

## Selectivity in Organic Group Transfer in Reactions of Mixed Lithium Diorganocuprates<sup>1</sup>

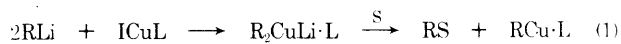
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Received August 29, 1973

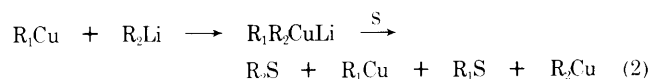
Solutions obtained by mixing 1 equiv of organo(ligand)copper(I) reagent (organo = *n*-butyl, *sec*-butyl, *tert*-butyl, phenyl, and 1-pentynyl) with 1 equiv of an organolithium reagent having a different organic group have been allowed to react with 1-bromopentane, methyl vinyl ketone, and nitrobenzene. The relative yields of products observed in these reactions of "mixed" lithium diorganocuprates, "R<sub>1</sub>R<sub>2</sub>CuLi," are summarized and used to infer the relative reactivities of the two organic groups in these complexes. Organic moieties that form stable, unreactive, copper(I) compounds (1-pentynyl, *tert*-butoxyl, aryl) show the smallest reactivity in these cuprates and are the most generally useful first components for mixed ate complexes in which it is intended that the second component react preferentially with substrate. However, use of these groups has one drawback in reactions involving certain substrates of low reactivity: the reactivity of the second organic group in the mixed complex is significantly decreased by inclusion in the complex, relative to that which would be expected from the corresponding symmetrical cuprate. If mixed cuprates made from stable organocopper compounds show insufficient reactivity, mixed complexes containing a highly basic organic group, particularly *tert*-butyl, may have advantages. A survey of the relative reactivity of several alkyl bromides toward lithium di-*n*-butylcuprate establishes a structure-rate profile for nucleophilic coupling characteristic of an S<sub>N</sub>2 reaction.

Lithium dialkyl-, diaryl-, and divinylcuprates are widely used in organic synthesis.<sup>2-4</sup> The most commonly employed preparations of these materials involve reaction between 2 equiv of an organolithium reagent and 1 equiv of copper(I) halide, either alone or complexed with a phosphine, phosphite, or sulfide; the resulting organocopper(I) compound is normally used without isolation (in eq 1, S represents the substrate being attacked by the cuprate).



This procedure suffers from three characteristics that frequently prove inconvenient in practical applications. The first is a consequence of the low thermal stability and solubility of many uncomplexed organocopper(I) compounds: the 1 or more equiv of trialkylphosphine or phosphite often included in the reaction mixture to stabilize and solubilize the organocopper(I) reagents severely complicates the work-up of the reaction. A second disadvantage of the procedure reflects the stoichiometry of most of the reactions of lithium dialkylcuprates commonly employed in organic synthesis, *viz.*, only one of the two alkyl groups of the dialkylcuprate is normally converted to product; the second, appearing as (unreactive) alkylcopper(I) compound, is usually lost to thermal decomposition or in work-up. This circumstance is clearly unattractive when the starting organolithium reagent is expensive or difficult to prepare.<sup>5</sup> The third is that organolithium reagents are required for the synthesis; the more readily available organomagnesium compounds do not always yield organocopper ate complexes having the same reactivity as lithium dialkylcuprates.<sup>6</sup>

Two types of partial solutions have been offered to the problems provided by this synthetic procedure. First, trimethyl phosphite<sup>6b</sup> and tris(dimethylamino)phosphine<sup>7</sup> have been suggested to be more readily separated from products during the work-up of reaction mixtures than are trialkylphosphines. Second, "mixed" ate complexes, R<sub>1</sub>R<sub>2</sub>CuLi, have been prepared by mixing 1 equiv of an organocopper(I) compound with 1 equiv of an organolithium compound derived from a different organic moiety; these solutions may show a pronounced and useful selectivity in transferring one of the two organic groups to substrate. Several groups R<sub>1</sub> have been used for this purpose: (CH<sub>3</sub>)<sub>3</sub>C,<sup>6a</sup> CN,<sup>8</sup> *n*-C<sub>3</sub>H<sub>7</sub>C≡C,<sup>7</sup> (CH<sub>3</sub>)<sub>3</sub>CC≡C,<sup>9</sup> (CH<sub>3</sub>)<sub>3</sub>CO.<sup>10</sup> Of these, the last two appear the most at-

