structural changes also result in increased reactivity with hindered substrates. In the parent ylide, methylenephosphorane, the methylene group lies in a plane that, with respect to the molecular orientation in Table I, forms a dihedral angle of approximately 20° with the Y–Z plane.[12] Deprotonation of the ylide results in a rotation of the remaining methylenic hydrogen to lie in the X–Z plane (Table I). This rotation orients the lone pair electrons of the carbanion in a sterically favorable position for the Dunitz trajectory[13] attack upon the carbonyl system of a hindered ketone. The arrangement of atoms in the carbanion moiety of the parent ylide precludes such an attack.

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Quantitative CIDNP Evidence for the S_H2 Reaction of Alkyl Radicals with Grignard Reagents. Implication to the Iron-Catalyzed Kharasch Reaction

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Despite years of study, the iron-catalyzed reaction of an alkyl halide and a Grignard reagent remains unsettled.[1-3] It is generally agreed that the Grignard reagent reacts with Fe(II) or Fe(III) to give an activated form of iron, possibly Fe(I) or Fe(0), by a nonradical pathway.[1] The organic products as a result of the reduction of iron appear to be exclusively disproportionation products of the alkyl iron intermediates, (1) and (2). The reduced form of iron is recycled by electron transfer to alkyl halide producing an alkyl radical and halide ion, (3). Both radical trapping experiments[2] and CIDNP results[3] indicate that free radicals are derived only from alkyl halide. Controversy exists over the importance of radical pair reactions in the product-forming steps. Due to the apparent lack of alkyl dimers, Kochi et al.[1,2] propose that free radicals are trapped by iron to give alkyl iron intermediates identical with those formed by reaction with Grignard reagent, (4). Allen et al.,[3] however, report that at high reagent concentration and rates, significant amounts of dimer are formed, (5). Free radicals have also been reported to react regeneratively with alkyl halide, (6), and with Grignard reagent by S_H2 reaction on Mg effecting halogen–metal exchange,[4] (7) (Scheme I). Reactions 4, 6, and 7 represent competitive reactions first order in free radicals whose relative rates should be dependent on the concentration of Fe, RX, and R′MgX, respectively. We wish to report here on quantitative CIDNP evidence which establishes the minimum rate constant for the S_H2 reaction of isobutyl radical and ethylmagnesium bromide, indicating that (4) is not important at typical catalyst concentrations.

Qualitative CIDNP during the reaction of a primary iodide and primary Grignard exhibits polarization predominantly from halide-derived radicals. The same reaction with a secondary Grignard results in approximately equal magnitude polarization from halide- and Grignard-derived radicals while the reaction with tertiary Grignard results in polarization almost exclusively from Grignard-derived radicals.[5] The reactivity toward Grignard–halide exchange therefore correlates with the radical stability of the alkyl fragment of the Grignard reagent. Product yields for the halide/Grignard pairs methyl/*n*-propyl, ethyl/isopropyl, and ethyl/*tert*-butyl support this conclusion.[2]

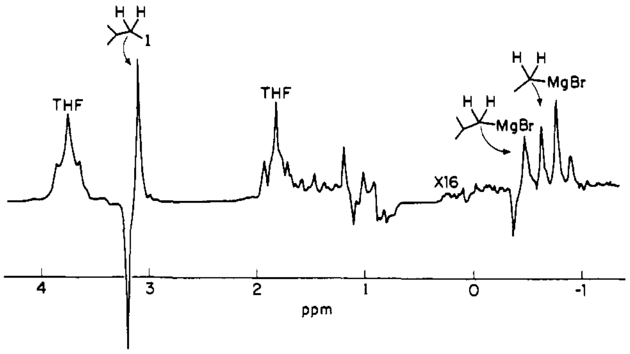

Figure 1. ^1H NMR spectrum (60 MHz) during the reaction of isobutyl iodide and ethylmagnesium bromide catalyzed by 2.0×10^{-5} M Fe(acac)$_3$.

