^{3/2})/V = 1 - 8/C^3V \quad (A23)$$

10 and A23 gives eq 11, which is solved for Y_{TZ} , so that both T_0

$$Y_{TZ}^3/(1 - Y_{TZ})^2 = F = \Delta^3/V = 3D^2k_1^3/4k_5C^3 \quad (11)$$

(eq A23) and C (eq 9) are obtained, allowing the computation of the concentration profile of T . Since TZ and TT are the only products, Y_{TT} (yield of TT, fraction of R or T consumed in TT formation) is simply $1 - Y_{TZ}$ (eq 12).

$$Y_{TT} = 1 - Y_{TZ} \quad (12)$$

Solution for P. Equation A24 is both the sum of eq A9 and

$$d^2P/dx^2 = P + (1/2)PT \quad (A24)$$

A10 ($P = R + Q$; $T = P + S$) and the corresponding equation for the mechanism of Figure 6. Defining U (eq A25) and substituting $4/U^2$ for T (eq 9) gives eq A26.

$$U = X + C \quad (A25)$$

$$d^2P/dU^2 = [1 + 6/U^2]P \quad (A26)$$

This equation is placed in Riccati–Bessel form by the substitution $z = iU$ (eq A27).⁷ The general solution is eq A28, where

$$z^2(d^2P/dz^2) + (z^2 - 6)P = 0 \quad z = iU \quad (A27)$$

$$P = A'j_2(z) + B'y_2(z) \quad (A28)$$

A' and B' are constants and $j_2(z)$ and $y_2(z)$ are independent spherical Bessel functions (eq A29 and A30).⁷

$$j_2(z) = (3z^2 - 1) \sin(z) - 3z^{-1} \cos(z) \quad (A29)$$

$$y_2(z) = -3z^{-1} \sin(z) - (3z^2 - 1) \cos(z) \quad (A30)$$

Replacing z with iU and the resulting trigonometric functions with their hyperbolic equivalents gives eq A31. Since P must

$$P = (A'/i)[(3/U^2 + 1) \sinh(U) - (3/U) \cosh(U)] + B'[(3/U^2 + 1) \cosh(U) - (3/U) \sinh(U)] \quad (A31)$$

be real, A' must be imaginary or zero. Let $A = A'/i$, where A is real, and replace $\cosh(U)$ by its equivalent $\exp(-U) + \sinh(U)$. Equation A32 results. The outer boundary condition, that P

$$P = (3/U^2 + 1)[B \exp(-U) + (B - A) \sinh(U)] + (3/U)[A \exp(-U) - (B - A) \sinh(U)] \quad (A32)$$

approaches zero as U (or X) approaches infinity, requires that $A = B$, eq A33–A35. In eq A35, P_0 and M_0 are the limits of

$$P = B \exp(-U) (U^2 + 3U + 3)/U^2 = BM \quad (A33)$$

$$M = \exp(-U) (U^2 + 3U + 3)/U^2 \quad (A34)$$

$$B = P_0/M_0 \quad (A35)$$

P_s and M_s as s approaches zero.

Equation A36 is an analogue of eq A22. Eq A37 follows from eq A33 by taking the derivative. Equations A13 and A14, A34

$$(dP/dx)_0 - (dP/dx)_{x=s} = V \quad (A36)$$

$$(dP/dx) = (dP/dU) = -B \exp(-U) [U^3 + 3U^2 + 6U + 6]/U^3 \quad (A37)$$

and A35, and A37 and the fact that $U_0 = C$ (eq A25) provide eq A38. The yield Y_{PZ} of PZ ($RZ + QZ$) is given by eq A39.

$$P_0 = VC/[\Delta C + (C^3 + 3C^2 + 6C + 6)/(C^2 + 3C + 3)] \quad (A38)$$

$$Y_{PZ} = \Delta P_0/V \quad (A39)$$

Thus, P_0 and Y_{PZ} can be calculated from Δ and V . They are independent, as they must be, of $G^2 - 1$, the scaled value of k_1 . The yield of SZ is given by eq A40.

$$Y_{SZ} = Y_{TZ} - Y_{PZ} \quad (A40)$$

Solution for R. The solution for R is precisely parallel to that for P . Defining u (eq A41 and A42) and substituting $4G^2/u^2$ for

$$u = G(X + C) = GU \quad (A41)$$

$$u_0 = GC \quad (A42)$$

T (eq 9) in eq A9 gives eq A43, which is identical in form with

$$d^2R/du^2 = [1 + 6/u^2]R \quad (A43)$$

eq A26 with R and u of eq A43 corresponding to P and U of eq A26. Equations A44–A46, analogues of eq A33–A35, express

$$R = A \exp(-u) (u^2 + 3u + 3)/u^2 = AN \quad (A44)$$

$$N = \exp(-u) (u^2 + 3u + 3)/u^2 \quad (A45)$$

$$A = R_0/N_0 \quad (A46)$$

the solution in terms of R_0 , the limit of R_s as s approaches zero. Equations A47–A50 are analogues of eq A37–A40.

$$(dR/dx) = G(dR/du) = -GA \exp(-u) [u^3 + 3u^2 + 6u + 6]/u^3 \quad (A47)$$

$$R_0 = VC/[\Delta C + (u_0^3 + 3u_0^2 + 6u_0 + 6)/(u_0^2 + 3u_0 + 3)] \quad (A48)$$

$$Y_{RZ} = \Delta R_0/V \quad (A49)$$

$$Y_{QZ} = Y_{PZ} - Y_{RZ} \quad (A50)$$

Yields of Solution Products. The yields of solution products are related to the integrals I of functions of T , P , and R from $X = 0$ to infinity (eq A51–A58), where T , P , and R are given by eq 9, A33, and A44.

