Table II. Relative Rates of Coupling of Grignard Reagents and Alkyl Halides Catalyzed by Copper(I) Halides[a]

		Rel rate[b]
	RMgX + EtBr	
EtMgBr	EtBr	1.0
n-PrMgBr	EtBr	1.3
i-PrMgBr	EtBr	25
tert-BuMgBr	EtBr	4.0
	EtMgBr + R-X	
EtMgBr	*n*-PrCl	<0.01
EtMgBr	*n*-PrBr	0.42
EtMgBr	*n*-PrI	4.1[c]
EtMgBr	*i*-PrBr	<0.01
EtMgBr	*tert*-BuBr	<0.01

[a] Reaction of 0.18 *M* RMgX, 0.16 *M* R'Br, and 5.8 × 10^{-4} *M* copper at 2°. [b] Based on less than 10% reaction to form REt. [c] Complications from alkyl exchange and the Wurtz reaction.

reaction

$$\text{RMgBr} + \text{Cu}^{\text{I}}\text{Br} \longrightarrow \text{RCu}^{\text{I}} + \text{MgBr}_2 \qquad (1')$$

$$\text{RCu}^{\text{I}} + \text{R'Br} \xrightarrow{\text{slow}} \text{RR'} + \text{Cu}^{\text{I}}\text{Br, etc.} \qquad (5')$$

Thus, coupling is catalyzed by copper(I) and long kinetic chains are only observed with primary alkyl halides which can be used in synthetic procedures for alkyl coupling.[12] Disproportionation of the alkylcopper intermediates (eq 3) represents a chain termination step and increases in importance with *sec*- and *tert*-alkyl derivatives (*vide infra*). Reinitiation is possible by reoxidation of the soluble copper by alkyl halide (*e.g.*, eq 9).

The catalytic reaction of secondary and tertiary alkyl halides with Grignard reagents was slow (Table II), due to the unfavorable displacement step (eq 5'). At higher copper concentrations, disproportionation was observed and it was also the favored process when stoichiometric amounts of ethylcopper(I) reacted with isopropyl bromide.

$$\text{EtCu}^{\text{I}} + i\text{-PrBr} \xrightarrow{59\%} \text{C}_2\text{H}_4 + \text{C}_3\text{H}_8 + \text{Cu}^{\text{I}}\text{Br} \qquad (8a)$$

$$\text{EtCu}^{\text{I}} + i\text{-PrBr} \xrightarrow{38\%} \text{C}_2\text{H}_6 + \text{C}_3\text{H}_6 + \text{Cu}^{\text{I}}\text{Br} \qquad (8b)$$

Catalytic disproportionation can also be induced by copper. Thus, treatment of a mixture of 0.2 *M* ethylmagnesium bromide and 0.3 *M* *tert*-butyl bromide with small amounts (2 × 10^{-3} *M*) of soluble copper[5] at 2° produced only ethane, ethylene, isobutane, and isobutylene. The reaction sequence below (eq 9–11 and 1) is consistent with this disproportionation, since styrene (as a radical trap) selectively scavenged only the *tert*-butyl moiety. Analogously, ethylmagnesium bromide and ethyl bromide under similar conditions yielded ethane (25%) and ethylene (25%) as well as butane (50%). Coupling also observed in the latter case is, no doubt, attributable to the more facile displacement reaction 5 shown by ethyl bromide compared to *tert*-butyl bromide (*vide supra*).

$$tert\text{-BuBr} + \text{Cu} \xrightarrow{\text{slow}} tert\text{-Bu}\cdot + \text{Cu}^{\text{I}}\text{Br} \qquad (9)$$[13]

$$tert\text{-Bu}\cdot + \text{Cu} \longrightarrow tert\text{-BuCu}^{\text{I}} \qquad (10)$$

$$tert\text{-BuCu}^{\text{I}}, \text{EtCu}^{\text{I}} \longrightarrow [\text{C}_2\text{H}_6, \text{C}_2\text{H}_4, i\text{-C}_4\text{H}_{10}, i\text{-C}_4\text{H}_8] + 2\text{Cu} \qquad (11)$$

