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N,N,N′,N′-Tetramethylethylenediamine-Copper Salt-catalysed Coupling of Aryl Grignard Reagents with Alkyl and Aralkyl Halides

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In the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and a small amount of copper salt, phenyl- and *p*-tolylmagnesium bromides react with alkyl or benzyl halide to give cross-coupling products in benzene or in a benzene–diethyl ether solvent. Among the alkyl iodides, normal iodides are most reactive, while secondary iodides do not react under our conditions. As copper salts, CuCl, $CuCl_2$, $CuCl_2$(TMEDA), and CuBr are all efficient for catalysis. This newly-developed catalytic system of TMEDA-copper salt is thought to be useful for the syntheses of polyalkyl-substituted aromatic hydrocarbons. As the reaction mechanism, the intermediate formation of TMEDA-coordinated organocopper(I) species and the nucleophilic displacement is proposed.

In general, Grignard reagents react very slowly, or not at all, with organic halides, except for some activated molecules, such as allylic halides.1) On the other hand it is well known that some transition metal salts catalyse these reactions efficiently for example, in the cobalt salt-catalysed "Kharasch reaction."3) Recent works4) have shown that, in these cobalt salt-catalysed reactions, zero-valent cobalt is a real catalytic species and that free radicals from organic halides are involved. In most of these metal salt-catalysed reactions, however, the cross coupling between the Grignard reagent and organic halide is not a predominant reaction.5)

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1) In some cases, reactions do occur by the use of a high temperature in high-boiling solvents or in neat, though the yields are generally low. It is also said that, in these high-temperature reactions, free radicals are involved.2)

2) "Methods of Elemento-Organic Chemistry," Vol. 2, ed. by A. N. Nesmeyanov and K. A. Kocheshkov, North-Holland, Amsterdam (1967) Chaps. 17 and 19.

3) M. S. Kharasch and O. Reinmuth, "Grignard Reagents of Nonmetallic Substances" Prentice-Hall, New York (1954).

4) F. W. Frey, Jr., *J. Org. Chem.*, **26**, 5187 (1961); J. Morizur, *Bull. Soc. Chim. Fr.*, **1964**, 1331; D. I. Davies, D. H. Hey, and M. J. Tiecco, *J. Chem. Soc.*, **1965**, 7062; M. H. Abraham and M. J. Hogarth, *J. Organometal. Chem.*, **12**, 1 (1968); D. I. Davies, J. N. Done, and D. H. Hey, *J. Chem. Soc., C*, **1969**, 1392.

5) a) Products from homocoupling, disproportionation, hydrogen abstraction or other radical involved reactions are major products. b) Of course there are special cases where cross couplings take place efficiently, for example: copper salt catalysed reaction of acetylenic Grignard reagent with allyl halide,6) vinyl halides react with Grignard reagents in the presence of iron affording cross coupling products in good yield,7) alkyl Griganrd reagents react with alkyl halides by the catalysis of copper(I) halide.8)

6) R. Ya. Levina and V. K. Daukshas, *Zh. Obshch. Khim.*, **30**, 1758 (1960).

7) M. Tamura and J. Kochi, *J. Amer. Chem. Soc.*, **93**, 1487 (1971).

8) M. Tamura and J. Kochi, *ibid.*, **93**, 1485 (1971).

We previously reported that the copper(I)-ethylenediamine complex can reduce benzyl chloride (Eq. (1)[9,10]), and aryl Grignard reagents are known to be easily oxidised by high-valent transition metal salts, such as copper(II),[11] and iron(III)[12,13] (Eq. (2)):

$$\mathrm{PhCH_2Cl} + \mathrm{Cu(I)(en)}_n \longrightarrow \mathrm{PhCH_2CH_2Ph} + \mathrm{Cu(II)(en)}_n \tag{1}$$