Scheme I

$$R'MgX + Fe_{ox} \xrightarrow{k_1} R'Fe_{ox} + MgX^+ \quad (1)$$

$$R'Fe_{ox} + RFe_{ox} \xrightarrow{k_2} RH,R'H + R(-H),R'(-H) + Fe_{red} \quad (2)$$

$$RX + Fe_{red} \xrightarrow{k_3} R\cdot + X^- + Fe_{ox} \quad (3)$$

$$R\cdot + Fe_{red} \xrightarrow{k_4} RFe_{ox} \quad (4)$$

$$R\cdot + R\cdot \xrightarrow{k_5} RH + R(-H) + RR \quad (5)$$

$$R\cdot + RX \xrightarrow{k_6} RX + R\cdot \quad (6)$$

$$R\cdot + R'MgX \xrightarrow{k_7} RMgX + R'\cdot \quad (7)$$

Figure 1 shows the CIDNP spectrum obtained during the reaction of 0.8 M isobutyl iodide and 1.6 M ethylmagnesium bromide in THF catalyzed by 2.0×10^{-5} M Fe(acac)$_3$.[6] As reported previously,[4] EA polarization in the α-protons of the newly formed isobutylmagnesium bromide (-0.5 ppm) is consistent with the scavenging of free isobutyl radicals by unreacted Grignard reagent. EA polarization is also apparent in the α-protons of the isobutyl iodide (3.1 ppm), indicating competitive scavengng of isobutyl radicals by unreacted iodide. A small contribution to the polarization in the iodide region due to ethyl iodide as well as an EA dehancement of the signal due to ethylmagnesium bromide indicates that ethyl radicals are present as well.

From a steady-state analysis of the competitive reactions 8–10

$$R^*\cdot + RI \xrightarrow{k_i} R^*I + R\cdot \quad (8)$$

$$R^*\cdot + R'MgBr \xrightarrow{k_m} R^*MgBr + R'\cdot \quad (9)$$

$$R^*\cdot \xrightarrow{1/T_{1,R}} R\cdot \quad (10)$$

(* denotes nonequilibrium nuclear spin population) and the assumption that the polarization intensity is much greater than the equilibrium Boltzmann intensity, the following relationship for the relative polarization intensities of isobutyl iodide and isobutylmagnesium bromide can be derived,[7]

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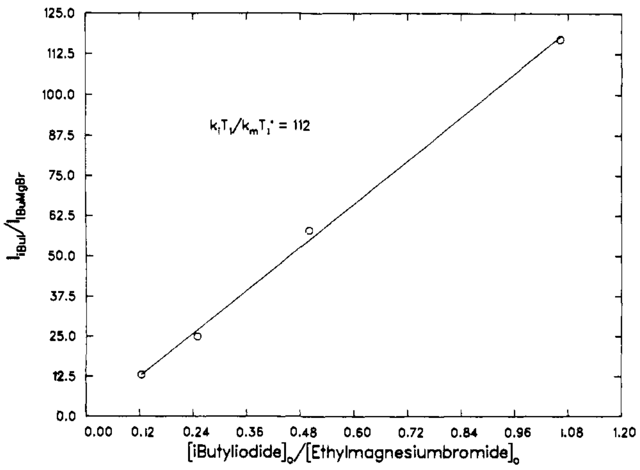

Figure 2. Polarization ratio of isobutyl iodide and isobutylmagnesium bromide as a function of initial concentration ratio of isobutyl iodide and ethylmagnesium bromide.

$$\frac{I_{i\text{-BuI}}}{I_{i\text{-BuMgBr}}} = \frac{k_iT_1[i\text{-BuI}]}{k_mT_1'[\text{EtMgBr}]}$$

where T_1, T_1', and $T_{1,\mathrm{R}}$ are the spin-lattice relaxation times of the α-protons of isobutyl iodide, isobutylmagnesium bromide, and isobutyl radical, respectively. Figure 2 shows the relative intensities of these two signals measured 20 s after the introduction of 2.0×10^{-5} M Fe(acac)_3 to 1.6 M ethylmagnesium bromide and 0.2–1.7 M isobutyl iodide. Since these solutions are relatively viscous, we make the approximation that $T_1 = T_1'$,[8] and find that $k_i/k_m \cong 10^2$. k_m must be $>10^5$ M^{-1} s^{-1} to be competitive with $1/T_{1,\mathrm{R}}$ and therefore $k_i > 10^7$ M^{-1} s^{-1}.[9]

It has been suggested that halogen–metal exchange occurs via alkyl iron intermediates formed according to (4) followed by transmetalation with Grignard reagent.[1,2]

$$\text{RFe} + \text{R'MgBr} \rightarrow \text{R'Fe} + \text{RMgBr} \qquad (11)$$

