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Reactivity of mixed organozinc and mixed organocopper reagents. Part 4: a kinetic study of group transfer selectivity in C—C coupling of mixed diorganocuprates

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The competitive rate data and Taft relationships for the coupling of bromomagnesium *n*-butyl (substituted phenyl) cuprates with alkyl bromides show that selective *n*-butyl transfer can be explained by an oxidative addition mechanism. Taft reaction constants also show that the residual group FG-C_6H_4 in the mixed cuprate *n*-Bu(FG-C_6H_4)CuMgBr changes the ability of the copper nucleophile to react with the electrophile RBr. These results provide support for the commonly accepted hypothesis regarding the dependence of the R^1 group transfer ability on the strength of R^2—Cu bond in reactions of R^1R^2CuMgBr reagents. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: alkylation of mixed cuprates; competitive kinetics; mixed magnesium cuprates; Taft plots

INTRODUCTION

Organocuprates, R_2CuM (M: Li, MgBr), represent a class of organometallic reagents most used in organic syntheses because of their reactivity toward carbon electrophiles.[1,2] However, in the reaction of R_2CuM, only one organic group is transferred to the electrophile. The solutions for this problem are (i) the use of mixed diorganocuprates of R^1R^2CuM type, in which one of the R^1 and R^2 groups has a lower transfer rate than the other and (ii) the use of mixed organocuprates of R_RR_TCuM type composed of one transferable group R_T together with the residual (non-transferable or dummy) group R_R. For the first type of mixed cuprates, organic groups bearing sp-C or sp^2C such as alkynyl,[3–5] aryl,[5,6] 2-thienyl,[7,8] and cyano groups[9] have been found to have a lower transfer rate. Selectivity in organic group transfer in reactions of mixed cuprates R^1R^2CuM has been investigated in detail by Whitesides,[5] House,[10] and Posner.[11] The relative rate of organic group transfer is known to be in the order of *n*-Bu ∼ s-Bu ∼ t-Bu » Ph alkynyl and vinyl Me » alkynyl. However, for the mixed cuprates R^1R^2CuLi.LiCN[12–14] the observed preference for Me over vinyl in substitution reactions gets reversed in 1,4-addition reactions.[13] Recently, Knochel has shown that mixed functionalized aryl cuprates containing Me_3CCH_2 or Me_2CPhCH_2 groups selectively transfer the functionalized aryl groups.[15] For the second type of mixed cuprates, organic groups such as RS,[16] R_2N,[17,18] and R_3P[17–19] have also been used as residual groups.

Among the atom-economic mixed diorganocuprates, the most attractive appeared to use cyanocuprates RCu(CN)Li or R(2-thienyl)CuLi[7] and their cyano analogs R(2-thienyl) CuLi.LiCN.[8,20] Bertz introduced a trimethylsilylmethyl (TMSM) group as a residual group and reported that the mixed cuprates R(TMSM)CuLi[21] are more reactive than the corresponding homocuprates R_2CuLi. A number of reactions of mixed lithium cuprates of R_1R_2CuLi type[5,10–15] and also R_RR_TCuLi type[6–9,16–21] have been reported. It is well known that the Grignard reagent derived magnesium cuprates do not have the same reactivity as lithium cuprates in some reactions; however, they are more readily available and thermally stable.[22] Mixed magnesium cuprates of R^1R^2CuMgBr type[22–24] and R_RR_TCuMgBr type[23,25] have been found as successful alternatives to mixed lithium cuprates. Mixed cuprates $R_R(R_T)_n$CuM$_n$ (M = Li, MgBr) ($n = 2,3$)[12] or their cyano analogs R_RR_TCuLi.MCN (M = MgBr,[12,13] Na[26]) have been reported to increase the group transfer selectivity in some reactions.

In mixed diorganocuprates of the R^1R^2CuM type, the organic group selectivity to transfer to an electrophile is considered to be a function of R^1—E or R^2—E formation in the reductive elimination of the Cu(III) intermediate R^1R^2ECu, which is formed in the oxidative addition step (Scheme 1).[1] Oxidative addition is the rate determining step in the substitution of diorganocuprates with alkyl halides.[1] However, studies on their 1,4-addition to enones indicated that the rate determining step may also be a reductive elimination of the Cu(III) intermediate step (Scheme 1).[27,28]

A widely accepted hypothesis for the transfer selectivity of the R^1 or R^2 group to an electrophile is that the group which has a stronger bond to Cu in R^1R^2CuE acts as the group of lower transfer selectivity.[1,5] However, detailed studies have also been reported regarding the controlling factors for the group transfer selectivity of mixed lithium cuprates in their 1,4-addition reactions.[29]

We are currently working on the reactivities of mixed organocopper and mixed organozinc reagents and controlling factors of group transfer selectivity in their reactions.[30,31] To the

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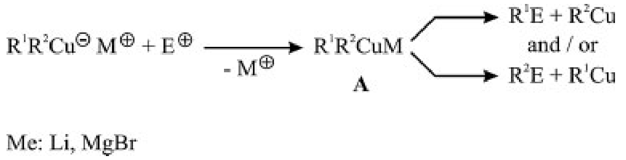


Scheme 1.

best of our knowledge, the control of group transfer selectivity in reactions of $R^1R^2CuMgBr$ type mixed cuprates has not been investigated in detail so far.

