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Historical Note

Homo coupling, disproportionation and cross coupling of alkyl groups. Role of the transition metal catalyst

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Abstract

Silver is an effective catalyst for the homo coupling of the Grignard reagent and alkyl halide when both alkyl groups are the same. Copper(I) catalyzes the cross coupling of Grignard reagents and alkyl bromides when carried out in tetrahydrofuran solutions at low temperatures. Facile vinylation of the Grignard reagent can be achieved with alkenyl bromides using an iron catalyst. Oxidation–reduction concepts are important in the formulation of these catalytic processes. © 2002 Published by Elsevier Science B.V.

Keywords: Catalytic; Alkyl coupling; Copper(I); Silver(I); Iron

1. Introduction

Thirty years ago, the homoleptic alkylmetals of the transition elements were considered by and large to be too unstable to serve as synthetic reagents and useful intermediates, although the seminal review by Cotton [1] and the encyclopedic monograph by Kharasch and Reinmuth [2] provided the cornerstones for some intriguing possibilities. We felt that the core of the problem lay in our lack of basic understanding of why (and how) the transition-metal analogues of main group organometals, particularly the alkyl derivatives, are so unstable.

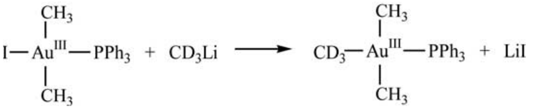
The formation of carbon–carbon bonds for organic synthesis can be represented by the coupling of organometallic reagents (including alkyllithium and Grignard reagents) with organic derivatives, such as alkyl halides among others.

$$\mathrm{RMgX} + R'\text{–}\mathrm{X} \xrightarrow{[\mathrm{M}]} \mathrm{R}\text{–}R' + \mathrm{MgX_2} \qquad (1)$$

The organic moieties, R and R′ in Eq. (1) can either be saturated alkyl, aryl, vinyl or acetylenic groups leading to a wide variety of hydrocarbon structures. The most effective catalysts represented in Eq. (1) as [M] are derived from transition-metal complexes. The role of the metal catalysts is varied in these reactions, but they are most commonly involved in the formation of organometallic intermediates RM which subsequently reductively eliminate to the coupled product. Reactions leading to the formation of the key intermediate R–M and the elucidation of the pathways for its decomposition are thus central to the understanding of these catalytic processes.

2. Formation of alkylmetal complexes

Organometals R–M are commonly prepared by metathesis of a transition metal complex with substitution-labile carbanionoid reagents such as Grignard and lithium derivatives.



$$\mathrm{I{-}\overset{CH_3}{\underset{CH_3}{Au^{III}}}{-}PPh_3} + \mathrm{CD_3Li} \longrightarrow \mathrm{CD_3{-}\overset{CH_3}{\underset{CH_3}{Au^{III}}}{-}PPh_3} + \mathrm{LiI} \qquad (2)$$

The formal oxidation state of the metal under these circumstances does not change. Similarly, no change in the formal oxidation state of the metal results from the insertion of an olefin into a ligand–metal bond.

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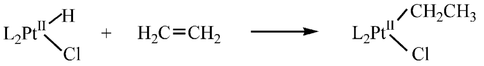
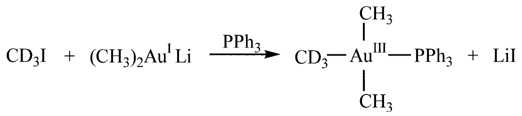


(3)

On the other hand, when either alkyl radicals or alkyl carbonium ions (or their precursors) are used as alkylating agents, the metal center undergoes a change in the formal oxidation state of either one or two, respectively.

$$CH_3^{\bullet} + Cr^{II}en^{2+} \rightarrow CH_3\text{–}Cr^{III}en^{2+} \quad (4)$$


(5)

$$CD_3I + (CH_3)_2Au^{I}Li \xrightarrow{PPh_3} CD_3\text{—}\overset{CH_3}{\underset{CH_3}{Au^{III}}}\text{—}PPh_3 + LiI \quad (5)$$

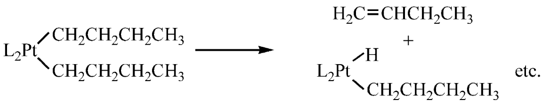
Alkylations of metal centers under these circumstances are considered as oxidative additions.

3. Decomposition of alkylmetal complexes

There are a number of modes by which carbon–metal bonds can be cleaved. Conceptually, they can be represented by the microscopic reverse of each of the processes in Eqs. (2)–(5) which lead to the alkylation of the metal center. Thus, the reverse of Eq. (2) is represented by the well-known electrophilic cleavage of organometals, i.e.

$$(CH_3)_3Au^{III}PPh_3 + HOAc \rightarrow (CH_3)_2Au^{III}(OAc)PPh_3 + H_3C\text{–}H \quad (6)$$

Similarly, β-elimination of hydrogen is probably the most common route by which alkylmetals decompose.