While this mechanism is not ruled out under different conditions, k_4 would have to be 10^{10} M^{-1} s^{-1} (faster than the diffusion-controlled rate in these viscous solutions) to make a significant contribution to exchange at the catalyst concentration used in this study. This suggests that the yield of alkyl dimer formed by radical pair coupling, (5), should be dependent on such reaction parameters as catalyst concentration and overall rate. At the relatively low reaction rates studied by Tamura and Kochi,[2] the second-order radical termination reaction, (5), may not be significant since the steady-state radical concentration is low. Free radicals may be trapped by reduced iron, alkyl halide, or Grignard reagents via reactions 4, 6, and 7 leading to no observed alkyl dimers. At the higher reaction rates necessary for the observation of CIDNP[3] the steady-state radical concentration increases, resulting in a sharp increase in probability of reaction 5 and the observation of dimeric products. Simulations[10] of the concentration profiles of the reactants, intermediates, and products[5] confirm this hypothesis and indicate that reactions 1–7 are so far sufficient to explain the predominant reaction pathways.

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Density Functional Approach to the Frontier-Electron Theory of Chemical Reactivity

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We here demonstrate that most of the frontier-electron theory of chemical reactivity[1] can be rationalized from the density functional theory of the electronic structure of molecules.[2,3]

Consider a species S with N electrons, having ground-state electronic energy $E[N,v]$ and chemical potential $\mu[N,v]$, where v is the potential acting on an electron due to all nuclei present. The chemical potential is the negative of the electronegativity.[4] The energy as a function of N has a discontinuity of slope at each integral N,[5] and so there are three distinct chemical potentials for each integral N, $\mu^- = (\partial E/\partial N)_v^-$ (from positive-ion side), $\mu^+ = (\partial E/\partial N)_v^+$ (from negative-ion side), and $\mu^0 = (\partial E/\partial N)_v^0 = {}^1/_2(\mu^+ + \mu^-)$ (unbiased).

Fundamental equations for changes in energy and chemical potential are

$$\mathrm{d}E = \mu\,\mathrm{d}N + \int \rho(\bar{r})\,\mathrm{d}v(\bar{r})\,\mathrm{d}\bar{r} \qquad (1)$$

and

$$\mathrm{d}\mu = 2\eta\,\mathrm{d}N + \int f(\bar{r})\,\mathrm{d}v(\bar{r})\,\mathrm{d}\bar{r} \qquad (2)$$

where $\rho(\bar{r})$ is the electron density, $\eta = {}^1/_2(\partial\mu/\partial N)_v$ is the hardness,[6] and the function $f(\bar{r})$ is defined by

$$f(\bar{r}) \equiv [\delta\mu/\delta v(\bar{r})]_N = [\partial\rho(\bar{r})/\partial N]_v \qquad (3)$$

The equality in this formula is a Maxwell relation for eq 1.[7] The function f is a local quantity, which has different values at different points in the species. It admits of contour maps.

Our argument will be that large values of f at a site favor reactivity of that site. We therefore call $f(\bar{r})$ the *frontier function* or *fukui function* for a molecule.

If a reagent R approaches S, what direction will be preferred (from among several directions that can produce the same type of chemical bond)? The quantity $\mathrm{d}\mu$ in eq 2 measures the extent of the reaction. *We assume that the preferred direction is the one for which the initial* $|\mathrm{d}\mu|$ *for the species S is a maximum.* The first term on the right side of eq 2 involves only global quantities and at large distances is ordinarily less direction sensitive than the second term. We may then assume, more or less equivalently in the usual cases, that *the preferred direction is the one with largest* $f(\bar{r})$ *at the reaction site.* Reactivity is measured by the fukui index of eq 3.

Equation 3 in fact provides three reaction indices, because $\rho(\bar{r})$ as a function of N, like $E(N)$, has slope discontinuities.[5] We therefore have the firm predictions, governing electrophilic attack,

$$f^-(\bar{r}) = [\partial\rho(\bar{r})/\partial N]_v^- \qquad (4)$$

governing nucleophilic attack,

$$f^+(\bar{r}) = [\partial\rho(\bar{r})/\partial N]_v^+ \qquad (5)$$

and governing neutral (radical) attack,

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