Here we report results of our competitive kinetic studies and Taft correlations for the alkylation of mixed *n*-butyl (substituted phenyl) cuprates in THF to provide a kinetic support for the hypothesis of the dependence of the R^1 group transfer ability on the strength of the R^2—Cu bond in reactions of $R^1R^2CuMgBr$ reagents.

RESULTS AND DISCUSSION

As model mixed magnesium cuprates, we chose *n*-butyl (substituted phenyl) cuprates, in which the *n*-butyl group has a much higher transfer selectivity than the phenyl group in their reactions. We selected the *n*-butyl–*n*-alkyl coupling reaction to test our hypothesis that the reaction rate of the *n*-butyl group depends on the strength of substituted phenyl—Cu bond.

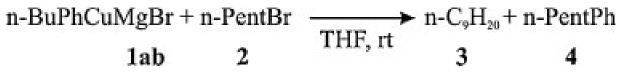
In order to find out suitable reaction conditions for the kinetic studies of alkylation of *n*-butyl (substituted phenyl) cuprates, we first carried out a brief investigation to see how the reaction conditions affect the group transfer selectivity in C—C coupling reactions. We chose the alkylation of bromomagnesium *n*-butyl (phenyl) cuprate **1** with *n*-pentyl bromide **2** in THF at room temperature as a model reaction (Scheme 2).

We focused on the following parameters: (i) preparation method of the mixed cuprates, reaction temperature and time, (ii) Cu(I) compounds used for Mg → Cu transmetallation, and (iii) co-solvents and additives. The relative transfer ability of *n*-Bu and Ph groups was determined by quantitative GC analysis using authentic samples of **3** and **4**.

(i) We prepared *n*-butylphenylcuprate **1ab** by using two different methods. In Method A, *n*-butylmagnesium bromide or phenylmagnesium bromide was first transmetallated to obtain the corresponding monocopper reagent and then allowed to react with the other Grignard reagent. Either phenylcopper or *n*-butylcopper was used as the organocopper reagent (Methods A_1 and A_2, respectively).

In Method B, di-*n*-butylcuprate **1aa** and diphenylcuprate **1bb** were mixed; either di-*n*-butyl cuprate or diphenylcuprate was added to the other cuprate reagent (Method B_1 and Method B_2, respectively).

Method A_1 and Method A_2 were tested to see if the organyl group originally bonded to Cu or Mg could make a change in the relative transfer ability of *n*-butyl and phenyl groups. Methods B_1 and B_2 were tried to find if the transfer ability of the groups would be affected by the possible equilibrium between di-*n*-butyl cuprate **1aa** and diphenylcuprate **1bb** to form *n*-butylphenylcuprate **1ab**.



$$\underset{\mathbf{1ab}}{n\text{-BuPhCuMgBr}} + \underset{\mathbf{2}}{n\text{-PentBr}} \xrightarrow[\text{THF, rt}]{} \underset{\mathbf{3}}{n\text{-}C_9H_{20}} + \underset{\mathbf{4}}{n\text{-PentPh}}$$

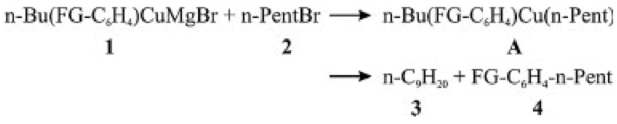
Scheme 2.

We used CuI as the transmetallation reagent for the preparation of mixed cuprate **1ab** and carried out the alkylation reaction with a ratio of 3:1 for **1ab**:**2** at room temperature for 3 h (optimized conditions). The total yield and the product ratio **3**:**4** were found to be 92% (97:3), 95% (100:0), 74% (98:2), and 81% (98:2) using the mixed cuprate **1ab** prepared by the Methods A_1, A_2, B_1, and B_2, respectively. As expected, Methods A_1 and A_2 gave a higher and almost equal total yield of coupling, and the original bonding of *n*-butyl group to Cu or Mg was found to be not important. We used the mixed cuprate **1ab** prepared according to Method A_2 for further experiments. The lower yields obtained using the mixed cuprate **1ab** prepared by Methods B_1 and B_2 may indicate that the *n*-butyl transfer is affected by the extent of the equilibrium between **1aa** and **1bb** to yield **1ab**. The background yields for alkylation of the mixed cuprate **1ab** was found to be 71% for di-*n*-butylcuprate **1aa** and 3% for diphenylcuprate **1bb**. It is surprising that the *n*-butyl group in the mixed cuprate **1ab** is alkylated with a higher yield than the *n*-butyl group in di-*n*-butylcuprate **1aa**.