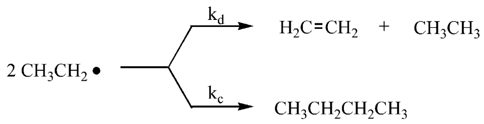


(7)

The homolytic cleavage of alkylmetal bonds, particularly those of main group metals, is known from Paneth's classic experiments to occur at high temperatures. The reverse of Eq. (4), however, does not usually represent the energetically most favored pathway in the decomposition of R–M. Alkyl coupling as a result of homolysis to free radicals, followed by dimerization.

$$R\text{–}M^{\bullet} \rightarrow [M^{\bullet} + R^{\bullet}] \rightarrow R\text{–}R, \quad \text{etc.} \quad (8)$$

is not ubiquitous, although such views were widely held due to the misguided belief that carbon–metal bonds, particularly those involving transition metals, are extremely weak. If alkyl radicals are intermediates in the catalyzed coupling of alkyl groups, they should undergo disproportionation in addition to dimerization.



(9a)
(9b)

Either bimolecular process is not possible without the other, since the ratio k_d/k_c of the rate constants is fixed by the structure of the radical [3]. However, a number of metal-catalyzed couplings are known to proceed without the formation of any disproportionation products, certainly in the amounts dictated by the values of k_d/k_c. Further, the coupling represented in Eq. (1) can occur without the scrambling of R and R′ as would be expected of free-radical intermediates.

The microscopic reverse of oxidative addition in Eq. (5) is represented by reductive elimination which can be intermolecular (Eq. (10a)) or intramolecular (Eq. (10b)).

$$dmgCo^{IV}CH_3 + Br^- \rightarrow dmgCo^{II} + CH_3Br \quad (10a)$$

$$(CH_3)_3Au^{III}PPh_3 \rightarrow CH_3Au^{I}PPh_3 + CH_3CH_3 \quad (10b)$$

Indeed, the combination of oxidative addition in Eq. (5) and reductive elimination in Eq. (10b) is the basis for a catalytic mechanism for alkyl coupling (vide infra).

Organometals are excellent electron donors by virtue of the powerful effect exerted by alkyl groups as σ-donor ligands. Coupled with the ubiquity of oxidation–reduction processes in catalytic cycles, such as the many types of oxidative additions and reductive eliminations, it is reasonable to inquire whether changes in the *formal* oxidation state of an organometal affect its reactivity and modes of reaction. In particular, the redox behavior of a series of dialkylbis(α, α′-bipyridine)iron(II) complexes which contain a pair of *cis*-dialkyl ligands can be exploited in mechanistic studies of reductive elimination [4]. Thus, Fig. 1 shows the existence of three distinct oxidative processes on the positive potential (cyclic voltammetric) scan of the dimethyl analogue *cis*-Me$_2$-

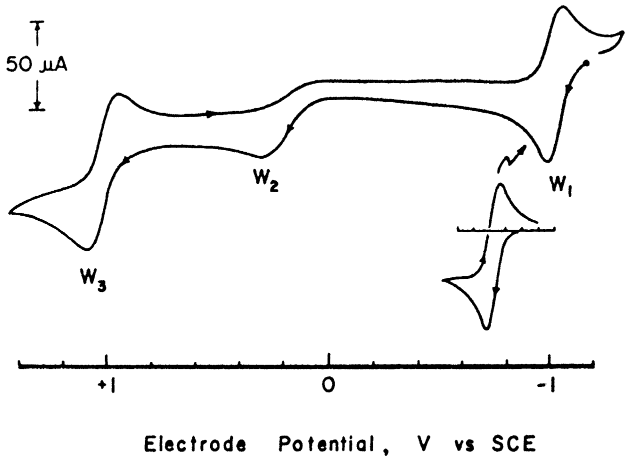


Fig. 1. Cyclic voltammetric behavior of *cis*-dimethyliron(bpy)$_2$ upon initial positive scan at 0.1 V s^{-1}.

$Fe(bpy)_2$ commencing at -1.2 V versus saturated NaCl SCE.

The first wave (W_1), which represents the reversible oxidation with $E^0 = -1.03$ V, is followed by an irreversible wave (W_2) with the anodic peak potential $E_p^a = 0.20$ V. The controlled potential oxidation of $Me_2Fe(bpy)_2$ at -0.35 V liberates one electron per iron. The electrolysis is accompanied by a marked change from the deep blue color of A to a dark green solution. The color change is reversible. Thus the controlled potential reduction of the green solution regenerates the original deep blue solution, and coulometry shows that it requires one electron per iron, i.e.

$$\underset{A}{Me_2Fe(bpy)_2} \rightleftharpoons \underset{B}{Me_2Fe(bpy)_2^+} + e \qquad (11)$$

The reversible one-electron oxidation of the iron(II) complex in Eq. (11) is characteristic of all the alkyl derivatives. Thus, the controlled potential oxidation of the ethyl and *n*-propyl analogues of A as well as the ferracyclopentane cleanly liberates one electron per iron to generate the corresponding iron(III) cation B. By an analogous procedure, the second wave W_2 is shown to be associated with the further 1e oxidation of $Me_2Fe(bpy)_2^+$ to finally afford the dicationic iron(II) species (W_3). Most importantly, Scheme 1 illustrates the distinctive routes by which each of the diethyliron(bpy)$_2$ species undergoes decomposition. Included in Scheme 1 are the major pathways by which the ferracyclopentane analogues of A, iron(II); B, iron(III); and C, iron(IV) afford butene−1 by *disproportionation*, tetramethylene biradical by *homolysis* and cyclobutane by *reductive elimination* respectively.