$$\mathrm{RX} \xrightarrow{\mathrm{Me}^{(n-1)+}} \mathrm{R{-}R} \tag{1'}$$

$$\mathrm{ArMgX} \xrightarrow{\mathrm{Me}^{n+}} \mathrm{Ar{-}Ar} \tag{2}$$

The combination of these two sets of reactions (Eqs. 1 and 2) suggests that the bidentate amine-copper salt system may be a good catalyst for the reaction between Grignard reagents and organic halides. From this point of view, we investigated the copper salt-*N,N,N',N'*-tetramethylethylenediamine(TMEDA)-catalysed reaction of aryl Grignard reagnets with alkyl and aralkyl halides. In this paper we will report that this system is a good catalyst for *cross* couplings.

$$\mathrm{ArMgX{+}RX'} \xrightarrow[\text{copper salt}]{\text{TMEDA}} \mathrm{Ar{-}R} \tag{3}$$

Experimental

Materials. The *N,N,N',N'*-tetramethylethylenediamine was prepared according to the method in the literature[14] and was cautiously distilled in nitrogen after having been refluxed on sodium. Commercial triethylamine was distilled on sodium. The reagent-grade alkyl iodides were used after distillation. The isobutyl and *sec*-butyl iodides were prepared from the corresponding alcohols.[15] All the substituted benzyl chlorides and benzyl chloride were used without further purification. Reagent-grade anhydrous cuprous chloride and bromide were further purified by the usual method. Anhydrous cupric chloride was obtained from the product of the dehydration of the dihydrate by heating *in vacuo* at 100°C for several days. $\mathrm{CuCl_2}$ (TMEDA) was prepared by Bertini's method[16] in butanol.

The standard substances for glc, propyl-, isobutyl-, *sec*-butyl-, amyl- and isoamylbenzene, and *p*-methyl-, *p,p'*-dimethyl- and *p*-chlorodiphenylmethane were prepared by the method described in this paper on a larger scale. They were identified by NMR, IR, and elemental analysis.

The benzene solution of the Grignard reagent-TMEDA complex was prepared by dropping phenyl- or *p*-tolylmagnesium bromide into a benzene sloution of TMEDA in the presence of magnesium turnings at 50°C;[17] afterward the solution was filtered and stored under a nitrogen atmosphere. The concentration was determined by chelate titration, mostly about 2.2—2.9×10^{-1} mol/*l*; 20—30 m*l* of the solution was used for a separate run. The Grignard reagent in diethyl ether was prepared in the usual manner and stored. The concentration was determined by acid-base titration.

Reaction Procedures. *Method A*: All the reactions were made under a nitrogen atmosphere. In a four-necked, round-bottomed flask equipped with a condenser, a thermometer, a nitrogen inlet, a dropping funnel, and a magnetic stirrer, 40 m*l* of benzene, organic halide, and a small amount of copper salt were placed. Then the reaction was started at 80°C by adding a benzene solution of the Grignard-TMEDA complex (25—30 m*l*) through the funnel. After completion, the reaction mixture was hydrolysed and extracted with ether, and the extract was condensed. The product analysis was made by glc with a 2 m Silicone DC550 column.

Method B: To the solution of organic halide, TMEDA, and copper salt in 40 m*l* of benzene, we dropped an ether solution of the Grignard reagent (20—25 m*l*) at 60°C. The other procedures were the same as in Method A.

Results and Discussion

As expected, cross coupling occurred between aryl Grignard reagents and alkyl or benzyl halides as a result of the use of the catalytic system of TMEDA-copper salt in benzene or in a benzene–ether solvent. As an amine ligand, TMEDA, is chosen because TMEDA has no active hydrogen and is known to be a good coordinating ligand not only for copper but also for a Grignard reagent.[18] The mole ratio of TMEDA to the Grignard reagent should be above one-to-one to obtain good results. On the other hand, the appropriate quantity of copper salt is around 5 mole percent. The use of an excess of copper salt usually increases unfavorable by-products. It should be noted that if one of pair of this catalytic system (TMEDA and copper salt) is absent, the reaction does not take place at all.