(ii) We screened a number of CuX compounds for transmetallation of *n*-butylmagnesium bromide to obtain *n*-butylcopper *n*-Bu(X)CuMgBr used for the preparation of *n*-butylphenylcuprate **1ab**. The use of CuBr, CuCl, and CuSCN lowered the total yield to 58–84% with almost complete *n*-butyl selectivity (**3**:**4** = 99:1). However, CuCN changed both the total yield and transfer ability of the *n*-butyl group since the mixed cuprate **1ab-CN** was alkylated with a total yield 59% and a lower *n*-butyl selectivity (**3**:**4** = 75:25). Using CuCN.2LiCl increased the total yield to 84% with a **3**:**4** ratio of 81:19. However, the obvious change obtained with the mixed cyanocuprate, which is expected to exist as *n*-BuPhCuMgBr.MgBr(CN), may seem reasonable since lithium analogs of mixed cyanocuprates $R^1R^2CuLi.LiCN$ have already been reported to exhibit alternative selectivity for organic group transfer.[12–14]

In the coupling reaction, we also used $n\text{-BuPh}_2\text{Cu(MgBr)}_2\text{.MgBrI}$ **1ab₂** and its cyano analog, $n\text{-BuPh}_2\text{Cu(MgBr)}_2\text{.MgBr(CN)}$ **1ab₂-CN**, which are higher order mixed cuprates prepared using CuI and CuCN, respectively, expecting that **1ab₂-CN** would give a lower yield and *n*-butyl selectivity than that obtained with **1ab₂**, similar to the results obtained with *n*-BuPhCuMgBr.MgBrI **1ab** and *n*-BuPhCuMgBr.MgBr(CN) **1ab-CN** as stated above. As expected, coupling of **1ab₂** resulted in a total yield of 50% and *n*-butyl selectivity of **3**:**4** = 84:16, whereas **1ab₂-CN** coupled with a low *n*-butyl selectivity of **3**:**4** = 70:30, but with a higher yield of 79%. As seen, the higher order cuprate **1ab₂** containing two residual Ph groups gave a much lower coupling yield of 50% compared to 95% obtained with the lower order cuprate **1ab**.

(iii) We carried out the alkylation reaction of mixed cuprate **1** in THF using a coordinating co-solvent, a Lewis base or acid as an additive. We had already reported success in the control of group transfer selectivity by changing the solvent or using an additive in the acylation of *n*-butylphenylzinc[30] and other mixed diorganozincs[31] in THF. However, using THF:HMPA (1:1), THF:DMPU (1:1), THF:NMP (1:1), or THF:diglyme (1:1) as solvent for the coupling of the mixed cuprate **1ab** did not make an appreciable change in the total yield, i.e., 70–90% compared to 92% yield in THF. The complete transfer selectivity of the *n*-Bu group also did not change. However, the *n*-butyl transfer yield lowered to 19% for the reaction in THF:TMEDA (1:1). Use of TMSCl, $MgCl_2$ and also



Scheme 3.

n-Bu_3P and bipyridyl as additives did not lead to a change in the total yield (85–99%) and n-Bu transfer ability.

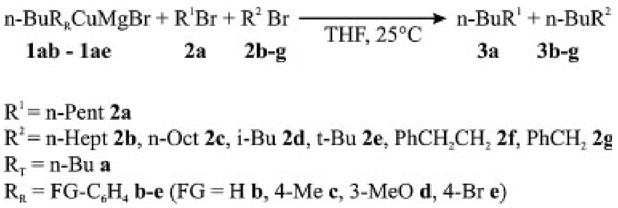
In summary, we observed that the complete transfer selectivity of the n-butyl group in the reaction of n-BuPhCuMgBr **1ab** with n-pentyl bromide **2** in THF does not change by reaction conditions. We also tested substituted phenyl groups as residual groups in mixed n-butylcuprate. We found that the alkylation of mixed cuprates, n-Bu (FG-C_6H_4)CuMgBr (FG: 4-Me, 3-MeO, 4-Br), takes place with a total yield of 47, 65, and 100%, respectively, with n-butyl selectivity higher than 95% compared to the total yield of 92% with n-BuPhCuMgBr **1ab**.

This result led to the idea that the transferable character of n-Bu group would change by changing the residual character of the substituted phenyl group. In accordance with the commonly accepted hypothesis for coupling of mixed cuprates, we would expect a significant effect of the strength of the FG-C_6H_4-Cu bond on the transfer rate of the n-Bu group (Scheme 3). In the formation of the Cu(III) intermediate **A** in the rate determining oxidative addition step, the FG-C_6H_4 group may form a stronger bond in the Cu(III) intermediate to stay on the Cu atom in reductive elimination. As the functional group is expected to affect the strength of the FG-C_6H_4-Cu bond, it would also affect the formation rate of the Cu(III) intermediate or, in other words, the n-butyl transfer rate of **1**.

We assumed, therefore, that the n-Bu-n-Pent coupling rate of n-Bu(FG-C_6H_4)CuMgBr reagents with n-PentBr would be affected by the electronic effects of the functional group on the residual group FG-C_6H_4. This study was undertaken to critically examine this assumption. For this purpose, we carried out a kinetic study in three steps. First, we found the rate constants of the coupling of n-Bu(FG-C_6H_4)CuMgBr reagents with n-PentBr and other alkyl bromides to see the dependence of the reaction rate on the residual group, FG-C_6H_4. Secondly, we applied Taft methodology to find the electronic effects in these reactions, and thirdly, we investigated the dependence of Taft reaction constants of n-Bu(FG-C_6H_4)CuMgBr reagents on the residual group, FG-C_6H_4.