$$I(P) = \int_0^\infty P \, dX \quad (A51)$$

$$I(R) = \int_0^\infty R \, dX \quad (A52)$$

$$I(TT) = \int_0^\infty T^2 \, dX \quad (A53)$$

$$I(PT) = \int_0^\infty PT \, dX \quad (A54)$$

$$I(RT) = \int_0^\infty RT \, dX \quad (A55)$$

$$I(PP) = \int_0^\infty P^2 \, dX \quad (A56)$$

$$I(RP) = \int_0^\infty RP \, dX \quad (A57)$$

$$I(RR) = \int_0^\infty R^2 \, dX \quad (A58)$$

For the integrations of eq A51–A58, we have used both numeric (trapezoid rule and Gauss quadrature from $X = 0$ to 20 with analytic integrations of the remaining tails, which have very small magnitudes, to infinity) and analytic methods, with agreement among them. Equations A59–A66 give the results of analytic integrations.

$$I(P) = B[(3/C)E_2(C) + 3E_1(C) + e^{-C}] \quad (A59)$$

$$I(R) = (A/G)[(3/GC)E_2(GC) + 3E_1(GC) + e^{-GC}] \quad (A60)$$

$$I(T^2) = 16/3C^3 \quad (A61)$$

$$I(PT) = (4B/C)[(3/C^3)E_4(C) + (3/C)E_3(C) + E_2(C)] \quad (A62)$$

$$I(RT) = (4A/C)[(3/G^2C^3)E_4(GC) + (3/GC)E_3(GC) + E_2(GC)] \quad (A63)$$

$$I(P^2) = B^2[(9/C^3)E_4(2C) + (18/C^3)E_3(2C) + (15/C)E_2(2C) + 6E_1(2C) + e^{-2C}/2] \quad (A64)$$

$$I(RP) = AB[(9/G^2C^3)E_4((G+1)C) + 9(G+1)/G^2C^3E_3((G+1)C) + 3(G^2+3G+1)/G^2C^3E_2((G+1)C) + 3(G+1)/G^2C^3E_1((G+1)C) + e^{-(G+1)C}/(G+1)] \quad (A65)$$

$$I(R^2) = (A^2/G)[(9/G^3C^3)E_4(2GC) + (18/G^3C^3)E_3(2GC) + (15/GC)E_2(2GC) + 6E_1(2GC) + e^{-2GC}/2] \quad (A66)$$

$$\int_0^\infty e^{-ay} dy/y^n = a^{-(n-1)} \int_0^\infty e^{-at} dt/t^n = a^{-(n-1)} E_n(ab) \quad (A67)$$

Here the $E_n(x)$ are exponential integrals (A67) that are described, for example, by Abramowitz and Stegun, who also tabulate their values and give accurate numerical approximations.⁸ Except for a multiplicative constant, each term of each integrand of eq A51–A58 (when expressed as a function of U) is of the form of eq A67.

The fluxes of formation of solution products, corresponding to the mass-action terms for product formation in eq A9–A11, are given by combinations of these integrals, taking into account the relationships among T , P , R , Q , and S . The yield of each product is the formation flux divided by V , the flux of formation of R (eq A68–A75).