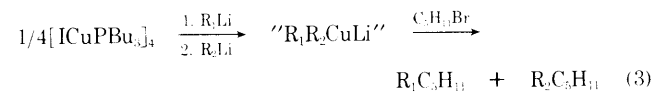


tractive in principle, in major part because (CH<sub>3</sub>)<sub>3</sub>COCu and (CH<sub>3</sub>)<sub>3</sub>CC≡CCu are both thermally stable and soluble in ethereal solvents in the absence of added ligands; they are, however, less readily available than CuCN or *n*-C<sub>3</sub>H<sub>7</sub>C≡CCu, and these latter materials may offer advantages in noncritical applications. The selectivities afforded by mixed dialkylcuprates are less clear-cut than those by mixed alkyl(alkylethynyl)cuprates, but these also may have use when high reactivity is required (see below).

In this paper we report the results of a survey of the selectivities exhibited by a number of mixed lithium diorganocuprates in the transfer of their organic moieties to substrates in three typical reactions of cuprates: nucleophilic coupling with 1-bromopentane,<sup>11,12</sup> oxidative coupling using nitrobenzene,<sup>12,13</sup> and conjugate addition to methyl vinyl ketone.<sup>3</sup> These experiments were carried out in order to establish the most generally useful of the groups R<sub>1</sub> (eq 2) in encouraging transfer of the group R<sub>2</sub> to substrate, to define the selectivities expected from various combinations of organic moieties, and to explore the possibility that the selectivities exhibited in reactions of mixed cuprates might be helpful in inferring their structures in solution.<sup>14</sup>

### Results

**Reactions of Mixed Lithium Diorganocuprates with 1-Bromopentane.** With the exceptions of cuprates containing acetylenic groups, organocopper reagents were prepared at -78° in tetrahydrofuran solution by addition of 1 equiv of one organolithium reagent to 1 equiv of tetrakis[iodo(tri-*n*-butylphosphine)copper(I)], followed by addition of 1 equiv of a second organolithium reagent. The



resulting homogeneous solutions of organocopper(I) reagents will be referred to for convenience simply as solutions of lithium diorganocuprates, "R<sub>1</sub>R<sub>2</sub>CuLi," although they probably contain mixtures of several different cuprates and almost certainly incorporate tri-*n*-butylphosphine and lithium iodide into certain of these species. These solutions were treated with 1 equiv of 1-bromopentane.

**Table I**  
**Yields of Coupled Products  $R_1C_5H_{11}$  and  $R_2C_5H_{11}$  from Reaction of Mixed Lithium Diorganocuprates " $R_1R_2CuLi$ " with 1-Bromopentane**

$R_1$	$R_2$	Registry no.	Yield, % <sup>a</sup>	
			$R_1C_5H_{11}$	$R_2C_5H_{11}$
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	24406-16-4		93
	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	49585-84-4	23, 45 <sup>b</sup>	65, 16 <sup>b</sup>
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	49585-85-5	26, 33 <sup>b</sup>	64, 9 <sup>b</sup>
	C <sub>6</sub> H <sub>5</sub>	49585-86-6	84, 62 <sup>b</sup>	7, 18 <sup>b</sup>
	C <sub>3</sub> H <sub>7</sub> C≡C	39697-41-1	79, 82 <sup>b</sup>	<1, <1 <sup>b</sup>
<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	23402-73-5		98
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	49585-88-8	61	32
	C <sub>6</sub> H <sub>5</sub>	49585-89-9	75	3
	C <sub>3</sub> H <sub>7</sub> C≡C	49585-90-2	80 <sup>b</sup>	<1 <sup>b</sup>
<i>t</i> -C <sub>4</sub> H <sub>9</sub>	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	23402-75-7		94
	C <sub>6</sub> H <sub>5</sub>	49585-91-3	61	2
	C <sub>3</sub> H <sub>7</sub> C≡C	39697-42-2	83 <sup>b</sup>	<1 <sup>b</sup>
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	23402-69-9		100
	C <sub>3</sub> H <sub>7</sub> C≡C	49585-93-5	6 <sup>b</sup>	<1 <sup>b</sup>

<sup>a</sup> Yields are based on the stoichiometry of eq 1, *viz.*, on the assumption that only one of the two alkyl groups of " $R_1R_2CuLi$ " is converted to product. Cuprate solutions contained 1 equiv of tri-*n*-butylphosphine and 1 equiv of lithium iodide, unless otherwise noted. <sup>b</sup> Phosphine- and halide-free solutions of cuprate were used. The low yields in certain of these reactions reflect the thermal instability of the cuprate solutions.