Coupling and disproportionation of Grignard reagents with alkyl halides can be clearly differentiated by a simple experiment carried out serially in which ethyl bromide was added at point A to a solution of ethylcopper(I) in the presence of excess ethylmagnesium bromide at 2°. Figure 1 shows that butane was formed quantitatively according to eq 5. The resulting solution of ethylcopper(I) slowly evolved equimolar amounts of ethane and ethylene (dotted lines) quantitatively until copper was reduced (*i.e.*, mostly precipitated, eq 3, R = C_2H_5), and the addition of ethyl bromide at this point B produced only ethane and ethylene according to eq 12.[13b]

$$\text{EtMgBr} + \text{EtBr} \xrightarrow[\text{metal}]{\text{Cu}} \text{C}_2\text{H}_6 + \text{C}_2\text{H}_4 + \text{MgBr}_2 \qquad (12)$$

Acknowledgment. We wish to thank the National Science Foundation for their financial support, the Dow Chemical Co. for a gift of a billet of triply sublimed magnesium, and the du Pont Co. for generous quantities of THF.

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[12] (a) Reactions 5 and 5' are, thus, mechanistically analogous to the reactions of the more stable lithium dialkylcuprates with alkyl halides; (b) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **90**, 5615 (1968); (c) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *ibid.*, **91**, 4871 (1969); (d) for use of Grignard reagents see M. Tamura and J. Kochi, *Synthesis*, in press.

[13] (a) Copper, either in the soluble form or as a copper metal, reacted with alkyl halides only when activated by excess Grignard reagent, and probably exists as a Grignard–Cu complex. Even in the soluble form copper may be aggregated. (b) Only ethane and ethylene (in equimolar amounts) were observed if copper metal was used as a catalyst. Under these conditions ethylcopper(I) can only be formed on the copper surface and the autocatalytic disproportionation by copper is presumably more facile[4] than coupling with ethyl bromide.

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Vinylation of Grignard Reagents. Catalysis by Iron

Sir:

Iron is representative of one of the most effective metal catalysts for the promotion of the reactions between Grignard reagents and organic halides.[1] Metathesis of Grignard reagents and iron(II,III) chlorides occurred readily at 2° in tetrahydrofuran solutions, and the alkyliron intermediates afforded a reduced form of soluble iron, together with alkane and alkene.[2]

The reaction between a variety of Grignard reagents and organic halides was catalyzed effectively by the soluble iron species at concentrations less than 10^{-5} *M*. For example, the reaction between 0.15 *M* ethyl bromide and 0.16 *M* ethylmagnesium bromide occurred smoothly at 2° in the presence of 1.2 × 10^{-5} *M* soluble iron to produce an equimolar mixture of ethylene and ethane. Less than 0.1% *n*-butane was formed.[3] The

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[1] M. Tamura and J. Kochi, submitted for publication.

[2] As yet the soluble iron species is not fully characterized, but our evidence points to an iron species which is readily aggregated and complexed with the Grignard reagent. Compare the preparation and characterization of the analogous cobalt species generated in a similar manner by M. H. Abraham and M. J. Hogarth, *J. Organometal. Chem.*, **12**, 1, 497 (1968), and G. Costa, G. Mestroni, and G. Boscarato, *Ric. Sci., Parte 1*, 315 (1964).

[3] (a) Coupling dimers were only observed when the alkyl group contained no β-hydrogens (*e.g.*, methyl and neopentyl). The reaction of methylmagnesium bromide and ethyl bromide at 25° afforded only

Table I. Alkenylation of Grignard Reagents with an Iron Catalyst[a]

RMgBr, mmol	R'Br, mmol	Temp, °C	R–R'	%[b]
$CH_3(CH_2)_5MgBr$ (40)	$CH_2{=}CHBr$ (204)	0	Octene-1	83
$H_2C{=}CH(CH_2)_4MgBr$ (30)	$CH_2{=}CHBr$ (102)	25[e]	1,7-Octadiene	64
$CH_3(CH_2)_5MgBr$ (40)	$CH_3CH{=}CHBr$[c] (355)	25[e]	Nonene-2	67[d]