$$Y_{PH} = I(P)/V \quad (A68)$$

$$Y_{RH} = I(R)/V \quad (A69)$$

$$Y_{QH} = [I(P) - I(R)]/V \quad (A70)$$

$$Y_{TT} = (1/2)I(T^2)/V = 8/C^3V \quad (\text{compare eq 12}) \quad (A71)$$

$$Y_{PP} = (1/2)I(P^2)/V \quad (A72)$$

$$Y_{PS} = 3[I(PT) - I(P^2)]/V \quad (A73)$$

$$Y_{SS} = (1/2)[I(T^2) + I(P^2) - 2I(PT)]/V \quad (A74)$$

$$Y_{RR} = (1/2)I(R^2)/V \quad (A75)$$

$$Y_{RQ} = 3[I(RP) - I(R^2)]/V \quad (A76)$$

$$Y_{QQ} = (1/2)[I(P^2) + I(R^2) - 2I(RP)]/V \quad (A77)$$

$$Y_{RS} = 3[I(RT) - I(RP)]/V \quad (A78)$$

$$Y_{QS} = 3[I(PT) + I(RP) - I(P^2) - I(RT)]/V \quad (A79)$$

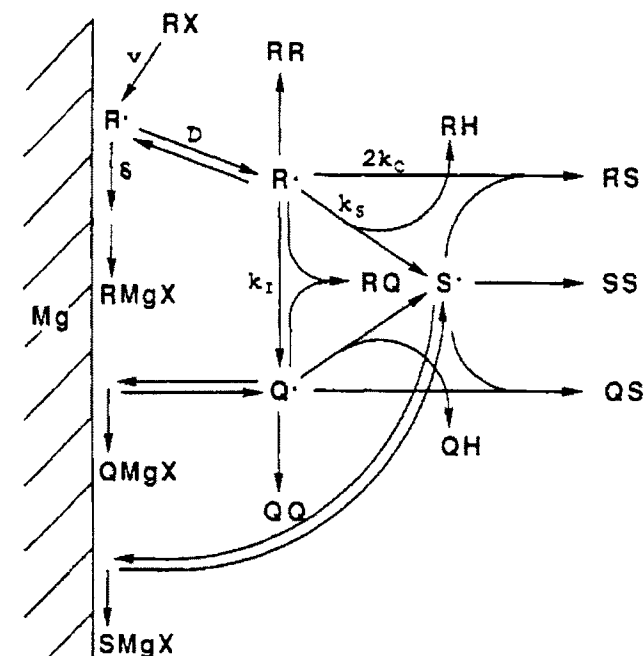
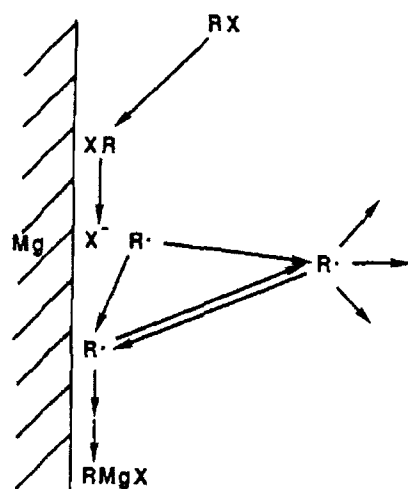
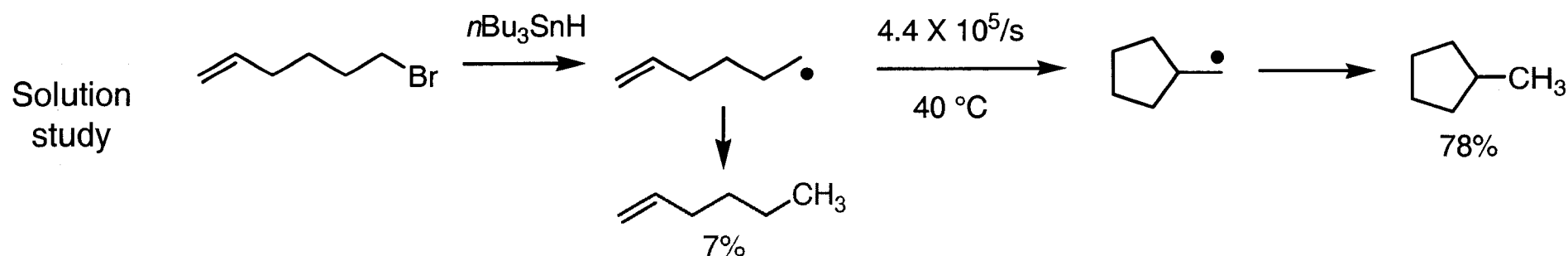


Figure 1. Basic D model for Grignard reagent formation. RX is converted to R• and X• at the magnesium surface. R• diffuses freely but must return to the surface to be converted there to Grignard reagent. While in solution, R• reacts with solvent, isomerizes, couples, etc.

- D = diffusion – refers to the fact that reactive intermediate diffuse freely in solution
- Mg surface is treated as a uniform plane of infinite extent ($x=0$, x axis goes perp. to plane)
 - R• is formed in solution at a constant flux v
- R• in solution can undergo surface reaction to give RMgX or solution reactions shown
 - Q• is an isomerized (first-order) version of R• (inversion, radical clocks, etc.)
- Important parameters – intermediates R•, Q•, and S• have the same diffusion coefficient, the reactions of R• and Q• with solvent have the same rate constant, reactions of R•, Q•, and S• among themselves have the same rate constant, and the reaction of R•, Q•, and S• at the surface have the same reactivity parameter. Other parameters are the flux of R• formation and the rate constant for the isomerization of R• to Q•



Grignard reagent formation

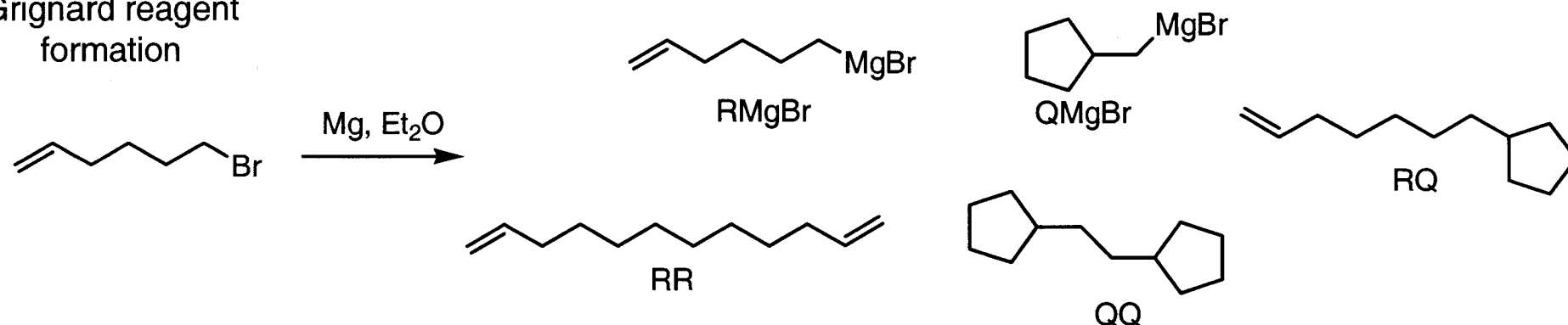


Table I. Products of the Reaction of 5-Hexenyl Bromide in Ether with Magnesium at 40 °C

	calcd ^a	exptl ^b
RMgBr	88%	85.5 (2.0)%
QMgBr	3.0%	2.5 (0.5)%
PP	8.7%	9.0 (3.0)%
RH (from R [•] + SH)	0.068%	
QH (from Q [•] + SH)	0.059%	
(RR)/(PP)	66%	64.5 (5.0)%
(RQ)/(PP)	26%	28.0 (2.5)%
(QQ)/(PP)	8.2%	7.5 (2.0)%

$$\text{PP} = \text{RR} + \text{QQ} + \text{RQ}$$

“The agreement between the calculated and experimental values is astonishing. With no adjusted parameters, the calculation reproduces closely every detail of the experimental product distribution, that is, the absolute yields of five products, two Grignard reagents, and three dimers.”

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Extent of Isomerization to Q
in experimental results:

Grignard reagent ~ 3%
dimers ~ 21%

What do the observed extents of
isomerization tell us about the mechanism?
Why are they different?