The reactions of lithium diorganocuprates with alkyl and aryl halides have been shown to be of first order in the cuprate and in the organyl halide and take place by displacement of the leaving group in the electrophile, E = R—A (Scheme 1) with diorganocuprate nucleophile to form a triorganyl Cu(III) intermediate in the rate determining step. There are a few reported works on the kinetics of the coupling of homocuprates.[32–35] However, the kinetics of reactions of mixed cuprates have not been investigated so far. Hence, our findings regarding the rate constants and Taft reaction constants for mixed cuprate–alkyl coupling reactions might provide support for the substitution mechanism of mixed cuprates as well as for our assumption regarding the group transfer ability of these reagents.

Bertz had recently reported[36] the observation of a Cu(III) intermediate in the reaction of $Me_2CuLi.LiX$ (X = I, SCN, SPh, CN) with ethyl iodide in THF and had also reported that any process that replaces a residual group with a transferable one (i.e., from X = SPh to X = Me) may result in diminished yield of the coupled product. This result also supports our idea.



Scheme 4.

In the kinetic study of the coupling reaction of n-butyl(phenyl)cuprate **1ab** with n-PentBr **2a**, we found the absolute rate measurements to be complicated and time consuming due to the heterogeneous reaction. So, we used the competitive kinetics method, in which a pair of R^1Br(n-PentBr) **2a** and R^2Br reacted with a limited amount of n-butyl(phenyl)cuprate **1ab** (Scheme 4). As alkyl bromides R^2Br **2b-f**, we chose a number of prim-alkyl bromides **2a-d**, t-butyl bromide **2e**, homobenzyl bromide **2f**, and benzyl bromide **2g**. Taft reaction constants were found for the reactions of a number of n-butyl (substituted phenyl) cuprates **1ab**–**1ae** by collecting their competitive rate data. Taft correlation was also found for the alkylation of bromomagnesium di-n-butylcuprate **1aa**.

In the competitive reaction of A^1 and A^2 with subequimolar B to give the products C^1 and C^2, assuming a first-order reaction in A, relative reactivities of A^1 and A^2 are calculated using Eqn (1)[37,38]

$$\left\{\begin{matrix}A^1\\A^2\end{matrix}\right\} + B \begin{matrix}\xrightarrow{k_1}\\ \xrightarrow{k_2}\end{matrix} \left\{\begin{matrix}C^1\\C^2\end{matrix}\right\} \qquad (1)$$

$$\frac{k_2}{k_1} = \frac{\log([A^2]_t/[A^2]_0)}{\log([A^1]_t/[A^1]_0)}$$

where k_2/k_1 is the competitive rate ratio (competition constant[39]), $[A]_t$ and $[A]_0$ are the concentrations of the competitive reactants (A_1 and A_2) at the time t (a suitable reaction time or the end of the reaction) and their initial concentrations, respectively. Among the reported methods[37–50] for competitive kinetics, Eqn (2) was also frequently used for calculation of competitive rate ratios,

$$\frac{k_2}{k_1} = \frac{\%\text{yield of } C^2}{\%\text{yield of } C^1} \qquad (2)$$

where the yield of products C_1 and C_2 are measured at a suitable reaction time or at the end of the reaction.[46–48]

For calculating the rate ratios for the competitive coupling of alkyl bromides R^1Br and R^2Br with a mixed cuprate, we adapted Eqn (1) as follows:

$$\frac{k_2}{k_1} = \frac{\log([R^2Br]_1/[R^2Br]_0)}{\log([R^1Br]_1/[R^1Br]_0)} \qquad (3)$$

where $[RBr]_t$ and $[RBr]_0$ are the amounts of competing reactants at time t and $t = 0$, respectively. However, being interested in the competitive formation rate of coupling products and also assuming small perturbations of side reactions, we made the simplification $[RBr]_t = [RBr]_0 - [n\text{-Bu-R}]_t$ and rearranged Eqn (3) in terms of the coupling products n-Bu-R^1 and n-Bu-R^2

as follows:

$$\frac{k_2}{k_1}=\frac{\log\left([\mathrm{R^2Br}]_0-[n\mathrm{-BuR^2}]_t/[\mathrm{R^2Br}]_0\right)}{\log\left([\mathrm{R^1Br}]_0-[n\mathrm{-BuR^2}]_t/[\mathrm{R^2Br}]_0\right)}=\frac{\log\left(1-([n\mathrm{-BuR^2}]_t/[\mathrm{R^2Br}]_0)\right)}{\log\left(1-([n\mathrm{-BuR^1}]_t/[\mathrm{R^1Br}]_0)\right)} \tag{4}$$

We have already used a similar equation successfully in the competitive amination kinetics of phenyl and substituted phenyl carbanions derived from Grignard reagents,[51,52] stoichiometric magnesium–copper reagents[51] and catalytic zinc-copper reagents.[52] We have also used the competitive rate date in the application of Hammett methodology for the amination reactions.[51,52]

With the same simplication, Eqn (2) can be adapted as follows:

$$\frac{k_2}{k_1}=\frac{\%\mathrm{yield\ of\ }n\mathrm{-BuR^2}}{\%\mathrm{yield\ of\ }n\mathrm{-BuR^1}} \tag{5}$$

with competing R^1Br (*n*-PentBr) and R^2Br.