There are two methods for the reaction. In "Method A," a Grignard reagent-TMEDA complex prepared in benzene is allowed to react with organic halide in the presence of copper salt in benzene at 80°C. In "Method B," a Grignard reagent prepared in diethyl ether is dropped into a benzene solution of organic halide, TMEDA, and copper salt at 60°C. The ratio of benzene to ether is about 2: 1.

$$\text{Method A}\quad \mathrm{ArMgBr(TMEDA)} + \mathrm{RX} \xrightarrow[\text{benzene}]{\text{copper salt}} \mathrm{Ar{-}R} + \mathrm{MgBrX(TMEDA)} \tag{4}$$

$$\text{Method B}\quad \mathrm{ArMgBr} + \mathrm{RX} \xrightarrow[\text{benzene-ether}]{\text{TMEDA, copper salt}} \mathrm{Ar{-}R} + \mathrm{MgBrX} \tag{5}$$

In THF or in diethyl ether, the reaction does not proceed.

Reactions with Alkyl Halides. Tables 1 and 2 show the results of the reaction of phenyl and *p*-tolylmagnesium bromide with a variety of alkyl halides. These results may be summarized as follows. i) The yields of cross-coupling products from the reaction of phenyl Grignard reagent with normal alkyl iodides

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9) K. Wada and H. Hashimoto, This Bulletin, **41**, 3601 (1968); K. Onuma, J. Yamashita, and H. Hashimoto, *ibid.*, **43**, 836 (1970).

10) Chromium(II)-ethylenediamine complex is known more powerful reductant: J. K. Kochi and J. W. Powers, *J. Amer. Chem. Soc.*, **92**, 137 (1970).

11) E. Sakellarios and Th. Kyrimis, *Ber.*, **57**, 322 (1924).

12) G. Champetier, *Bull. Soc. Chim. Fr.*, **47**, 1131 (1930).

13) W. B. Smith, *J. Org. Chem.*, **26**, 4206 (1961); also see Ref. 2.

14) R. W. Moshier and L. Spialter, *ibid.*, **21**. 1050 (1956).

15) H. Stone and H. Shechter, "Organic Syntheses," Coll. Vol. IV, (1963), p. 323.

16) I. Bertini and F. Mani, *Inorg. Chem.*, **6**, 2032 (1967).

17) E. C. Ashby and R. Reed, *J. Org. Chem.*, **31**, 971 (1966).

18) In the presence of TMEDA Grignard reagent can be prepared in nonpolar solvent, see Ref. 17.

TABLE 1. REACTION WITH ALKYL HALIDE, METHOD A PhMgBr·TMEDA: 6×10^{-3} mol or 7.5×10^{-3} mol, RX: 5×10^{-3} mol, CuCl: 5.3±0.1 mol %, in benzene, 24 hr.

RX	Temp. °C	PhMgBr/RX	Yield[a] of Ph-R (%)
n-BuBr[b]	80	1.2	44
n-BuI	80	1.2	65
n-BuI	80	1.5	79
n-PrI	80	1.5	64
n-PrI	80	1.5	69
EtI	70	1.5	85
MeI	40	1.5	93
n-AmI	80	1.5	73
i-BuI	80	1.5	33
i-AmI	80	1.5	62

a) Based on alkyl halide.
b) 10 hr.

TABLE 2. REACTION WITH ALKYL HALIDE, METHOD B ArMgBr: 6×10^{-3} mol, R′X: 5×10^{-3} mol, TMEDA: 8.5×10^{-3} mol (TMEDA/R′X∼1.7), CuCl: 5.3±0.1 mol %, in benzene–ether (2: 1), 60°C, 24 hr.