[a] Conditions not necessarily optimum. In 150 ml of THF with 5 × 10^{-2} mmol of $FeCl_3$. [b] Isolated yield based on Grignard reagent. [c] A 70:30 mixture of *cis*- and *trans*-1-bromopropene. [d] A 53:47 mixture of *cis*- and *trans*-nonene-2. [e] Exothermic reactions.

$$\mathrm{EtMgBr} + \mathrm{EtBr} \xrightarrow{\mathrm{Fe}} C_2H_6 + C_2H_4 + MgBr_2 \qquad (1)$$

rates of formation of ethane and ethylene could be expressed by eq 2,[4] the kinetic form of which is related

$$\frac{d[C_2H_6]}{dt} = \frac{d[C_2H_4]}{dt} = k[\mathrm{Fe}]^{1.0}[\mathrm{EtBr}]^{0.8}[\mathrm{EtMgBr}]^{0} \qquad (2)$$

to the earlier study of the silver catalyst.[5] Similarly, the reaction between 0.18 *M* ethylmagnesium bromide

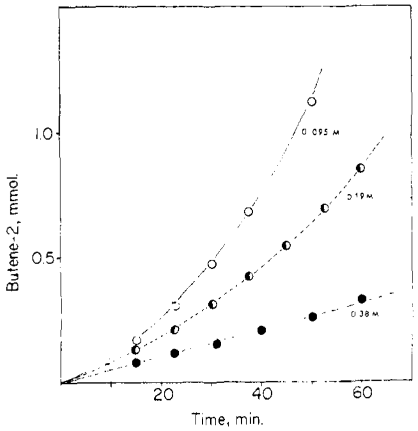


Figure 1. The retarding effect of methylmagnesium bromide on the rate of iron-catalyzed propenylation: in THF solution containing 0.57 *M* propenyl bromide, 2.4 × 10^{-5} *M* iron, and (○) 0.095 *M*, (◐) 0.19 *M*, and (●) 0.38 *M* methylmagnesium bromide at 25°.

and 0.30 *M* *tert*-butyl bromide at 2° was catalyzed by 2.4 × 10^{-4} *M* iron according to eq 4. However, in the

$$\mathrm{EtMgBr} + tert\text{-}\mathrm{BuBr} \xrightarrow{\mathrm{Fe}} \underset{(1.46)}{[C_2H_6} + \underset{(1.36)}{C_2H_4} + \underset{(1.45)}{i\text{-}C_4H_{10}} + \underset{(1.55)}{i\text{-}C_4H_8]} + MgBr_2 \qquad (3)$$

presence of 0.4 *M* styrene, reaction 3 produced only ethane and ethylene, but no isobutane or isobutylene. The selective trapping by styrene of the alkyl moiety derived from the organic halide (as *tert*-butyl radical) could also be demonstrated in the reaction between ethylmagnesium bromide and *n*-propyl bromide (*n*-propyl radical trapped).[6]

These observations support a mechanism (eq 4–7) for the catalytic disproportionation, which is a combination of those previously postulated for silver and copper.[5]

$$\mathrm{RBr} + \mathrm{Fe} \longrightarrow \mathrm{R}\cdot + \mathrm{FeBr} \qquad (4)$$

$$\mathrm{R}\cdot + \mathrm{Fe} \longrightarrow \mathrm{RFe} \qquad (5)$$

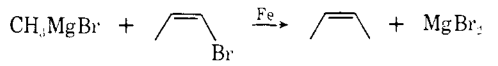
$$\mathrm{R'MgBr} + \mathrm{FeBr} \longrightarrow \mathrm{R'Fe} + MgBr_2 \qquad (6)$$

$$\mathrm{RFe, R'Fe} \longrightarrow [\mathrm{RH, R'H, R(-H), R'(-H)}] + 2\mathrm{Fe, etc.} \qquad (7)$$

1-Alkenyl halides, in marked contrast to alkyl halides, reacted readily with Grignard reagents in the presence of iron to afford cross-coupling products in good yields. *n*-Propylmagnesium bromide and vinyl bromide afforded pentene-1. Methylmagnesium bro-

$$\mathrm{RMgBr} + CH_2{=}CHBr \xrightarrow{\mathrm{Fe}} RCH{=}CH_2 + MgBr_2 \qquad (8)$$

mide (0.2 *M*) was converted (>95%) in 45 min to butene-2 by an excess of 1-propenyl bromide (0.6 *M*) in THF solution at 25° by 1.2 × 10^{-4} *M* iron catalyst. These reactions were stereoselective, since *cis*- and *trans*-propenyl bromide afforded *cis*- and *trans*-butene-2, respectively. In THF solution, *trans*-propenyl bromide