Before collecting the rate data leading to a suitable reactivity profile, we carried out preliminary experiments to see whether the alkylation of mixed cuprate **1ab** would meet the requirements of the competitive kinetics method. As we could arrange the experimental conditions to keep the amounts of the products *n*-BuR^1 (*n*-C_9H_{20}) and *n*-BuR^2 much higher than the experimental error during the progress of the reaction and since we also observed that the difference between the reaction rates of R^1Br and R^2Br are not large, we decided that competitive coupling of alkyl bromides R^1Br and R^2Br with a mixed cuprate **1ab** would allow us to collect reliable data.

We optimized the scale for competition to be $[R^1Br]:[R^2Br]:[\mathbf{1}] = 7:7:1$ and we found the amount of *n*-BuR^1 and *n*-BuR^2 by GLC analysis. Carrying out the reaction in the presence of an internal standard, taking 4–8 samples at 5 or 10 min intervals and quenching the samples, and calculating the amount of products in each sample and taking the average of k_2/k_1 values did not give reproducible results, possibly owing to the heterogeneous reaction. Therefore, we applied the method that we used in the competitive amination study of phenyl carbanions,[51,52] i.e., 4–8 competition experiments were carried out in different flasks in the presence of an internal standard and the reactions were quenched at different time points. This method of analysis gave more reproducible results in the evaluation of reactivity profiles for competitive alkylation. We also used Eqn (5) to calculate the competitive rate ratios and found that these values are in accordance with those found by using Eqn (4). However, taking the average k_2/k_1 values found by Eqn (5) led to a lower mean deviation of 4–8% than that found by Eqn (4), both are in the error limit of GLC analysis.

We carried out experiments for the alkylation kinetics of *n*-butyl (phenyl) cuprate **1ab**, *n*-butyl (4-tolyl) cuprate **1ac**, *n*-butyl (*p*-anisyl) cuprate **1ad**, and *n*-butyl (4-bromophenyl) cuprate **1ae** with competing alkyl bromides **2a–g** in THF at room temperature. The competitive rate ratios k_2/k_1 are given in Table 1.

The competitive rate ratios k_2/k_1 were also found for the alkylation kinetics of di-*n*-butyl cuprate **1aa** and are given in Table 1. Taft inductive substituent constants σ^* and steric

Table 1. Competitive rate ratios for the alkylation of bromomagnesium di-*n*-butylcuprate **1aa**, *n*-butyl phenylcuprate **1ab**, and *n*-butyl (substituted phenyl) cuprates **1ac–1ae** with alkyl bromides **2b–f** in the presence of *n*-pentyl bromide **2a** in THF at 25 °C

$$\underset{\mathbf{1}}{\mathrm{n-BuR_RMgBr}}+\underset{\mathbf{2a}}{\mathrm{R^1Br}}+\underset{\mathbf{2b-g}}{\mathrm{R^2Br}}\xrightarrow[\mathrm{THF,\ 25^\circ C}]{}\underset{\mathbf{3a}}{\mathrm{n-BuR^1}}+\underset{\mathbf{3b-g}}{\mathrm{n-BuR^2}}$$

$$\mathrm{R_R}=\underset{\mathbf{a}}{\mathrm{n-Bu}}\quad\underset{\mathbf{b}}{\mathrm{H-C_6H_4}}\quad\underset{\mathbf{c}}{\mathrm{4-MeC_6H_4}}\quad\underset{\mathbf{d}}{\mathrm{3-MeOC_6H_4}}\quad\underset{\mathbf{e}}{\mathrm{4-BrC_6H_4}}$$

$$\mathrm{R^1=n-Pent}$$

			k_2/k_1[a,b]				
			R_R				
R^2	σ^*[c]	E_s[c]	H-C_6H_4 **b**	4-MeC_6H_4 **c**	3-MeOC_6H_4 **d**	4-BrC_6H_4 **e**	*n*-Bu **a**
n-Pent **2a**	−0.16	−0.40	1.00[d]	1.00[d]	1.00[d]	1.00[d]	1.00[d]
n-Hept **2b**	−0.17	−0.17	1.14	1.34	1.15	1.18	1.21
n-Oct **2c**	−0.17	−0.17	1.05	1.07	—	—	0.92
i-Bu **2d**	−0.125	−0.93	0.14	0.18	0.16	0.13	0.13
t-Bu **2e**	−0.30	−1.64	0.08	0.11	0.14	0.13	0.18
$PhCH_2CH_2$ **2f**	0.08	−0.55	0.68	0.69	0.69	0.69	0.70
$PhCH_2$ **2g**	0.215	—	23	84	51	65	76

[a] $k_2/k_1 = k_{R2Br}/k_{R1Br}$.

[b] The average of k_2/k_1 values (4–8 experiments) was calculated from the competition experiments using Eqn (5). The relative error of the values does not exceed 8%.

[c] Inductive substituent σ^* and steric constants E_s to use in the Taft–Ingold equations are taken from Reference [53].