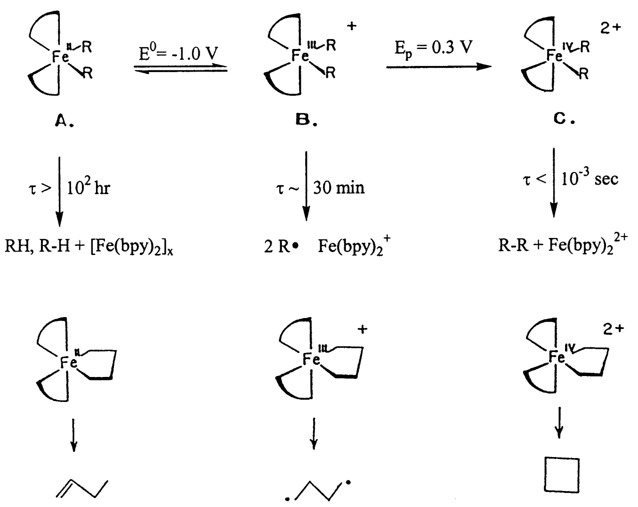
The decomposition of *n*-propylcopper(I) in THF solution produces propylene and propane in ca. equal amounts consistent with the results obtained from *n*-butyl(tri-*n*-butylphosphine)copper(I) in diethyl ether [5]. Careful examination of the rate of decomposition of ethylcopper(I) at 0 °C reveals an induction period followed by a rapid decomposition.

$$CH_3CH_2CH_2Cu^I \underset{THF}{\rightarrow} \times \underset{51\%}{CH_3CH{=}CH_2} + \underset{49\%}{CH_3CH_2CH_3} + Cu \qquad (12)$$

The induction period is removed when a solution of partially decomposed ethylcopper(I) is deliberately added to a solution of ethylcopper(I). Other alkylcopper(I) compounds have varying degrees of stability but otherwise shows the same behavior.

The autocatalytic decomposition of alkylcopper(I) species can be attributed to the presence of copper(0) intermediates during decomposition, as illustrated in Fig. 2, in which catalytic amounts of soluble silver(0), palladium(0), and copper(0) species stimulate the decomposition of *n*-propylcopper(I) in a rather dramatic way. This behavior is not restricted to organocopper species since the more stable alkylmanganese compounds also show a marked catalytic decomposition.

The visible absorption spectrum and the electron paramagnetic resonance (epr) spectrum of organocopper species in THF solution show interesting changes during these transformations. If a solution of ethylcopper(I) in THF is held at −10° for ca. 30 min, it gradually turns purple and remains homogeneous, but no decomposition is apparent. [The change is probably due to association of the organocopper(I) species into clusters.] No epr (microwave) absorption occurs during this period of color change. Raising the temperature to 0° shortens the period of quiescence and accelerates the rate of decomposition of copper(I). The epr spectrum shown in Fig. 3 is obtained only *during decomposition* of copper(I). The amplitude of the spectrum reaches a maximum at ca. half-decomposition and disappears when the reaction is complete. The lifetime of the paramagnetic species can be sustained for longer periods if the solution is quickly chilled.



Scheme 1.

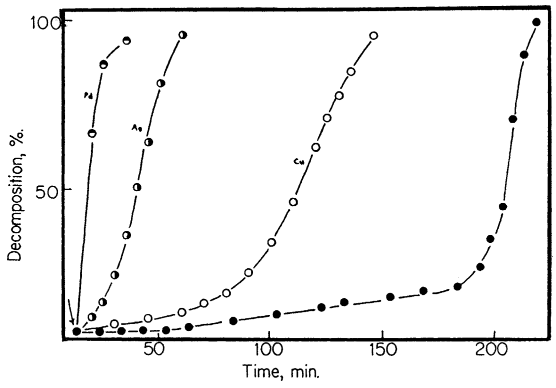


Fig. 2. The autocatalytic decomposition of *n*-propylcopper(I) in THF at 2 °C (●). The decomposition of *n*-propylcopper(I) after addition of 10 mol% soluble Pd^0 , Ag^0 (◑) or Cu^0(○), at point of arrow.