	τ (s)	$[R^\bullet]$ (M)
“Solution”	$>10^{-4}$	$<10^{-6}$
Grignard	$\sim 3 \times 10^{-8}$	10^{-5} to 10^{-3}

- Lifetimes of alkyl Grignard radicals are limited by r (reduction to $RMgX$) to at least three orders of magnitude shorter than the lower limit of lifetimes of “solution” radicals
- “solution” radicals will undergo reactions with first-order rate constants up to 10^4 s^{-1} while “Grignard” radicals will not – they don’t stay around long enough
 - Example: cyclization of 5-hexenyl radical ($k = 4 \times 10^5 \text{ s}^{-1}$)
 - solution – cyclization is essentially complete
 - Grignard – only about 3-10% cyclization

Kharasch-Reinmuth "In the cases of such highly reactive free radicals as the phenyl, or even the methyl, the notion that they could survive long enough in the presence of any of the usual Grignard solvents to undergo the reaction $2R\bullet \rightarrow R_2$ to an appreciable extent is absurd."

C = coupling (second order)
S = solvent reaction (first order)

$$\text{rate}_C / \text{rate}_S = 2k_C[R\bullet]^2 / k_S[R\bullet] = (2k_C/k_S)[R\bullet]$$

Typical values:
 $2k_C = 3 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$
 $k_{S,\text{THF}} = 6 \times 10^3 \text{ s}^{-1}$

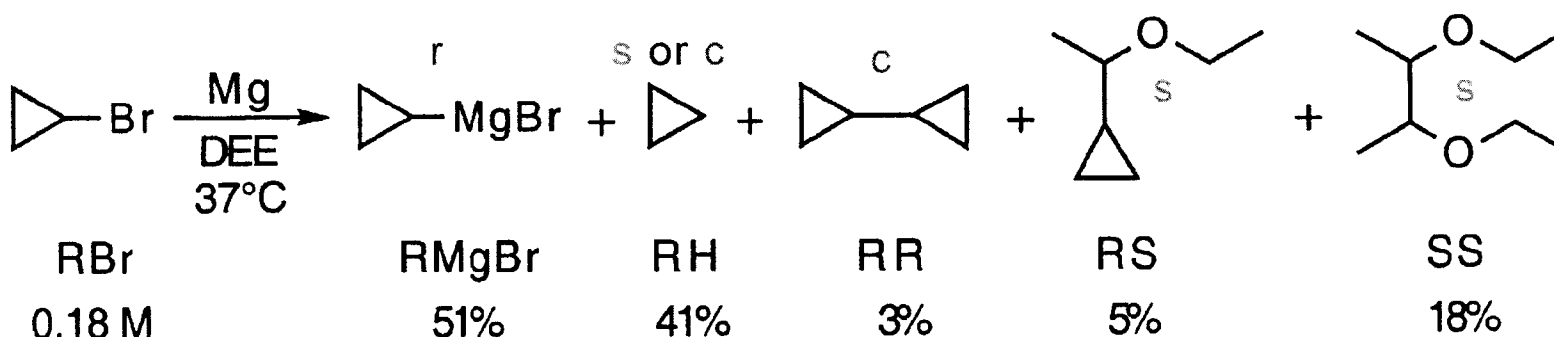
$$\text{so, } 2k_C/k_S = 5 \times 10^5 \text{ M}^{-1}$$

If steady state $[R\bullet] = 2 \times 10^{-6} \text{ M}$, yields of coupling and solvent cleavage are the same.

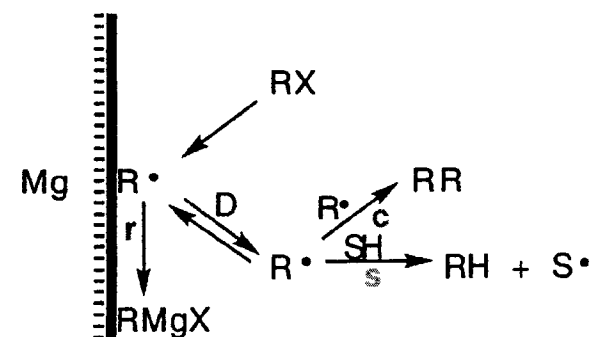
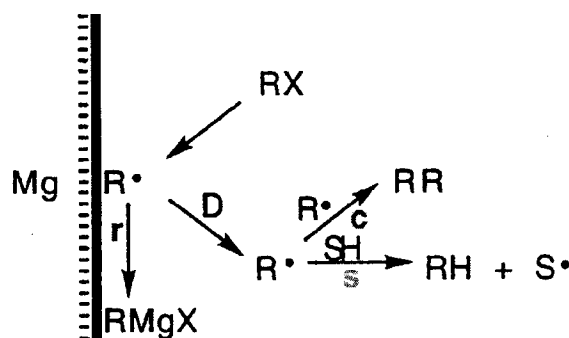
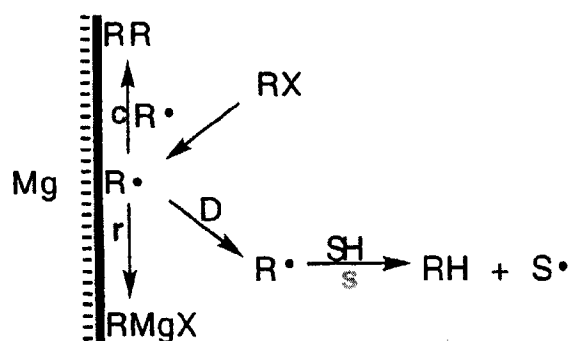
Typical radical concentrations in solution are much less, so solvent reaction dominates.

Radicals formed at a solid surface tend to "pile up", even if they are freely diffusing in solution.
In a Grignard reaction, steady-state $[R\bullet]$ can reach or exceed 10^{-4} M , a value where coupling is 50 times that of reaction with solvent.

Some early conclusions about the fate of diffusing radicals are incorrect



Since cyclopropyl bromide gives significant quantities of s products, a simple experiment can be done to distinguish between the three mechanisms below:



mechanism	prediction		
	r	c	s
AAD	same	same	same
ADD	same	up	down
DDD	up	up	down

What simple experimental change will allow us to fill in this table with predictions for the effect on yield for each set of reactions? Fill in the table.