tane at  $-78^\circ$  and the resulting mixtures were allowed to warm to room temperature over the course of 2 hr. The mixtures were analyzed directly by glpc. The order in which the organolithium reagents were added to the solution, and precipitation of lithium halide with dioxane, had no influence on the yields of products. Omission of tri-*n*-butylphosphine, however, had a significant influence on the product distribution in some cases; for example, in the reactions of  $LiCu(n-C_4H_9)(sec-C_4H_9)$  and  $LiCu(n-C_4H_9)(tert-C_4H_9)$  with 1-bromopentane the relative yields of products were reversed by omission of the phosphine. Experiments involving 1-pentynylcopper(I) were carried out by adding 1 equiv of an organolithium reagent to a suspension of 1 equiv of this acetylenic copper reagent at  $-78^\circ$  and stirring for 30 min at  $-78^\circ$  before adding 1-bromopentane. Less than half of the 1-pentynylcopper(I) seemed to dissolve under these circumstances, and the resulting suspensions were used without filtration.

In certain instances, solutions containing phosphines showed significantly higher reactivity toward 1-bromopentane than did phosphine-free solutions, although the relative yields of  $R_1C_5H_{11}$  and  $R_2C_5H_{11}$  obtained from phosphine-free and phosphine-containing solutions were very similar for cuprates containing the 1-pentynyl moiety. Thus, the homogeneous solution resulting from addition of 2 equiv of tri-*n*-butylphosphine to solutions containing 1-pentynylcopper showed higher reactivity toward 1-bromopentane than did the partially heterogeneous mixtures: in the presence of phosphine, reaction was complete in 30 min at  $0^\circ$ ; in the absence of phosphine, 8–10 hr at  $-20^\circ$  was required to maximize yields. Nonetheless, the yields of  $R_1C_5H_{11}$  and  $R_2C_5H_{11}$  were similar in both the phosphine-free and phosphine-containing solutions. The observed yields of the two possible products of coupling of the groups  $R_1$  and  $R_2$  of these mixed lithium cuprates with the 1-pentyl moiety are summarized in Table I. Two features of these data deserve brief comment. First, although the selectivities in alkyl group transfer characterizing mixed cuprates in which both  $R_1$  and  $R_2$  are alkyl moieties is not high, 1-pentyne and phenyl clearly resist transfer. This observation supports the suggestion<sup>7-9</sup> that acetylenic moieties are useful first components of mixed ate complexes from which it is desired to transfer the second organic group; since a phenyl moiety is also retained on copper, this group should also be useful for this purpose. Second, the yields of  $R_2C_5H_{11}$ , based on the quanti-

**Table II**  
**Yields of Coupled Products from Reaction of (*sec*-C<sub>4</sub>H<sub>9</sub>)(*t*-C<sub>4</sub>H<sub>9</sub>)CuLi with 1-C<sub>5</sub>H<sub>11</sub>X**

X	Registry no.	Solvent <sup>b</sup>	Yield, % <sup>a</sup>		Ratio <sup>c</sup>
			<i>sec</i> -C <sub>4</sub> H <sub>9</sub> -C <sub>5</sub> H <sub>11</sub>	<i>t</i> -C <sub>4</sub> H <sub>9</sub> -C <sub>5</sub> H <sub>11</sub>	
Br	110-53-2	Et <sub>2</sub> O	58	33	1.8
		THF-HMPA (1:1)	54	31	1.7
		Dimethoxyethane	45	23	1.9
		Pentane	~1	~1	<i>d</i>
Cl	543-59-9	THF	61	32	1.9
			46	43	1.1
I	628-17-1		57	34	1.7
OTs	4450-76-4		57	35	1.6

<sup>a</sup> Yields are calculated on the same basis as those in Table I. <sup>b</sup> Each solvent contained *ca.* 20% hexane which originated as the solvent for the lithium reagents. One equivalent of lithium iodide and tri-*n*-butylphosphine was present in each cuprate solution. <sup>c</sup> Ratio = (yield *sec*-C<sub>4</sub>H<sub>9</sub>-C<sub>5</sub>H<sub>11</sub>)/(yield *t*-C<sub>4</sub>H<sub>9</sub>-C<sub>5</sub>H<sub>11</sub>). <sup>d</sup> The accuracy of these yields is sufficiently low that their ratio would not be significant.