R-⌬-MgBr	R′I	Yield[a] of R-⌬-R′ (%)
H	n-PrI	81
H	n-BuI	85
H	i-PrI	7
H	EtI	83
H	MeI[b]	9[c]
H	n-AmI	83
H	sec-BuI	4
H	i-BuI	61
H	i-BuI	68[d]
H	i-AmI	71
CH_3	EtI	82
CH_3	n-BuI	80

a) Based on alkyl halide.
b) At 40°C.
c) Methyl iodide reacts with TMEDA before Grignard reagent is added.
d) 48 hr.

are generally good, and alkyl substitution on the aromatic ring does not affect the yields. This provides a useful synthetic procedure for a variety of alkyl-substituted aromatics. ii) Among alkyl halides, alkyl iodides are most reactive. iii) The steric effect is rather significant; that is, secondary iodides do not react, and the yields with alkyl iodides which are branched at the β or γ position are considerably decreased. iv) Method A is more susceptible to this steric effect.[19] v) In the case of methyl iodide, which is very reactive toward TMEDA,[20] Method B is not applicable, but in Method A an ordinary reaction takes place smoothly, suggesting that coordinated TMEDA reacts no more with the iodide.

TABLE 3. EFFECT OF ADDED TMEDA IN METHOD B PhMgBr: 6×10^{-3} mol, n-BuI: 5×10^{-3} mol, CuCl: 5.3±0.1 mol %, in benzene–ether (2: 1), 60°C.

TMEDA/n-BuI	Reaction time hr	Yield[a] of ⌬-Bu^n (%)
1.0	5	35
1.0	24	52
1.3	24	77
1.6	24	86
1.9	24	85
2.1	24	86

a) Based on alkyl halide.

As the large steric hindrance may be partly attributable to the bulky TMEDA molecule, we tried to use triethylamine instead of TMEDA, but in the presence of triethylamine even normal alkyl iodides do not react. In Method B, as is shown in Tables 2 and 3, more than 1.6 times as much TMEDA as alkyl halide is necessary.[21]

The formation of biphenyl (or p,p′-bitolyl), which is the homocoupling product of Grignard reagent, as a by-product in the reaction is unavoidable; the yield is 10—25% in Method A and 2—4% in Method B. The increased percentage in Method A may be due to the relatively high reaction temperature.

Reactions with Benzyl Chlorides. The results of the reactions of phenyl and p-tolylmagnesium bromide with p-substituted benzyl chlorides are tabulated in Tables 4 and 5. Though the yields of the diphenylmethane derivatives are satisfactory, the p-methyl

TABLE 4. REACTION WITH BENZYL CHLORIDE, METHOD A R_1-⌬-MgBr·TMEDA: 6×10^{-3} mol or 7.5×10^{-3} mol, R_2-⌬-CH_2Cl: 5×10^{-3} mol, CuCl: 5.3±0.1 mol %, in benzene, 80°C, 5 hr

R_1-⌬-MgBr ·TMEDA (I)	R_2-⌬-CH_2Cl (II)	Yield[a] of R_1-⌬-CH_2-⌬-R_2 (%)	
		(I)/(II) =1.2	1.5
H	H	74	81
H	CH_3	79	84
H	Cl	78	79
CH_3	H	58	64
CH_3	CH_3	73	73

a) Based on benzyl chloride.

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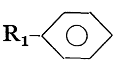
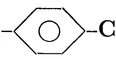
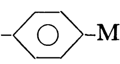
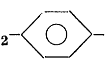
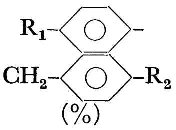
[19] This may be due to the fact that TMEDA is more tightly held to the complex in benzene than in benzene–ether solution.

[20] TMEDA is fairly basic amine, especially in nonpolar solvent: P. Paoletti, R. Barbucci, A. Vacca, and A. Dei, *J. Chem. Soc., A*, **1971**, 310.

[21] In our conditions alkyl iodides do not react with free TMEDA except for methyl iodide.

Table 5. Reaction with benzyl chloride, method B

R$_1$--MgBr: 6×10^{-3} mol, R$_2$--CH$_2$Cl: 5×10^{-3} mol, TMEDA: 6×10^{-3} mol, CuCl: 5.3± 0.1 mol%, in benzene–ether (2: 1), 60°C, 10 hr.