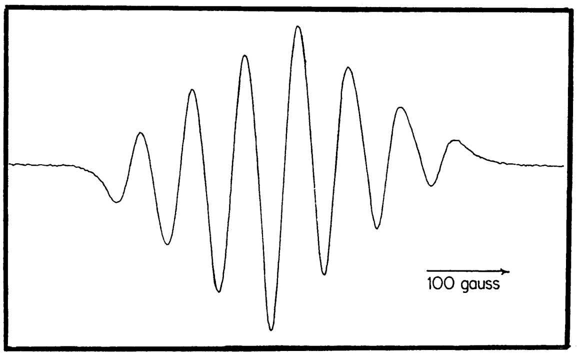


Fig. 3. The epr spectrum of the binuclear copper(0) complex formed during decomposition of ethylcopper(I) in THF at 0 °C.

The presence of hyperfine splittings consisting of seven equally spaced components (with ca. the correct intensity distribution of 1:2:3:4:3:2:1) indicates that the paramagnetic species has two copper nuclei undergoing spin exchange in (nearly) the same ligand field. The g value of 2.0024 is close to the spin-only value and is consistent with an electron associated primarily with as s-orbital (of a copper(0) species) and showing a minimum of spin–orbit coupling characteristic of copper(II) complexes. Both of these parameters vary in a small but discrete manner with the alkyl moiety and indicate those alkyl groups are within the coordination sphere of the two copper nuclei. The observed line width of 26 G, however, places an upper limit to the magnitude of the hyperfine splitting due to such ligands.

The presence of binuclear copper species during the catalytic decomposition of alkylcopper(I) suggests that they play important roles in the mechanism (Scheme 2).

The thermal stability of organometals of the transition series generally depends on the solvent. For example, organocopper(I) species are appreciably more stable in THF than in diethyl ether solutions (even with the aid of phosphine ligands). The increased stability of organometals in this and related solvents enables kinetic studies to be carried out with greater facility. Furthermore, the presence of binuclear copper intermediates during the decomposition of organocoper(I) derivatives (with and without tributylphosphine ligands) cannot be observed in diethyl ether.

$$\mathrm{RCu^{I} + Cu^{0} \longrightarrow [RCu^{I}Cu^{0}]} \qquad (13a)$$

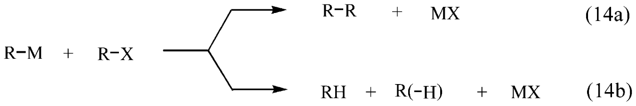
$$\mathrm{[RCu^{I}Cu^{0}] \xrightarrow{fast} R(\text{-}H) + Cu^{0} + Cu^{I}H} \qquad (13b)$$

$$\mathrm{RCu^{I} + Cu^{I}H \longrightarrow RH + 2\,Cu^{0}}, \text{ etc.} \qquad (13c)$$

Scheme 2.

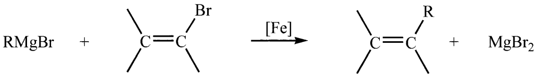
4. Alkyl transfers from organometallic intermediates in catalytic processes

The oxidation–reduction reactions of organometallic intermediates presented in the foregoing description can be applied, in combination, to a variety of catalytic processes, such as the metal-catalyzed alkyl transfer reactions of Grignard reagents originally investigated by Kharasch and Reinmuth [2]. We have found that the catalytic reactions between labile organo-metals and alkyl halides can be generally classified into two categories, coupling in Eq. (14a) and disproportionation in Eq. (14b), depending on the catalyst. For example, silver(I) and copper(I) are effective catalysts in the coupling of alkyl groups, whereas iron effects only disproportionation except when aryl and vinylic halides are employed. Each catalyst shows unique features which are best described within the following mechanistic context.



4.1. *Iron catalysis in the cross coupling of alkenyl halides and Grignard reagents*

Grignard reagents are cross-coupled stereospecifically with alkenyl halides such as 1-bromopropene in the presence of catalytic amounts of iron complexes [6].



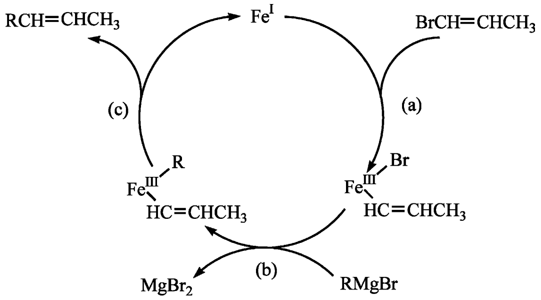
(15)