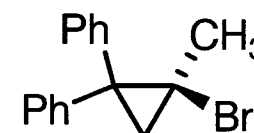
Cyclopropyl Bromide: Results

Solvent isotope effects on yields of product of reactions of cyclopropyl bromide

Solvent	[MgX ₂] ₀	RBr _{0.40 M} $\xrightarrow[\text{SH(D), 37}^\circ\text{C}]{\text{Mg}}$				
		RMgBr ^a	+ RR ^a	+ SS ^a	+ RS ^a	
DEE	0	52	3	7	3	
DEE-d ₁₀	0	54	14	1.2	3	r up, c up, s down
DEE	2.6 M MgBr ₂	71	2	5	2	
DEE-d ₁₀	2.6 M MgBr ₂	84	4	0.04	0.3	r up, c up, s down
THF	0	58	—	16	10	
THF-d ₈	0	70	—	0.3	3	r up, s down
THF	0.50 M MgCl ₂	68	—	4	6	
THF-d ₈	0.50 M MgCl ₂	80	—	0.07	6	r up, s down

^a Yield (%). — means solvent interference prevented accurate GC determination, yields “appeared to be low”

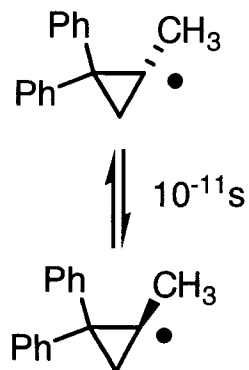
Best fit is DDD



Similar results for Walborsky's cyclopropane (from his data!!) – they “ignore the implications”

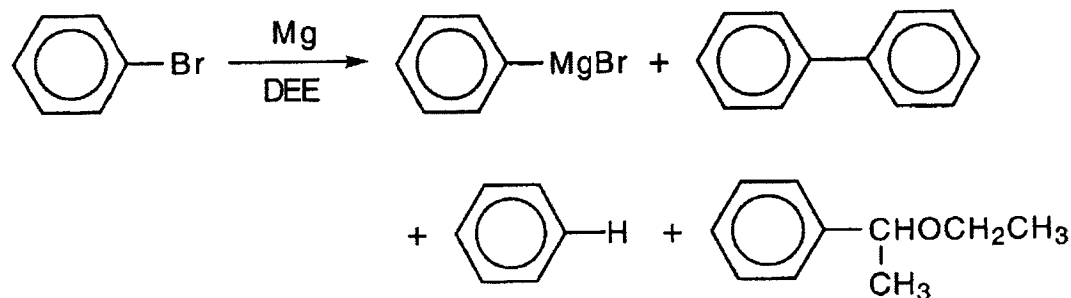
Proves R•'s that leave the surface of Mg – can be converted to RMgBr

“Even so, simple DDD cannot be the whole mechanistic story. It does not account for observations of partial retention of configuration.”



Lifetime of R• = 10⁻⁷ s, plugging in these values to the D-model gives a predicted retention of ~1% while 26% is observed.

Vinyl halides – similar Grignard reactions – DDD is major mechanism by analogy – but again, not the whole story



Radical products form, but often in very low yield – perhaps radical mechanism is only a minor pathway

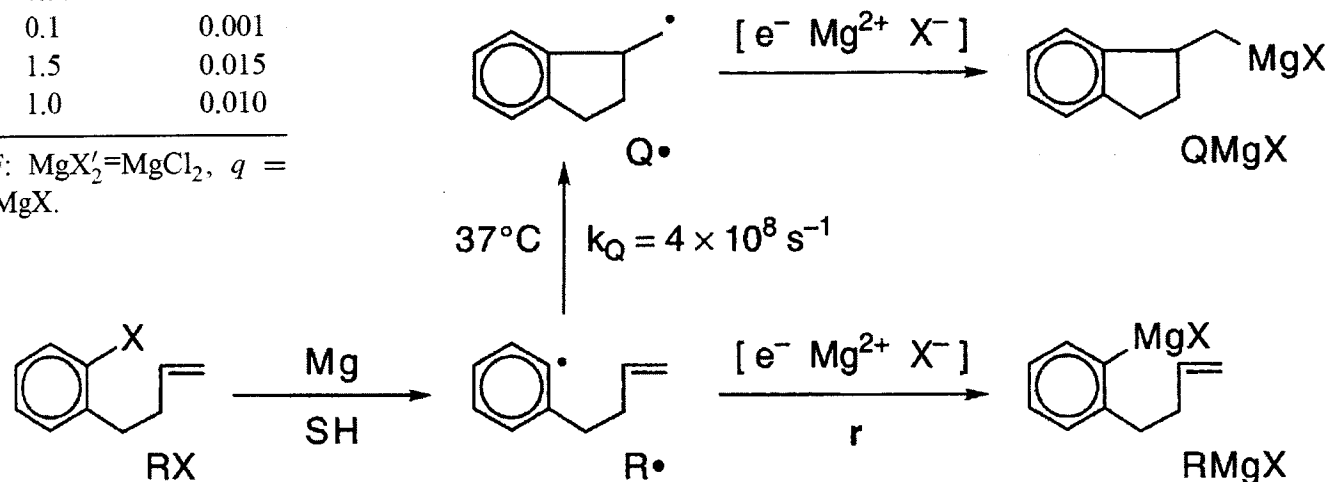
Cyclization in Grignard reactions of *o*-(3-butenyl)phenyl bromide and iodide
RMgX (%) = GC yield of RH after quench

Solvent	X	[MgX ₂ '] ₀ (M)	RMgX (%)	QMgX (%)	<i>q</i>
DEE	Br	0	82	16	0.20
DEE	Br	2.6	82	3.7	0.045
DEE	I	0	56	25	0.45
DEE	I	2.6	90	8.3	0.092
THF	Br	0	101	0.35	0.0035
THF	Br	0.50	101	0.1	0.001
THF	I	0	98	1.5	0.015
THF	I	0.50	96	1.0	0.010