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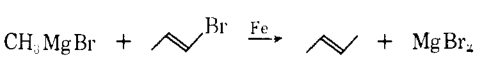
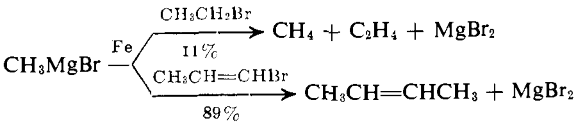


(10)

reacted 15 times faster than the cis isomer, whereas in diethyl ether it was only four times more reactive. Neither reaction was affected adversely by 0.5 *M* styrene. The rate of formation of butene-2 was first order in propenyl bromide but inversely related to the concentration of methylmagnesium bromide as illustrated in Figure 1.

Some representative examples of cross-coupled alkenes which were readily prepared by this simple procedure are presented in Table I.[7]

The iron-catalyzed reaction of Grignard reagents with *1-alkenyl* halides could be readily differentiated from the reaction with *alkyl* halides. Thus, a mixture of 0.57 *M* propenyl bromide and 0.16 *M* ethyl bromide on reaction with 0.19 *M* methylmagnesium bromide (eq 11) afforded no cross-over products such as pentene-



$$CH_3MgBr \xrightarrow[11\%]{Fe,\ CH_3CH_2Br} CH_4 + C_2H_4 + MgBr_2 \qquad (11a)$$

$$CH_3MgBr \xrightarrow[89\%]{Fe,\ CH_3CH{=}CHBr} CH_3CH{=}CHCH_3 + MgBr_2 \qquad (11b)$$

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equimolar amounts (94%) of methane and ethylene together with propane (6%) in the presence of 2.4 × 10^{-4} *M* ferric chloride. (b) In the following equations coordination around the metal species is unspecified unless necessary for discussion.

[4] (a) This empirical rate expression was applied to the first 10% of reaction. (b) At lower concentrations of iron (<10^{-5} *M*) or higher temperatures (>25°) ethane predominated.

[5] (a) M. Tamura and J. Kochi, *J. Amer. Chem. Soc.*, 93, 1483, 1485 (1971). (b) At this juncture the oxidation state of iron in eq 4–7 is a formalism and somewhat arbitrary since the primary intent is only to denote 1-equiv changes in the catalytic cycle. (c) The state of aggregation of the various iron species is unspecified; see ref 1.

[6] The latter results were complicated somewhat by alkyl exchange.

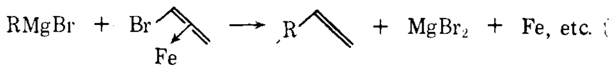
[7] (a) Other procedures for alkenylation by the reaction of alkyllithium and 1-bromoalkenes also have been recently reported; (b) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969); (e) E. J. Corey and G. H. Posner, *Tetrahedron Lett.*, 315 (1970).

2 or propylene. The latter certainly would have resulted if a propenyliron species (for example, from reactions 5 and 6, R = propenyl) were involved in the catalytic process. Moreover, the ethyliron species which were involved (eq 4–7) in the disproportionation reaction 11a could not have participated in the alkenylation reaction.

$$CH_3CH_2Fe + CH_3CH{=}CHBr \not\rightarrow CH_3CH{=}CHCH_2CH_3 + FeBr\text{, etc.} \quad (12)$$

The conclusion that the mechanism of the reaction of alkenyl halides differs from alkyl halides is based on the following observations: (a) the high yields and stereospecificity of the cross-coupled products, (b) the inverse dependence of the rate on the concentration of the Grignard reagent, (c) the effect of styrene, and (d) the one and one-half times greater reactivity of propenyl bromide compared to ethyl bromide despite the higher bond dissociation energy of the former.