Iron(III) complexes are employed, but they are rapidly reduced by Grignard reagent in situ to generate a catalytically active reduced iron species, presumably iron(I). Among various iron complexes examined, *tris*-dibenzoylmethido-iron(III), Fe(DBM)$_3$, was found to be the most effective, particularly with respect to deactivation of the catalyst. The yields of olefins obtainable by this catalytic process vary according to the structure of the alkyl moiety in the Grignard reagent. Thus, high yields of cross coupled products are obtainable with methylmagnesium bromide. Under the same conditions, ethylmagnesium bromide afforded ethane and ethylene as side products in addition to the expected cross coupled product. The difference can be attributed to the availability of β-hydrogens in the latter, a factor which is also important in a variety of other organometallic reactions. We have carried out a thorough analysis of the products formed during the reaction of ethylmagnesium bromide with (Z)- and (E)-1-bromopropene in the presence of *tris*-dibenzoylmethido-iron(III). A complete accounting of the material balance as well as the electron balance has been achieved. Together with stereochemical and isotopic labeling studies, they provide substantial mechanistic information about this interesting catalytic process. Five major types of side products are produced during the catalytic process, in greater or lower yields depending on the relative concentrations of the reactants, the temperature of the reaction and the structure of the alkylmagnesium bromide. Thus, alkene R(–H) and alkane RH from the Grignard component as well as propylene, propenylmagnesium bromide and 2,4-hexadiene from 1-bromopropene are always formed. No simple relationship could be found for the formation of these side products in relationship to the predominant cross coupled product. The latter suggests that the side products are intimately connected with the principal reaction, and that both processes involve common reactive intermediates. Alternatively, the side products could arise via concurrent but largely independent reactions from the cross-coupling process. The rigorous delineation between these basic mechanistic categories is extremely difficult to make in a catalytic system in which the isolation of intermediates is impractical (Eq. (15)).

Any mechanistic formulation of the catalytic process must take into account the diversity of side products, as well as the isotopic labeling and stereochemical results. In the following discussion we wish to present a reaction scheme which is consistent with the available data, while at the same time keeping the number of intermediates to a minimum.

The catalyst is best described as an iron(I) species formed by the facile reduction of the iron(III) precursor by the Grignard reagent [7]. It is a mestastable species subject to deactivation on standing, probably by aggregation. Formally, iron(I) species consist of a d^7 electron configuration, isoelectronic with manganese(0) and cobalt(II). Only a few complexes of iron(I) have been isolated, but a particularly relevant one is the paramagnetic hydrido complex, $HFe(dppe)_2$, which is stabilized by the *bis*-phosphine ligand, dppe[Ph_2PCH_2-CH_2PPh_2]. A toluene solution shows a strong ESR signal centered at $\langle g \rangle = 2.085$ with poorly resolved fine structure. A broad intense ESR spectrum ($\langle g \rangle = 2.08$) is also obtained if $Fe(DBM)_3$ is treated with excess ethylmagnesium bromide in THF solutions at −40 to 0 °C. A broad resonance is also observed when $FeCl_3$ [$\langle g \rangle = 2.15$] or $Fe(acac)_3$ [$\langle g \rangle = 2.07$] are employed. The spectrum centered at $\langle g \rangle = 2.00$ retains the same general features when *n*-pentyl- or *sec*-butyl-magnesium bromides are employed as reducing agents [8]. It is destroyed immediately by molecular oxygen, and is the dianion-radical of the ligand ($PhCOCHCOPh^{2-\bullet}$).

The mechanism of the cross-coupling reaction can be accommodated by an oxidative addition of 1-bromopropene to iron(I) followed by exchange with ethylmagnesium bromide and reductive elimination. Scheme 3 is intended to form a basis for discussion of the catalytic mechanism. In order to maintain the stereospecificity, the oxidative addition of bromo-propene in *step a* should occur with retention. Similar stereochemistry has been observed in oxidative additions of platinum(0) and nickel(0) complexes [9]. The metathesis of the iron(III) intermediate in *step b* is expected to be rapid in analogy with other alkylations. The formation of a new carbon–carbon bond by the reductive elimination of a pair of carbon-centered ligands in *step c*, has been demonstrated to occur with organogold(III), organonickel(II), organoplatinum(IV) and organorhodium(III) complexes [10].

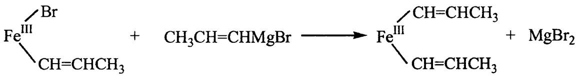


Scheme 3.

The iron(III) intermediates in Scheme 3 serve as focal points for the formation of the side products. For example, metathetical exchange of propenyl-iron(III) with Grignard reagent would afford propenylmagnesium bromide in Eq. (16) [11].

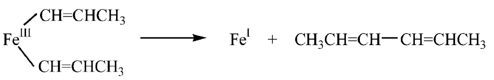
$$\begin{aligned} &\mathrm{Fe^{III}\text{–}CH{=}CHCH_3 + R\text{–}MgBr} \\ &\quad \rightarrow \mathrm{Fe^{III}\text{–}R + CH_3CH{=}CHMgBr} \qquad (16) \end{aligned}$$

Further exchange in Eqs. (17a) and (17b) would produce *bis*-(1-propenyl)iron(III) species which reductively eliminate to produce the 2,4-hexadienes stereospecifically [12].