ty of the group  $R_2$  present in the solution using both  $R_1 = C_3H_7C\equiv C$  and  $R_1 = C_6H_5$ , are in most instances appreciably higher than those obtained using the unmixed complexes. Note that to compare the yields of, *e.g.*,  $R_1C_5H_{11}$ , derived from  $R_1R_1CuLi$  and  $R_1R_2CuLi$ , the reported yield for the former should be divided by two; the yields in Table I assume that only one of the two organic groups of either ate complex reacts. Hence the maximum yield, based on  $R_1$ , that could be obtained from  $R_1R_2CuLi$  is 50%. Thus, the mixed copper complexes provide a more economical reagent for converting  $R_2Li$  to product than do the unmixed complexes.

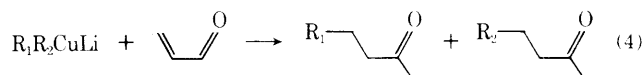
Brief study suggests that the selectivities exhibited in Table I are generally insensitive both to the solvent in which the reaction is carried out and to the leaving group of the *n*-pentyl moiety. Table II summarizes the relative yields of the products *sec*-C<sub>4</sub>H<sub>9</sub>-C<sub>5</sub>H<sub>11</sub> and *t*-C<sub>4</sub>H<sub>9</sub>-C<sub>5</sub>H<sub>11</sub> obtained on reaction of (*sec*-C<sub>4</sub>H<sub>9</sub>)(*t*-C<sub>4</sub>H<sub>9</sub>)CuLi with several *n*-pentyl derivatives in representative solvents. With the single exception of the reaction of this cuprate with 1-chloropentane, the ratio of the yields of the two coupled products is essentially invariant throughout these experiments.

**Table III**  
**Yields of Conjugate Adducts  $RC_4H_9O$  from**  
**Reaction of Mixed Lithium Diorganocuprates**  
**" $R_1R_2CuLi$ " with Methyl Vinyl Ketone**

$R_1$	$R_2$	Yield, % <sup>a</sup>	
		$R_1C_4H_9O$	$R_2C_4H_9O$
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>		100
	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	44	49
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	53	35
	C <sub>6</sub> H <sub>5</sub>	46	6
	C <sub>3</sub> H <sub>7</sub> C≡C	39 <sup>b</sup>	<1
<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>		92
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	60	23
	C <sub>6</sub> H <sub>5</sub>	32	10
	C <sub>3</sub> H <sub>7</sub> C≡C	31	<1
<i>t</i> -C <sub>4</sub> H <sub>9</sub>	<i>t</i> -C <sub>4</sub> H <sub>9</sub>		94
	C <sub>6</sub> H <sub>5</sub>	40	2
	C <sub>3</sub> H <sub>7</sub> C≡C	37	<1
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>		40
	C <sub>3</sub> H <sub>7</sub> C≡C	4	<1

<sup>a</sup> Reactions were carried out using a 50% excess of methyl vinyl ketone unless otherwise noted. Yields are based on cuprate, and assume that only one alkyl group of each complex reacts. Cuprate solutions originally contained 1 equiv of tri-*n*-butylphosphine and 1 equiv of lithium iodide, unless noted otherwise. <sup>b</sup> When 0.9 equiv of methyl vinyl ketone/equiv of cuprate was used in this reaction, and the yield was calculated on the basis of ketone,<sup>8</sup> this yield is 51%.

**Conjugate Addition of Mixed Lithium Diorganocuprates to Methyl Vinyl Ketone.** Similar experiments were carried out to determine the selectivity with which organic groups are transferred in conjugate addition (eq 4). The



results of these experiments are summarized in Table III. In these reactions the yields, based on starting organolithium reagent, of conjugate adduct derived from the mixed cuprate are comparable to but not superior to those using unmixed complexes. No effort was made to compare the yields of conjugate adduct obtained from phosphine-free and phosphine-containing solutions of lithium dialkylcuprates. It is, however, worth noting that mixed cuprates containing the 1-pentynyl moiety give very low yields of conjugate adducts on the absence of added phosphine.