[d] By definition, $R^2Br = R^1Br$.

constants E_s for alkyl groups to be used in the Taft equation and Taft–Ingold equation are also given in Table 1.[53–56]

First, we compared the competitive ratios for alkylation of bromomagnesium *n*-butyl (substituted phenyl) cuprates **1ab–ae** with the same alkyl bromide. As seen, the rate ratio diminishes in the order of **1ac** > **1ad** or **1ae** > **1ab** in the alkylation with *n*-HeptBr **2b** and $PhCH_2Br$ **2g**, and in the order of **1ac** > **1ad** > **1ab** ~ **1ae** in the alkylation with i-BuBr **2c**. The rate ratio has been found to be constant in the alkylation of **1ab–ae** with $PhCH_2CH_2Br$ **2f** for a reason as yet unknown. In the alkylation with sterically hindered t-BuBr **2e**, however, the highest rate ratio was obtained with **1ad** and **1ae**.

As we assumed the oxidative addition to be the rate determining step in the coupling of mixed cuprates, as in the coupling of homocuprates, we tried to explain the role of the substituted phenyl ligand group on the competitive rate ratio. In the reactions of monoorganocoppers $R^1Cu(Z)LMgBr$ and diorganocuprates $R^1{}_2CuLMgBr.MgBrZ$ prepared from 1 or 2 equivalents of R^1MgBr and 1 equivalent of CuZ or CuZ.L (Z = Cl, Br, I, CN, and L = Ligand), Z and L are known to favor oxidative addition in the coupling with RA if they are σ-donor–π-acceptor ligands.[57,58] However, reductive elimination of Cu(III) intermediates, $R^1RCu(Z)L$ or $R^1{}_2RCuL$, which are formed by coupling of $R^1Cu(Z)LMgBr$ and $R^1{}_2CuLMgBr.MgBrZ$, respectively is expected to be fast with σ-acceptor ligands.[58,59] If in the coupling of *n*-butyl (substituted phenyl) cuprates **1ab, ac,** and **ae**, the σ-donor properties of substituted phenyl ligands for a soft acid center Cu(I) decrease in the order of 4-MeC_6H_4 > **c** C_6H_5 **b** > 4-BrC_6H_4 **e**, then the rate ratios of **1ab, ac,** and, **ae** for coupling with the same alkyl bromide are expected to decrease in the same order. As expected, in the alkylation of mixed *n*-butylcuprates we found the highest rate ratio for the cuprate containing 4-MeC_6H_4 **c** as the residual group and the lowest rate ratio for the cuprate containing C_6H_5 **b** or 4-BrC_6H_5 **e** as the residual groups. However, σ-donor properties of $FG\text{-}C_6H_4$ groups will decrease the ease of reductive elimination of *n*-Bu($FG\text{-}C_6H_4$)RCu intermediates to give *n*-BuR and then formation of *n*-BuR will take place possibly with a lower yield in the case of *n*-Bu(4-MeC_6H_4)RCu than that in the case of *n*-Bu(C_6H_5)RCu and *n*-Bu(4-BrC_6H_4)RCu. In the coupling of *n*-Bu($FG\text{-}C_6H_4$)MgBr reagents with *n*-PentBr, the yield of *n*-C_9H_{20} was found to be 47, 92, and 100% using 4-MeC_6H_4, C_6H_5, and 4-BrC_6H_5 as the residual groups, respectively. These results support our assumption that the coupling rate of a mixed cuprate changes, depending on the residual group.

The competitive rate ratios for *n*-$Bu_2CuMgBr$ **1aa** were found to be higher than those obtained for *n*-Bu(C_6H_5)CuMgBr **1ab**, but comparison with those obtained for **1ac–ae** did not give a satisfactory result.

Secondly, the competitive rate ratios for the alkylation of mixed *n*-butylcuprates **1ab–ae** and also alkylation of di-*n*-butylcuprate **1aa** were subjected to the one parameter version of the Taft equation, $\log(k_2/k_1) = \rho^*\sigma^*$ rather than its two parameter version, the Taft–Ingold equation, $\log k_2/k_1 = \rho^*\sigma^* + \delta E_s$.[53–56] The successful use of the one parameter Taft equation was already reported in the copper(I) catalyzed acylation of Grignard reagents.[60] The plots of $\log(k_2/k_1)$ against the Taft inductive substituent constants σ^* for the coupling of *n*-Bu($FG\text{-}C_6H_4$)CuMgBr reagents **1ab–ae** and *n*-$Bu_2CuMgBr$ **1aa** gave positive reaction constants: for *n*-Bu($FG\text{-}C_6H_4$)CuMgBr reagents, $\rho^* = 4.044$ ($r = 0.921$) (FG = H); 4.951 ($r = 0.995$) (FG = 4-Me); 5.521 ($r = 0.966$) (FG = 3-MeO); 4.775 ($r = 0.957$) (FG = 4-Br); and for *n*-$Bu_2CuMgBr$ $\rho^* = 4.619$ ($r = 0.949$).