$$\underset{\searrow \mathrm{CH{=}CHCH_3}}{\overset{\nearrow \mathrm{Br}}{\mathrm{Fe^{III}}}} + \mathrm{CH_3CH{=}CHMgBr} \longrightarrow \underset{\searrow \mathrm{CH{=}CHCH_3}}{\overset{\nearrow \mathrm{CH{=}CHCH_3}}{\mathrm{Fe^{III}}}} + \mathrm{MgBr_2}$$

(17a)



$$\underset{\searrow \mathrm{CH{=}CHCH_3}}{\overset{\nearrow \mathrm{CH{=}CHCH_3}}{\mathrm{Fe^{III}}}} \longrightarrow \mathrm{Fe^{I}} + \mathrm{CH_3CH{=}CH{-}CH{=}CHCH_3}$$

(17b)

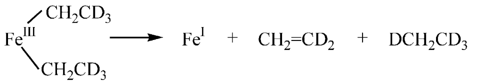
Disproportionation products are postulated to arise from alkyliron(III) and/or dialkyliron(III) species formed by an analogous metathesis between iron(III) species and alkylmagnesium bromide. Thus, the disproportionation processes may proceed as follows (vide

$$\mathrm{RMgBr + Cu^{I}Br \longrightarrow RCu^{I} + MgBr_2} \qquad (21)$$

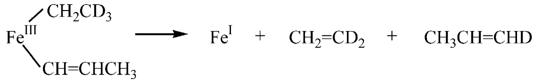
$$\mathrm{RCu^{I} + R'Br \xrightarrow{slow} R\text{-}R' + Cu^{I}Br} \qquad (22)$$

Scheme 4.

infra):

 (18)

$$\mathrm{Fe^{III}(CH_2CD_3)_2} \longrightarrow \mathrm{Fe^{I}} + \mathrm{CH_2{=}CD_2} + \mathrm{DCH_2CD_3} \quad (18)$$

 (19)

$$\mathrm{Fe^{III}(CH_2CD_3)(CH{=}CHCH_3)} \longrightarrow \mathrm{Fe^{I}} + \mathrm{CH_2{=}CD_2} + \mathrm{CH_3CH{=}CHD} \quad (19)$$

These disproportionations could proceed directly or by a 2-step mechanism involving prior transfer of a β-hydrogen to iron followed by reductive elimination. Similar disproportionation processes have been described with organo-copper(I), organomanganese(II), and organoplatinum(II) complexes [13].

The mechanism in Scheme 3 accommodates much of the data on the iron-catalyzed cross-coupling reaction of Grignard reagents and alkenyl halides. The side products derive naturally from organoiron(III) intermediates by reasonably well-established pathways. However, there are a number of interesting observations which merit further scrutiny in the light of this mechanism. For example, it is commonly held that organometallic compounds such as the alkyl- and propenyl-iron(III) species in Scheme 3 undergo elimination of β-hydrogens in the order: *tert*-R > *sec*-R > *prim*-R. However, the results run counter to this expectation. Furthermore, if the oxidative addition of 1-bromopropene to iron(I) is rate-limiting, the reactivities of the (Z) and (E) isomers should be relatively independent of the Grignard reagent. It is found, however, the (Z)-bromopropene is more reactive than the (E) isomer with primary alkylmagnesium bromide, but the converse is true of methyl, secondary and tertiary alkylmagnesium bromides. The degree of association and complex formation of the latter no doubt affect a quantitative evaluation, but even a qualitative rationalization of this result remains obscure. Changes in the concentration of the reactants as well as the temperature of the reaction could affect the rates and equlibria of the various reactions outlined in Scheme 3 and Eqs. (16)–(19), in a manner to change the product distribution. Nonetheless, the anomalies presented above ultimately must be resolved before this mechanistic formulation can be accepted with more confidence.

Finally, the mechanism in Scheme 3 bears a resemblance to the nickel-catalyzed reaction of methylmagnesium bromide and aryl bromides [8,14]. However, there are outstanding differences between iron and nickel in their abilities to effect cross-coupling reactions. Iron is a catalyst which is effective at lower temperatures and concentrations than used with nickel. Even more importantly, cross coupling can be effected completely stereospecifically with an iron catalyst and no alkyl isomerization of the Grignard component has been observed.

4.2. Cross coupling of Grignard reagents and alkyl halides with copper(I) catalysts

Copper(I) specifically catalyzes the cross coupling (Eq. (20)) between Grignard reagents and alkyl bromides when carried out in THF solutions at 0 °C or lower [15].

$$\mathrm{RMgX} + R'\mathrm{X} \xrightarrow{[\mathrm{Cu^I}]} \mathrm{R}\text{–}R' + \mathrm{MgX_2} \quad (20)$$

The yield of homodimers, R–R and R′–R′, under these conditions is negligibly small. This cross-coupling reaction is most facile with primary alkyl halides, but unlike silver(I) catalysis, secondary and tertiary alkyl halides are generally inert and give poor yields of coupled products and mainly disproportionation. The structure of the Grignard reagent is not as important, in analogy with the cross coupling observed with lithium dialkylcuprates [16].