These data, and corresponding data outlined in the preceding section for reactions of lithium diorganocuprates with 1-bromopentene, suggest that, of the organic groups examined, an acetylenic moiety is most effective in inducing transfer of a second group in a mixed ate complex. We have briefly tested this suggestion by examining the conjugate addition of several mixed cuprates to mesityl oxide. This  $\alpha,\beta$ -unsaturated ketone was chosen because it represents a relatively difficult substrate for conjugate addition: the methyl substituents on the double bond both in-

crease the reduction potential of the system<sup>15</sup> and sterically hinder attack at the double bond. Table IV lists yields of conjugate adducts obtained from several mixed cuprates with this substance. The significant conclusion that can be drawn from the data of Table IV is that the mixed alkyl(alkynyl)cuprates have relatively low overall reactivity. Experience with the materials described in this paper and in other work<sup>16</sup> suggest that the reactivity of the organometallic groups in mixed clusters is qualitatively intermediate between the reactivity of the constituent components; thus, the reactivity of the *n*-butyl groups of lithium (*n*-butyl)(1-pentynyl)cuprate is intermediate in some qualitative sense between those of lithium di-*n*-butylcuprate and lithium di-1-pentynylcuprate. Since acetylenic copper compounds are among the least reactive derivatives of this metal, the reactivity of even the *n*-butyl group of (*n*-butyl)(1-pentynyl)cuprate is low. From a practical vantage, the data of Table IV point out the utility of mixed cuprates containing the *tert*-butyl group in reactions involving unreactive substrates; this utility had been noted previously.<sup>6a</sup>

**Oxidative Coupling of the Organic Groups of Mixed Ate Complexes.** Oxidation of lithium dialkylcuprates with a variety of oxidants [e.g., C<sub>6</sub>H<sub>5</sub>NO<sub>2</sub>, O<sub>2</sub>, Cu(II)] yields dimers formed from the organic moieties of the ate complex.<sup>12,13,17</sup> This reaction provides a useful method for forming symmetrical dimers from certain organolithium reagents; in principle, oxidation of mixed ate complexes might offer a practical method of forming unsymmetrical dimers, provided that the mixture of symmetrical and unsymmetrical dimeric products formed contained an appreciable fraction of the latter. The oxidation of mixed cuprates is interesting for a further reason: since the oxidation reaction is (qualitatively) very rapid, and since it probably takes place by collapse of organic groups on the surface of a partially oxidized organocopper cluster, the relative yields of symmetrical and unsymmetrical dimers might provide some insight into the composition or structure of the cluster before oxidation. Results of oxidation of a number of mixed lithium diorganocuprates with nitrobenzene are listed in Table V. It is immediately clear that these oxidations do not yield statistical distributions of dimeric products. Useful yields of unsymmetrically coupled products are formed in certain of these reactions; however, sterically hindered groups (*tert*-butyl) and oxidatively stable groups (C<sub>3</sub>H<sub>7</sub>C≡C and, to a lesser degree, C<sub>6</sub>H<sub>5</sub>) show little tendency to couple, either with themselves or with one another. Thus, although 2,2,3-trimethylpentane is formed in useful yield on oxidation of lithium (*tert*-butyl)(*sec*-butyl)cuprate, oxidation of (*tert*-butyl)(phenyl)cuprate yields primarily biphenyl. No significant yields of products containing the pentynyl group were detected on oxidation of any mixed cuprate containing this group.

**Relative Reactivities of Alkyl Bromides toward Lith-**

**Table IV**  
**Yields of Conjugate Adducts from Reaction of Mixed Lithium Diorganocuprates**  
**" $R_1R_2CuLi$ " with Mesityl Oxide**

$R_1$	$R_2$	Registry no.	Phosphine	Yield, % <sup>a</sup>	
				$R_1C_6H_7O$	$R_2C_6H_7O$
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	C <sub>3</sub> H <sub>7</sub> C≡C		( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P	40	0
			[(CH <sub>3</sub> ) <sub>2</sub> N] <sub>3</sub> P	43	0
			None	30	0
			( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P	78	0
			None	33	0
			None	8	0
<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	(CH <sub>3</sub> ) <sub>3</sub> C	41655-89-4	( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P		100
			None	24	0
			None		
<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	N≡C	41742-63-6	( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P		100
			None	24	0
			None		

<sup>a</sup> Yields are calculated on the same basis as those of Table I. Cuprate solutions originally contained 1 equiv of lithium iodide.