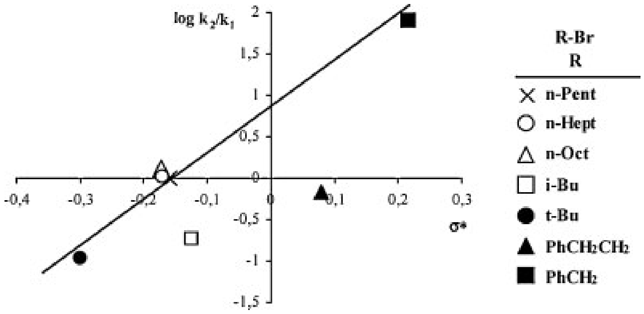


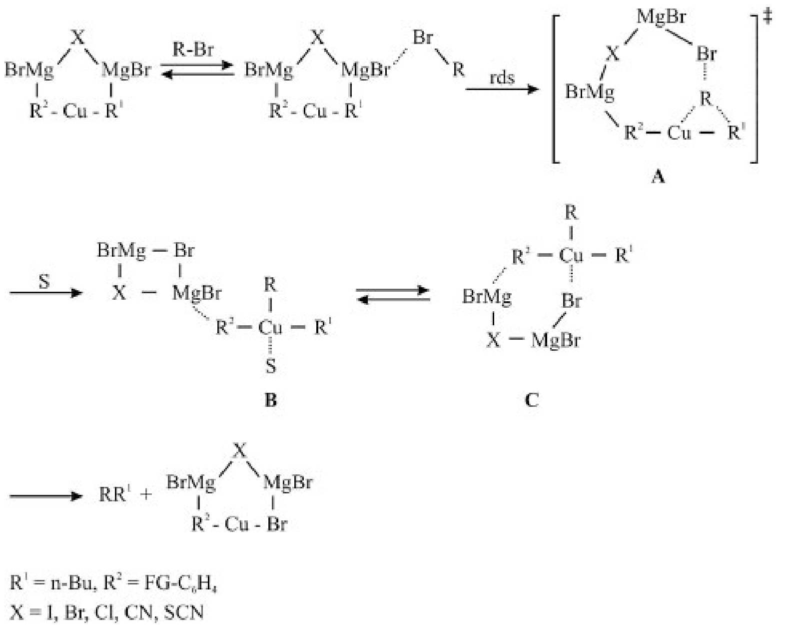
Figure 1. Taft plot for the competitive coupling kinetics of phenyl (4-tolyl) cuprate **1ac** with alkyl bromides in THF at 25 °C

Taft plot for competitive alkyl coupling of *n*-Bu(4-MeC_6H_4)CuMgBr **1ac** is given in Fig. 1. A reasonably good linear relationship was obtained for each reaction except for the points for coupling partners, i-BuBr **2d** and $PhCH_2CH_2Br$ **2f**. These points were found to be lying significantly outside the linear plots. The linearity of Taft plots supports the assumption of a first-order reaction in the cuprate *n*-$BuR_RCuMgBr$ and *n*-$Bu_2CuMgBr$ for the calculation of competitive rate ratios. The reaction constants ρ^* are all positive, as expected, i.e., these reactions are accelerated by electron-attracting alkyl groups in RBr that help in the formation of the *n*-BuR_RRCu intermediate between a copper nucleophile *n*-$BuRCu^{\delta-}$ and electrophile $R^{\delta+}$ in the rate determining step. The magnitudes of ρ^* for mixed cuprates *n*-Bu($FG\text{-}C_6H_4$)CuMgBr show that the amount of negative charge developed at the reaction center, R-Br, changes depending on the residual group, $FG\text{-}C_6H_4$.[53] However, both electron donating and electron-attracting substituents on the residual group of the copper nucleophile, increase the sensitivity of the reaction to change in the R group of RBr.

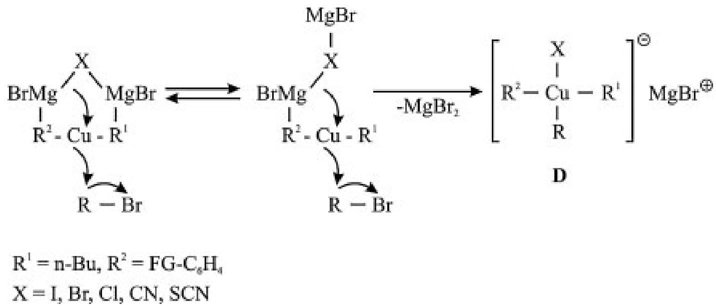
Due to the downward deviation of i-BuBr **2d** from the linear ρ^*–σ^* plot, we subjected the competitive rate ratios to the two parameter Taft–Ingold equation to determine whether the steric effect is important in the coupling of mixed *n*-butylcuprates **1ab–ae** with alkyl bromides. However, correlations gave negative inductive reaction constants, $\rho^* = -0.307 - (-0.437)$ and steric reaction constants, $\delta = 0.778 - 1.039$ with a far greater scatter of points than that obtained with the Taft equation. So, instead of evaluating the steric effect, we applied a transformation to change the two-parameter plot to a one-parameter plot.[54] This approach gave a satisfactory result with positive inductive reaction constants $\rho^* = 0.451 - 0.683$ for mixed *n*-butylcuprates **1ab–ae** and $\rho^* = 0.369$ for di-*n*-butylcuprate. These results also provide support for our assumption that the residual group in the mixed cuprate changes the ability of the copper nucleophile to react with the electrophile.

In order to propose a reaction pathway for *n*-butyl transfer in the coupling of mixed *n*-butylcuprates with alkyl bromides, we assumed a heterodimer contact ion pair structure for bromomagnesium cuprates similar to lithium cuprates and assumed pathways similar to the mechanisms proposed by Nakamura and Yoshikai[14,32] and also recently by Bertz[36] for the coupling of lithium diorganocuprates.