The coupling of ethylmagnesium bromide and ethyl bromide to *n*-butane follows overall third-order kinetics, being first order in each component and the copper(I) catalyst. There is no evidence for alkyl radicals in the copper(I)-catalyzed coupling process, and we propose the following two-step mechanism:

The rate-limiting step (Eq. (22)) can be shown independently by examining the stoichiometric reaction of alkylcopper(I) directly with organic halides. However, the extent to which *decomposition* of the alkylcopper(I) intermediate competes with the catalytic coupling reaction introduces disproportionation products. The latter involves a copper(0)-catalyzed sequence (see Scheme 2) similar to that observed with iron (vide infra), and it is especially important with secondary and tertiary alkyl systems [5,17]. The effects of structural variation are consistent with a rate-limiting step involving nucleophilic displacement of halide in Eq. (22). The involvement of a nucleophilic copper(I) center, i.e. oxidative addition, followed by reductive elimination has direct analogy to the mechanism which has been established with the analogous gold(I) catalyst.

$$\mathrm{RCu^I} + R'\mathrm{X} \rightarrow \mathrm{R}(R')\mathrm{Cu^{III}X} \quad (23)$$

$$\mathrm{R}(R')\mathrm{Cu^{III}X} \rightarrow \mathrm{R}\text{–}R' + \mathrm{Cu^IX} \quad (24)$$

Organocopper(III) intermediates presented in Eq. (23) are formally related to the species formed in the association of alkyl radicals with copper(II) complexes [18], with both showing a marked propensity for reductive elimination. Although the observation of these highly metastable intermediates is unlikely, the analogous organogold intermediates are more stable and can be isolated or observed directly by NMR. Oxidative addition of alkyl halides to alkyl(PPh_3)gold(I) follows the expected pattern: MeI > EtI > *i*-PrI [19]. The subsequent reductive elimination of trialkylgold(III) complexes to coupled dimer was described earlier (Eq.

(10b)). The parallel between copper(I) and gold(I) is further shown in the behavior of the corresponding cuprate(I) and aurate(I) complexes. Thus, alkylgold(I) reacts with an equimolar amount of alkyllithium to afford an isolable lithium dialkylaurate(I). The anionic dimethyl-aurate(I) species formed in this manner is at least 10^6 times more reactive to oxidative addition of methyl iodide than the neutral methyl(PPh_3)gold(I). The same pattern is qualitatively established with organocopper(I) species in comparing the coupling reaction in Eq. (22) with that for lithium dialkylcuprates.

4.3. Homo-coupling with silver(I)

Silver is an effective catalyst for the coupling of Grignard reagents and alkyl halides, and it is especially useful when both alkyl groups are the same [20].

$$\mathrm{RMgX} + R'\mathrm{X} \xrightarrow{[\mathrm{Ag^I}]} \mathrm{R}\text{–}R' + \mathrm{MgX_2} \qquad (25)$$

When different alkyl groups are employed, a mixture of three coupled products is obtained. Disproportionation becomes increasingly important with secondary and tertiary groups, independently of whether they are derived from the Grignard reagent or the alkyl halide. The rate of production of butane from ethylmagnesium bromide and ethyl bromide is roughly first order in silver and ethyl bromide, but zero order in Grignard reagent [21]. The reactivity of alkyl halides follows the order: *t*-butyl > *i*-propyl > *n*-propyl bromide in the ratio 20:3:1, and structural variations in the Grignard reagent show no apparent systematic trend.

The results can be accommodated by Scheme 5, in which the coupling arises from alkyl silver(I) intermediates generated via two largely independent pathways:

The rate-limiting step in this mechanism is given by Eq. (28) in which the alkyl halide is responsible for the re-oxidation of silver(0) produced in Eq. (27). This slow step is closely akin to the production of alkyl radicals by the ligand transfer reduction of alkyl halides with other reducing metal complexes [22]. More direct evidence for the selective formation of alkyl radicals from the alkyl halide is shown by trapping experiments as well as stereochemical studies. Thus, the catalytic reaction of *cis*-propenylmagnesium bromide with methyl bromide yielded *cis*-butene-2, in accord with the retention of stereochemistry during the reductive coupling of vinylsilver(I) complexes [23]. On the other hand the reverse combination, *cis*-propenyl bromide and methylmagnesium bromide, is catalytically converted to a mixture of *cis*- and *trans*-butene-2, consistent with the formation and rapid isomerization of the 1-propenyl radical in Scheme 4 (Eqs. (28) and (30)).

$$\mathrm{R'MgX} + \mathrm{Ag^IX} \longrightarrow \mathrm{R'Ag^I} + \mathrm{MgX_2} \qquad (26)$$

$$\mathrm{RAg^I, R'Ag^I} \longrightarrow [\mathrm{R\text{-}R, R'\text{-}R, R'\text{-}R'}] + 2\mathrm{Ag^0} \qquad (27)$$

$$\mathrm{Ag^0} + \mathrm{R\text{-}X} \longrightarrow \mathrm{R\bullet} + \mathrm{Ag^IX} \qquad (28)$$

$$\mathrm{R\bullet} + \mathrm{Ag^0} \longrightarrow \mathrm{RAg^I} \quad \text{etc.} \qquad (29)$$

Scheme 5.