R$_1$--MgBr	R$_2$--CH$_2$Cl	Yield$^{a)}$ of  (%)
H	H	81
H	CH$_3$	89
H	Cl	85
CH$_3$	H	68, 78$^{b)}$
CH$_3$	CH$_3$	76

a) Based on benzyl chloride.
b) 20 hr.

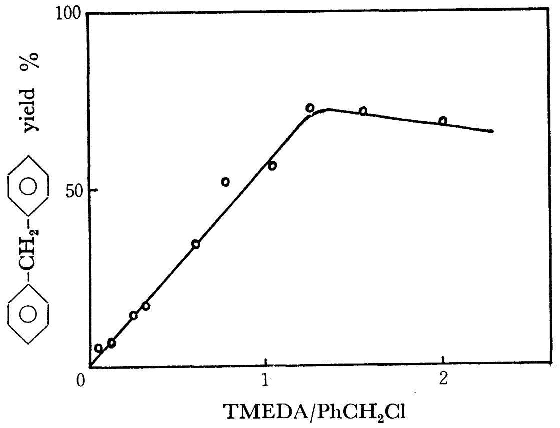


Fig. 1. Effect of added TMEDA in Method B PhMgBr: 6×10^{-3} mol, PhCH$_2$Cl: 5×10^{-3} mol, CuCl: 5.3±0.1 mol % in benzene–ether (2: 1) 60°C, 5 hr.

substitution of a Grignard reagent reduces the reactivity somewhat.

The elucidation of the substituent effect on benzyl chloride is rather difficult, because a side reaction between benzyl chloride and TMEDA takes place. Concerning this, there are some experimental facts. a) In Method B, the optimum ratio of TMEDA to benzyl chloride is around 1.2:1 (Fig. 1) and the presence of an excess of TMEDA reduces the yield, in keen contrast to the case of alkyl iodide. b) Also, in Method A, the further addition of TMEDA can not increase the yield, but such a further addition of TMEDA evidently shortens the necessary reaction time. c) In the presence of an excess of TMEDA, scarcely no unreacted benzyl choride is recovered, suggesting that it disappeared as a quaternary ammonium salt after the treatment. It is clear form these results that active benzyl chloride reacts with a non-coordinated excess TMEDA molecule to form ammonium salt. Therefore, an excess of TMEDA can not increase the yield of the cross-coupling product. As alkyl iodides do not react with free TMEDA, an excess of TMEDA can serve only for the promotion of the reaction.

In the reaction with benzyl chloride, biphenyl, bibenzyl, and a small amount of toluene are also obtained as by-products. The rough percentages of these by-products are as follows. In Method A, the biphenyl derivatives are 5—25% and the bibenzyl derivatives are 1—10%. In Method B. the biphenyl derivatives are 3—7% and the bibenzyl derivatives are 1—4%. Generally speaking, Method B gives a little better results.

Copper Salts. The cupric chloride-TMEDA complex (CuCl$_2$TMEDA) was prepared and used as a catalyst, but the yield of cross coupling is only around 10%. In the presence of a large amount of TMEDA, that is, under ordinary reaction conditions, the catalytic activity of the CuCl$_2$TMEDA complex is just the same as that of cuprous chloride. This suggests that the coordination of TMEDA not only to copper but also to a Grignard reagent is important. The coordination of TMEDA must increase the carbanion character of the organic moiety of the Grignard reagent.[22]

CuCl$_2$ and CuBr as well as CuCl and CuCl$_2$TMEDA have similar reactivity. The use of copper(II) salt, however, increases the formation of biphenyl, only a little but obviously.

Other transition metal salts, such as ferric chloride, cobaltous chloride, and chromous chloride, can also bring about the reaction, but homocouplings are predominant, as in an ordinary "Kharasch reaction."