We propose that the alkenylation reaction proceeds *via* an Fe-assisted displacement of the alkenyl halide by the Grignard reagent (eq 13). Retention of configuration during substitution implies an intramolecular delivery of the Grignard reagent, a process which may be possible *via* a ternary complex. The retardation by the Grignard reagent or added triphenylphosphine is consistent with coordination of the active Fe species in competition with the alkenyl halide.



(13)

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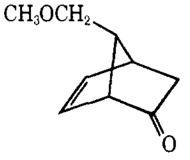
Methoxymethylation of Thallous Cyclopentadienide. A Simplified Preparation of a Key Intermediate for the Synthesis of Prostaglandins

Sir:

The bicyclic ketone I has been used as a key intermediate for the synthesis of all *six* of the primary prostaglandins[1] in naturally occurring form.[2-4] The synthetic approach to prostaglandins *via* I or its 7-benzyloxymethyl analog is currently being utilized on a substantial scale in several industrial laboratories and appears to be the most effective route for the production of these medically important substances. This communication describes a new preparation of I which involves novel chemistry and has several advantages over the procedure outlined earlier, most important of which is its operational simplicity and suitability for use on a large scale.

The first step in the synthesis of I as originally described[2a] was the alkylation of sodium cyclopentadienide with chloromethyl methyl ether in tetrahydrofuran at −55° to give after evaporation, addition of cold ether, and washing with pH 7 phosphate buffer (all operations <0°) the alkylated cyclopentadiene II. The diene II was utilized without delay in a diene addition to 2-chloroacrylonitrile at 0° in the presence of cupric tetrafluoroborate to generate the adduct III, from which the ketone I could be derived by alkaline hydrolysis. The preparation of II and III in this way, though acceptable as a research operation, left much to be desired for several reasons. Most importantly, isomerization of II to form the undesired IV occurs readily in the presence of acidic or basic substances even below 0°, and for this reason experimental results vary widely. As the scale of the alkylation reaction is increased, isolation requires more time, and isomerization becomes a serious side reaction so that chromatographic purification of the adduct III is required to separate the isomeric adduct V and other by-products in the bicyclo[3.2.0]heptane series.[5] Definite improvement in the alkylation process was effected by the use of the less basic lithium cyclopentadienide and the more reactive bromomethyl methyl ether as reactants in ether as solvent at −45°, followed by the usual low-temperature washing with a small amount of concentrated pH 7 buffer to remove inorganic salts. However, an outstanding and clearly superior procedure could be developed based on thallous cyclopentadienide rather than the conventionally employed alkali metal salts. One considerable advantage of the thallium derivative is its ready availability from aqueous thallous sulfate, potassium hydroxide, and cyclopentadiene (nitrogen atmosphere, >97% yield).[6] Another advantage is ease of handling and storage, since thallous cyclopentadienide is relatively stable in air.



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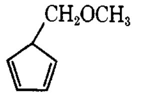

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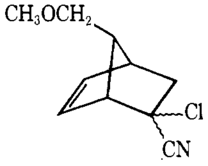
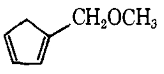
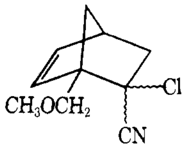


III



IV



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(1) S. Bergström, *Science*, **157**, 382 (1967).

(2) Prostaglandins $F_{2\alpha}$ and E_2: (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).

(3) Prostaglandins $F_{1\alpha}$ and E_1: E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970).

(4) Prostaglandins $F_{3\alpha}$ and E_3: E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).

(5) The reaction of 2-chloroacrylonitrile with cyclopentadienes under catalysis by cupric fluoroborate produces in addition to the expected norbornene adducts smaller amounts (10–40% depending on medium and temperature) of 2 + 2 cycloadducts of the bicyclo[3.2.0]heptane type; *cf.* (a) W. L. Dilling, R. D. Kroening, and J. C. Little, *ibid.*, **92**, 928 (1970), and (b) H. W. Thompson and D. G. Mellilo, *ibid.*, **92**, 3219 (1970).

(6) (a) H. Meister, *Angew. Chem.*, **69**, 533 (1957); (b) F. A. Cotton and L. T. Reynolds, *J. Amer. Chem. Soc.*, **80**, 272 (1958).