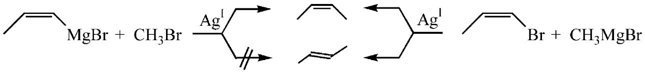
$$\mathrm{Fe^I} + \mathrm{RBr} \longrightarrow \mathrm{Fe^{II}Br} + \mathrm{R\bullet} \qquad (32)$$

$$\mathrm{R\bullet} + \mathrm{Fe^I} \longrightarrow \mathrm{RFe^{II}} \qquad (33)$$

$$\mathrm{R'MgBr} + \mathrm{Fe^{II}Br} \longrightarrow \mathrm{R'Fe^{II}} + \mathrm{MgBr_2} \qquad (34)$$

$$\mathrm{RFe^{II}, R'Fe^{II}} \longrightarrow [\mathrm{RH, R'H, R-H, R'-H}] + 2\mathrm{Fe^I}, \text{ etc.} \qquad (35)$$

Scheme 6.



(30)

4.4. Catalysis of alkyl disproportionation by iron

Alkyl disproportionation is the sole reaction observed during the iron-catalyzed reaction of ethylmagnesium bromide and ethyl bromide [24]. The catalyst is a reduced iron species formed in situ by the reaction of iron(II,III) with Grignard reagent, and effective in concentrations as low

$$\mathrm{CH_3CH_2MgBr} + \mathrm{CH_3CH_2Br} \xrightarrow{[\mathrm{Fe}]} \mathrm{CH_3CH_3} + \mathrm{CH_2{=}CH_2} + \mathrm{MgBr_2} \qquad (31)$$

as 10^{-5} M. Although the reaction has limited synthetic utility, it merits study since it can provide insight into some of the complications involved with organometallic intermediates discussed above.

The rate of reaction shows first order dependence on the concentration of iron and ethyl bromide, but is independent of the concentration of ethylmagnesium bromide. The rate, however, varies with the structure of the Grignard reagent, and disproportionation usually results except when the alkyl group is methyl, neopentyl or benzyl which possess no β-hydrogens. The reactivities of the alkyl bromides (*t*-butyl > i-propyl > *n*-propyl) as well as the kinetics are the same as the silver-catalyzed coupling described above and suggest a similar mechanism:

According to this postulate, the difference between coupling with silver and disproportionation with iron rests on the decomposition of the alkylmetal intermediate in Eq. (35). Indeed, it has been shown separately in Eq. (27) that the decomposition of alkylsilver(I) proceeds by reductive coupling. Unfortunately, the highly unstable alkyliron intermediate in Scheme 6 is not yet accessible to independent study, but the somewhat analogous dialkyl-manganese(II) species in Eq. (36)

undergoes similar reductive disproportionation by a mechanism [25] reminiscent of dialkylplatinum(II) complexes described in Eq. (7).

$$R_2Mn^{II} \rightarrow RH + R\text{–}H + Mn^0 \tag{36}$$

Selective trapping of alkyl radicals from the alkyl halide component during the course of the catalytic disproportionation is the same as the previous observation with silver, and it indicates that the prime source of radicals in the Kharasch reaction lies in the oxidative addition of alkyl halide to reduced iron in Eq. (32). Separate pathways for reaction of *i*-propyl groups derived from the organic halide and the Grignard reagent are also supported by deuterium labeling studies which shows that they are not completely equilibrated [26]. Furthermore, the observation of CIDNP (AE multiplet effect) in the labeled propane and propene derived only from the alkyl halide component can be attributed to a bimolecular disproportionation of isopropyl radicals arising from diffusive displacements. However, the latter can only be a minor fate of the alkyl radicals derived from the alkyl halide, since the coupled dimer is not formed in amounts required by the bimolecular reaction of alkyl radicals previously discussed in Eq. (9).

Cross coupling of Grignard reagents with 1-alkenyl halides, in marked contrast to alkyl halides, occurs readily with the reduced iron catalyst, as described above. The iron-catalyzed reaction of Grignard reagents with 1-alkenyl halides can, however, be differentiated from the reaction with alkyl halides. Thus, a mixture of propenyl bromide and ethyl bromide on reaction with methylmagnesium bromide afforded butene-2, but no cross-over products such as pentene-2 or propylene. The latter certainly would have resulted if a propenyliron species per se were involved in the catalytic process.

5. Conclusions

The complex catalytic reactions leading to the coupling of organic substrates induced by metal complexes can be rationally dissected into a variety of elementary steps involving oxidation–reduction reactions of organometallic intermediates. Electron-transfer interactions are important considerations in differentiating concerted from stepwise processes, especially with regard to chain processes. Crucial to the design of new synthetic procedures and the understanding of catalytic processes is the information to be gained from the scrutiny of transient alkylmetal species.

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