Reaction Mechanism. Some features of the reaction with alkyl halide can be summarized as follows: (i) The order of the reactivity of alkyl halide is I$\gg$Br$\gg$Cl. (ii) The steric hindrance is relatively large. iii) CH$_3$I and C$_2$H$_5$I are excellently reactive. These results suggest that the reaction type is very similar to the bimolecular nucleophilic displacement.

The addition of cyclohexene (a mild radical scavenger) or acrylonitrile does not affect it at all, showing that the formation of a free radical is unlikely. It can be said, therefore, that the mechanism of copper catalysis is different from that of cobalt,[4] silver,[23] or iron[7] salt, where the formation of a free radical by the reduction of an organic halide by a zero-valent metal is observed.

Tamura and Kochi[8] reported recently that, in the copper salt-catalysed coupling of an alkyl Grignard reagent with alkyl halide in THF, the formation of organocopper, followed by its nucleophilic displacement, is the key step in the catalysis; the results obtained here support this idea.

To make sure that the copper metal is not operative, the Grignard reagent was first allowed to react with a catalytic amount of cuprous chloride. When the deposition of copper metal began after 1 hr, alkyl iodide was added to this solution. The yield of the cross-coupling product by this procedure was significantly lowered. On the other hand, as has been mentioned already, the use of copper(II) salt as a

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[22] In case of organolithium compounds such polarizing effect is apparent: M. D. Rausch and D. J. Ciappenelli, *J. Organometal. Chem.*, **10**, 127 (1967); A. J. Chalk and T. J. Hoogeboom, *ibid.*, **11**, 615 (1968).

[23] M. Tamura and J. Kochi, *J. Amer. Chem. Soc.*, **93**, 1483 (1971).

catalyst increases the biphenyl formation from the Grignard reagent, which means that copper(II) is first reduced to the copper(I) state by the Grignard reagent. The intermediate formation of the organocopper species from the Grignard reagent and copper(I) is, therefore, most probable. Organocuprate complexes are known to be very reactive toward alkyl and aryl halides.[24]

Thus, we propose as the reaction mechanism the formation of organocopper and its nucleophilic displacement;

$(\mathrm{L})\mathrm{CuX} + \mathrm{PhMgBr(L)} \longrightarrow (\mathrm{L})\mathrm{CuPh} + \mathrm{MgBrX(L)}$[25] (6)

$(\mathrm{L})\mathrm{CuPh} + \mathrm{RI} \longrightarrow \mathrm{Ph{-}R} + (\mathrm{L})\mathrm{CuI}$[26] (7)

L: TMEDA

The displacement may be assisted by copper:

$$\begin{tikzcd}(\mathrm{L})\mathrm{Cu} \arrow[d, dash] & \mathrm{I} \arrow[l] \arrow[d, dash] \\ \mathrm{Ph} \arrow[r] & \mathrm{R}\end{tikzcd}$$

Finally, we want to emphasize again that this reaction takes place only when the catalytic system of TMEDA-copper salt is present. TMEDA plays an important role as a coordinating ligand on both the Grignard reagent and copper.

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[24] E.J. Corey and G.H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); E.J. Corey and G.H. Posner, *ibid.*, **90**, 5615 (1968); G.M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, *ibid.*, **91**, 4871 (1969).

[25] It is possible that real organocopper species is not (L)CuPh but complexes with magnesium like LCuPh(MgBrXL): R. J. Depasquale and C. Tamborski, *J. Org. Chem.*, **34**, 1736 (1969).

[26] Considering the effect of TMEDA coordination which can stabilize high valent state there can not be excluded the possibility of reaction path of Eq. 8:

$\mathrm{LCuPh{+}RI} \rightarrow \mathrm{ILCu(III)}\cdot\mathrm{Ph}\cdot\mathrm{R} \rightarrow \mathrm{R{-}Ph{+}LCuI}$ (8)

such redox cycle is probable in copper catalysis but there are no evidence at present: H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).