We may suggest that the oxidative addition of a mixed cuprate can take place through the formation of the transition state **A** according to the mechanism proposed by Nakamura and Yoshikai (Scheme 5).[14,32] The R^1R^2RCu intermediate is formed after the rate determining halide displacement step as the



Scheme 5.



Scheme 6.

unstable transient species **B** and **C** which have a T-shape geometry with the fourth ligand (solvent or halide). In the case of coupling of mixed cuprates *n*-Bu(FG-C_6H_4)CuMgBr, R^2 was assumed to be FG-C_6H_4 for the elimination of *n*-BuR. However, it seemed to us less speculative to propose a mechanism involving the reactive intermediate proposed by Bertz (Scheme 6).[36] Oxidative addition of *n*-Bu(FG-C_6H_4)CuMgBr can take place through the formation of the R^1R^2RCu intermediate as transient species **D**. Assumption of the formation of **D** may help to explain the difference in the ease of reductive elimination of *n*-BuR in the case of different X ligands.

In conclusion, the competitive rate data and Taft relationships obtained in this study show that selective *n*-butyl transfer in the coupling of bromomagnesium *n*-butyl (substituted phenyl) cuprates with alkyl bromides can be explained by an oxidative addition mechanism.

Taft reaction constants for the coupling of mixed cuprates *n*-Bu(FG-C_6H_4)CuMgBr show that the amount of negative charge developed at the reaction center RBr by the copper nucleophile changes depending on the residual group FG-C_6H_4, and provide support for our assumption that the residual group in the mixed cuprate changes the ability of the copper nucleophile to react with the electrophile. These results also support the commonly accepted hypothesis regarding the dependence of the R^1 group transfer ability on the strength of R^2—Cu bond in reactions of R^1R^2CuMgBr reagents.

EXPERIMENTAL

All reactions were carried out under dry nitrogen atmosphere using oven-dried glassware. Reagents and solvents were handled by using standard syringe–septum cap techniques.[61] Quantitative GLC analyses were performed on a Thermo Finnigan gas chromatograph equipped with a ZB-5 capillary column packed phenyl–polysiloxane using an internal standard technique. THF was distilled from sodium benzophenone dianion. Pure HMPA, NMP, DMPU, and diglyme were distilled just before use. *n*-BuBr, C_6H_5Br, 4-MeC_6H_4Br, 3-$MeOC_6H_4Br$, and 4-BrC_6H_4Br were obtained commercially and purified using literature procedures. Mg turnings for Grignard reagents were used without purification. CuI,[62] CuBr,[63] CuCl,[63] CuCN,[64] and CuSCN[62] were purified according to the published procedures. Grignard reagents, *n*-BuMgBr, and FG-C_6H_4MgBr (FG = H, 4-Me, 3-MeO, 4-Br) were prepared in THF according to the standard procedure and their concentrations were found by titration prior to use.[65] *n*-Bu_2CuMgBr **1aa** was prepared by the addition of 2 molar equivalent of *n*-BuMgBr to a suspension of 1 molar equivalent of

CuI in THF at −20 °C and stirring at that temperature for 15–30 min. Mixed *n*-butyl (phenyl) cuprates *n*-Bu (FG-C_6H_4) CuMgBr **1ab–ae** (FG = H **b**, 4-Me **c**, 3-MeO **d**, 4-Br **e**) were prepared according to the method A_2. To *n*-BuCu prepared by the addition of 1 mol equiv of *n*-BuMgBr to a suspension of CuI in THF at −20 °C was added 1 molar equivalent of FG-C_6H_4MgBr at this temperature with continuous stirring for 15–30 min.

The general procedure for the competitive coupling of a pair of *n*-PentBr **2a** and **2b–g** with a cuprate is given below for the coupling of *n*-butyl (phenyl) cuprate **1ab** with *n*-PentBr **2a** and PhCH$_2$Br **2g**. The scale for competition is 1:7:7 for cuprate: **2a**:**2b–g**. To a flame-dried two-necked and round bottom flask equipped with a septum cap and a stirring bar, CuI (0.5 mmol) in 3 cm^3 of THF was added at −20 °C and *n*-BuMgBr (0.5 mmol) was placed by a syringe and the mixture was stirred for 2 min. To the light yellow *n*-BuCu suspension was added PhMgBr (0.5 mmol) by syringe at −20 °C. Heterogeneous solution of *n*-BuPhMgBr **1ab** was stirred at that temperature for 15 min. To the cuprate **1ab**, a mixture of *n*-PentBr **2a** (3.5 mmol) and PhCH$_2$Br (3.5 mmol) prepared separately was added rapidly. The flask was removed from the cooling bath and the reaction mixture was stirred at 25 °C for an appropriate time (5, 10, 15,. . ., 40 min or 10, 20, 30, 40, 50 min or 15, 30, 45, 60 min). The internal standard, di-*n*-pentylether (0.9918 mmol, 0.2 cm^3) was added and the mixture was hydrolyzed with saturated NH$_4$Cl solution containing 20% NH$_3$. The aqueous phase was extracted with diethyl ether and the product mixture was analyzed by GLC.

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