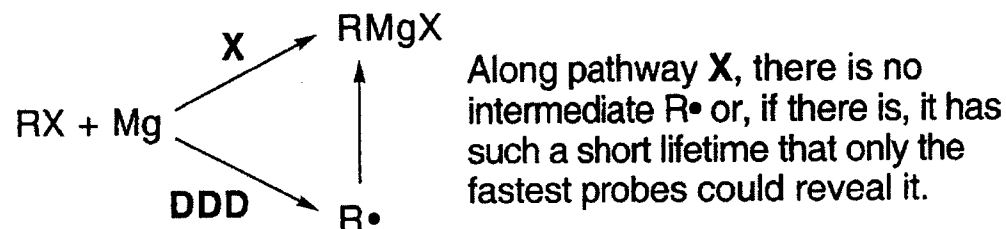
Reactions at 37°C. DEE: MgX₂'=MgBr₂, THF: MgX₂'=MgCl₂, *q* = [QMgX + s]/RMgX. Since *s* = 0, *q* = QMgX/RMgX.

DDD fails to calculate products accurately for aryl halides. A secondary path (perhaps the major path in this case) is proposed.

Radical trap experiment

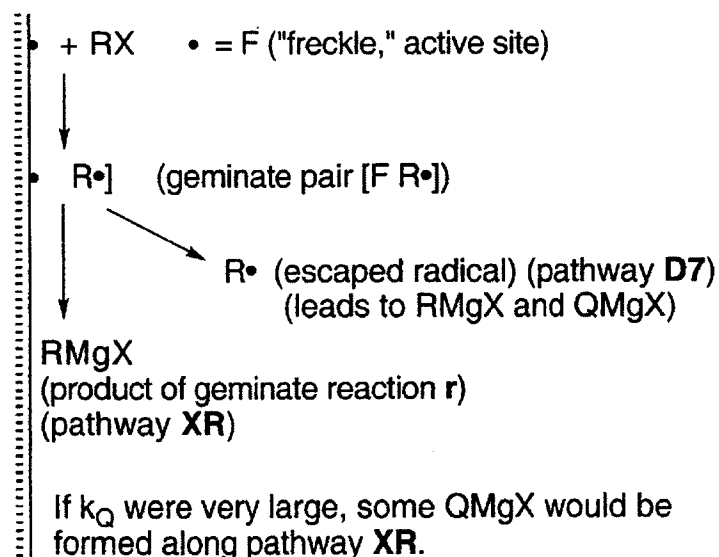


DDD/X

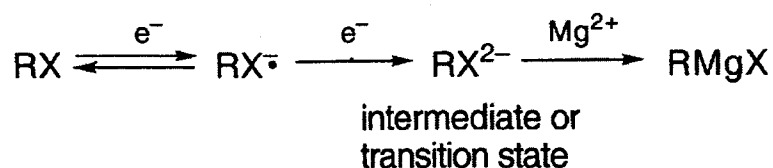


D7/XR

no intermediate = D7/X0



Dianion Pathway XD_i

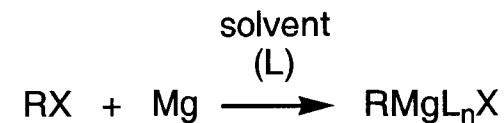


Mg^{2+} counterions are present at all stages.

2.10.13. Conclusions

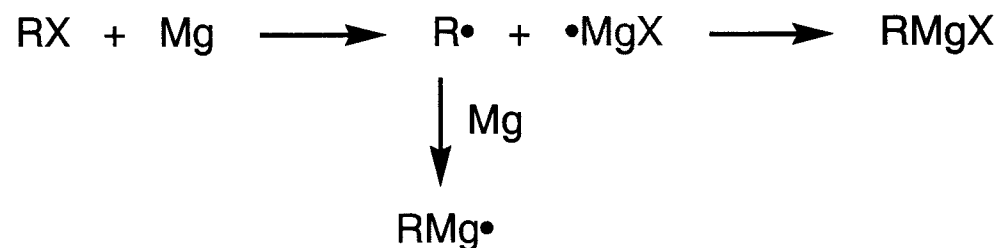
- (1) **DDD** cannot be the exclusive pathway for aryl halides because some of the implied lifetimes τ_R of R^\bullet are unrealistically short. There must be a pathway **X**.
- (2) If aryl halides react partly through **D7**, **DDD** with $\tau_R = 1 \times 10^{-7}$ s, and partly through a pathway **X0**, along which there is no isomerization, then the extent of **X0** is sometimes very nearly 100%.
- (3) A pathway **XR**, along which R^\bullet is an intermediate with an extremely short lifetime, is an alternative to **X0**.
- (4) Attempts to detect **XR** using very fast probes have provided inconsistent results that are subject to other interpretations.
- (5) If a pathway **XR** applied, then the lifetimes of intermediate radicals R^\bullet would be so short that many would remain at Mg_Z in geminate pairs $[R^\bullet X^-]$ until they were reduced to $RMgX$. Since radicals R^\bullet interact with partial bonding to adjacent halide ions, $[R^\bullet X^-]$ is really a version of the anion-radical $RX^{\bullet-}$. Because reductions of $RX^{\bullet-}$ proceed through dianion transition states $[RX^{2-}]^\ddagger$ a pathway through $[R^\bullet X^-]$ is a dianion pathway **XD_i**.
- (6) If there is a transition state that resembles π^*-RX^{2-} , a pathway **XD_i** could explain why the extent of pathway **X** increases with increasing conjugation.
- (7) **XD_i** should be favored by the increased reducing power provided by the more polar ether THF and the presence of salts ($MgBr_2$, $MgCl_2$), as is observed.
- (8) The balance of available evidence favors **XD_i** as the pathway that competes with **R**. If so, then **XD_i** is negligible for alkyl halides and **R** is negligible for aryl halides in THF. In other cases pathways **R** and **XD_i** are both significant.

Grignard reagent formation – Mg goes from unsolvated metallic state to Mg^{2+} ionic state, coordinated by solvent molecules

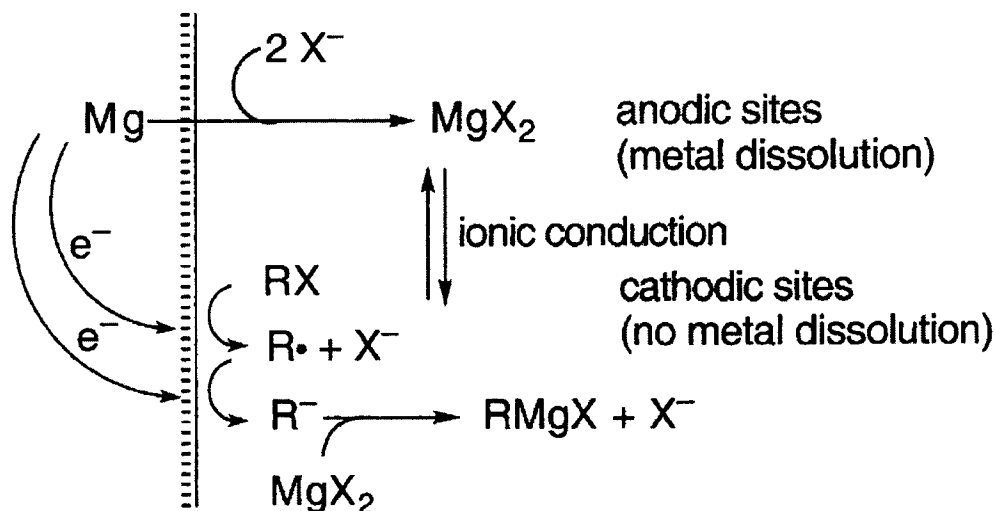


In solution: $2\text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2$ Schlenk equil.
aggregation, complex ion formation, and solubilities also governed by complex equilibria

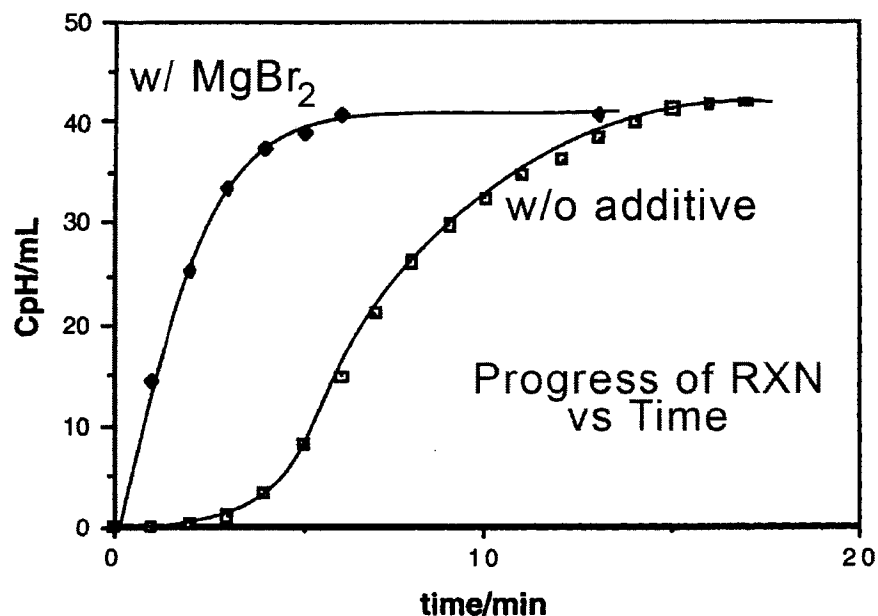
Often seen in the literature:



No evidence for $\cdot\text{MgX}$ or $\text{RMg}\cdot$ has been discovered



- Reduction of RX and R^\bullet driven by dissolution of Mg^{2+} from Mg at anodic sites
- If no reduction occurred (no RX), Mg would be left with extra electrons – and corrosion process would soon stop (development of unlike charge separation)

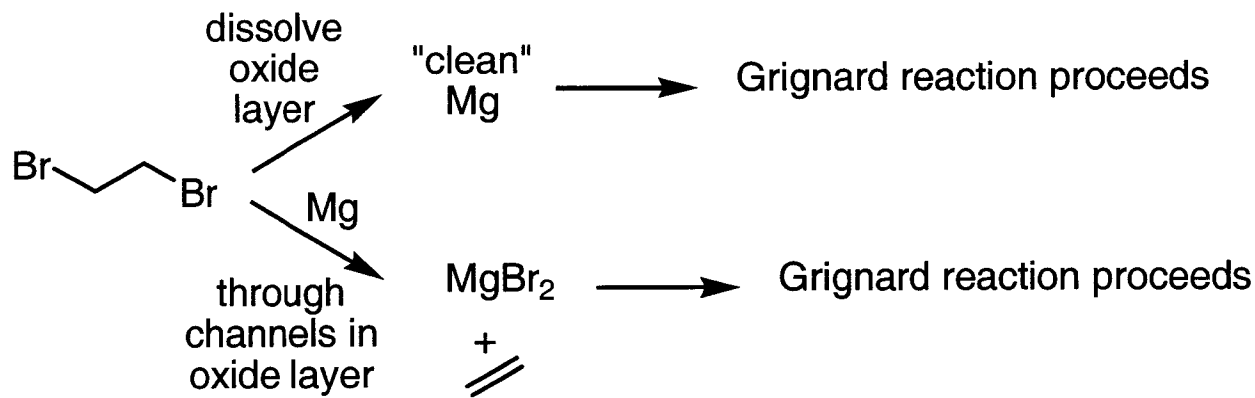


Could explain why MgX_2 additive eliminates the induction period in normal Grignard reactions

X-ray photoelectron spectroscopy (XPS) shows the “oxide” layer is $\text{Mg}(\text{OH})_2$ about 16 Å thick, containing some $\text{Mg}(\text{HCO}_3)_2$ on the outside

What is responsible for the induction period when dibromoethane is used?

- surface cleaning of the oxide layer (Mg obtains metallic luster as RXN proceeds)
- autocatalysis – polar solutes promote Grignard reactions

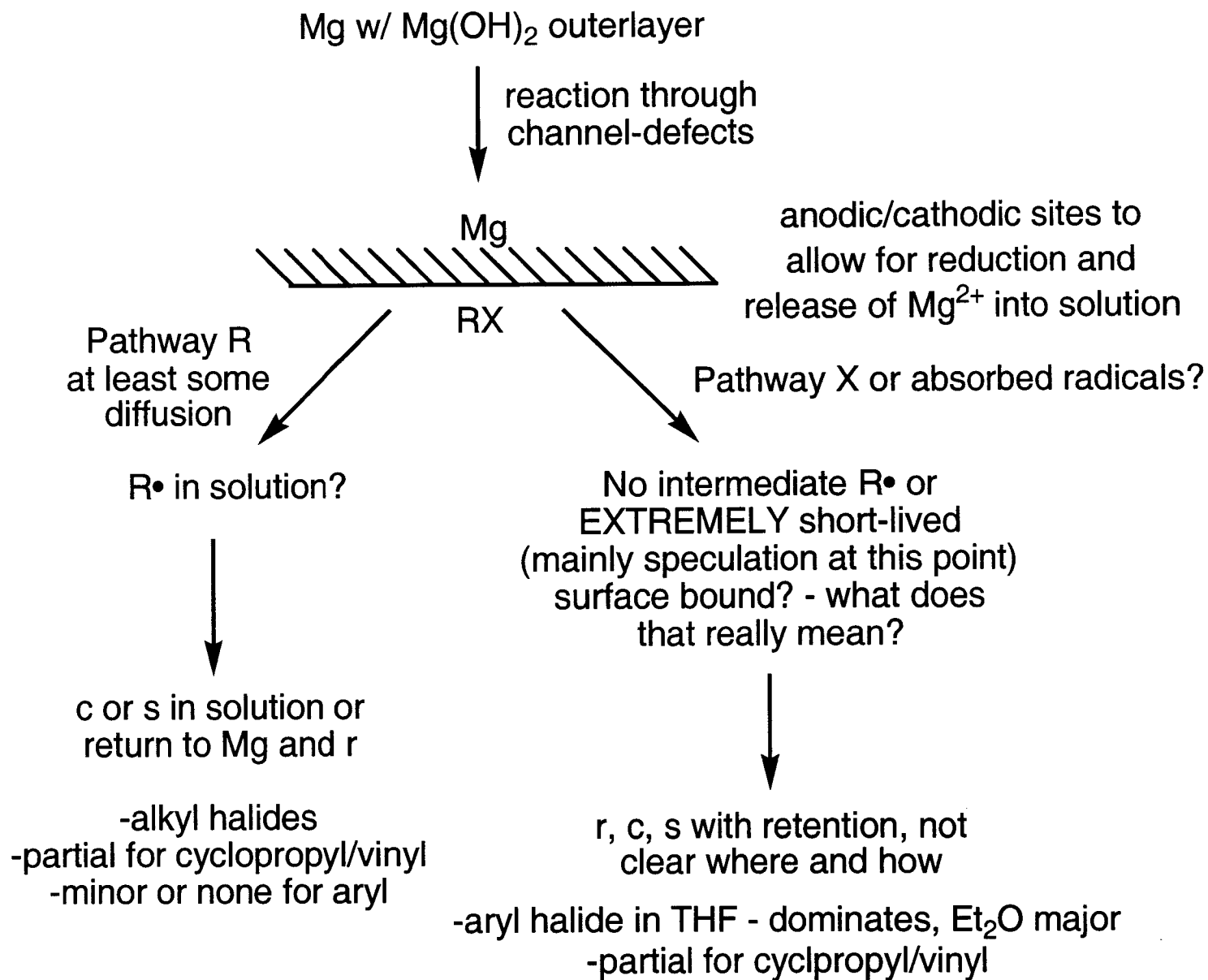


Prepared Mg surfaces of differing “purity” – more or less channel-defects and found:

- $\text{Mg}(\text{OH})_2$ stops reaction of DBE w/ Mg – DBE doesn't dissolve it.
- Seepage through channel-defects allows reaction to take place
- Hydroxide crust flakes off by underlying reaction giving “clean” Mg
- Doesn't explain why there is NO induction period with MgX_2 additive in DEE – perhaps it swells or dissolves the $\text{Mg}(\text{OH})_2$ and increases the reducing power of Mg by stabilizing Mg^{2+} in solution

Conclusions – Overall Mechanistic Picture

31



Garst about Adsorption Model:

“A theory that lacks sufficient predictive competence to be falsifiable also lacks sufficient predictive competence to be useful. A useless theory has no value to science, regardless of how plausible or esthetically pleasing it may be...The predictive incompetence of adsorption models diminishes the usefulness of a correct theory and makes it hard to disprove an incorrect one.”

Walborsky about the D-model:

“this model was based on assumptions, accommodations in the kinetic treatment, and error in both diffusion concept and nature of the reactive surface...the basic assumption...that all radicals generated in the reaction leave the magnesium surface and diffuse freely in solution – is untenable.”

J.F. Garst, B.L. Swift, *J. Amer. Chem. Soc.* **1989**, *111*, 241.

C. Hamdouchi, H.M. Walborsky, in: G.S. Silverman, P.E. Rakita (Eds.), *Handbook of Grignard Reagents*, Dekker, New York, 1996, pp. 145-218.