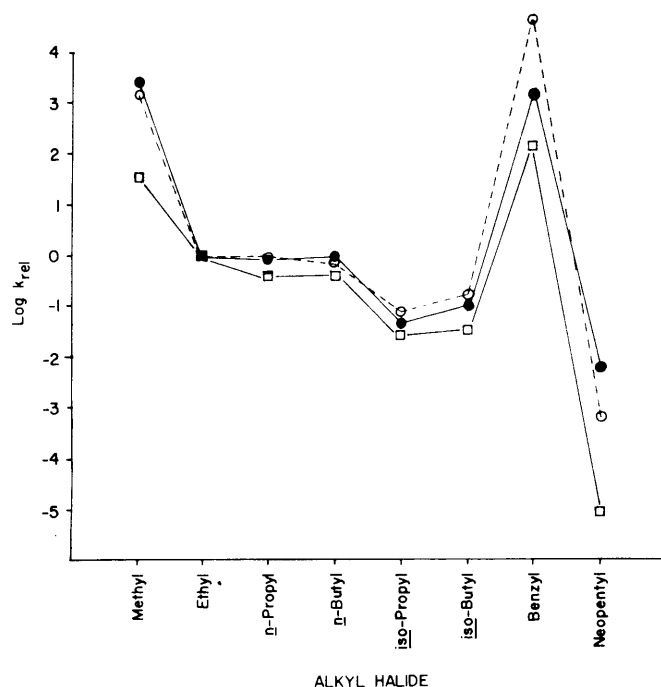
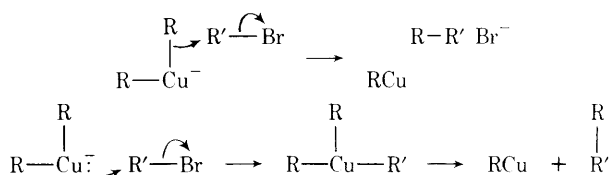
**Table V**  
**Yields of Dimers Obtained on Oxidation of Mixed Lithium Diorganocuprates "R<sub>1</sub>R<sub>2</sub>CuLi" with Nitrobenzene**

R <sub>1</sub>	R <sub>2</sub>	Yield, % <sup>a</sup>		
		R <sub>1</sub> -R <sub>1</sub>	R <sub>1</sub> -R <sub>2</sub>	R <sub>2</sub> -R <sub>2</sub>
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>		90	
	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	46	64	<1
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	36	60	<1
	C <sub>6</sub> H <sub>5</sub>	30	63	30
<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	C <sub>3</sub> H <sub>7</sub> C≡C <sup>b</sup>	92	1	<1
	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>		80	
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	36	45	<1
	C <sub>6</sub> H <sub>5</sub>	<1	43	48
<i>t</i> -C <sub>4</sub> H <sub>9</sub>	C <sub>3</sub> H <sub>7</sub> C≡C <sup>b</sup>	70	1	<1
	<i>t</i> -C <sub>4</sub> H <sub>9</sub>		3	
	C <sub>6</sub> H <sub>5</sub>	<1	33	56
	C <sub>3</sub> H <sub>7</sub> C≡C <sup>b</sup>	4	1	<1
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>		87	

<sup>a</sup> Yields for R<sub>1</sub>-R<sub>1</sub> or R<sub>2</sub>-R<sub>2</sub> are calculated from yield R<sub>1</sub>R<sub>1</sub> (%) = 100 × 2 (moles of R<sub>1</sub>R<sub>1</sub> formed)/(moles of R<sub>1</sub> initially present); yield R<sub>1</sub>R<sub>2</sub> (%) = 100 (moles of R<sub>1</sub>R<sub>2</sub> formed)/(moles of R<sub>1</sub> initially present). Cuprate solutions originally contained 1 equiv of tri-*n*-butylphosphine and 1 equiv of lithium iodide, unless otherwise noted. <sup>b</sup> Phosphine- and halide-free solutions of cuprate were used.

**ium Di-*n*-Butylcuprate.** The central purpose of these studies was to survey the relative reactivities of the organic groups in mixed lithium dialkyl- and alkylarylcuprates in representative reactions for which the utility of symmetrical cuprates is well established. During the course of these studies, we have examined briefly the effect of structural variation in the alkyl moiety of several alkyl bromides on the relative rates of coupling of these alkyl bromides with lithium di-*n*-butylcuprate. Although not directly related to the subject of reactivity of alkyl group transfers in mixed cuprates, these results are of obvious pertinence to considerations both of synthetic application of these reagents and of the mechanism of the coupling reaction, and are accordingly reported here.

Lithium di-*n*-butylcuprate was prepared by the procedures described previously; solutions containing tri-*n*-butylphosphine and lithium bromide were used. Relative rates of reaction of alkyl bromides were determined by competition of a mixture of 10 equiv of each of two alkyl bromides for 1 equiv of lithium di-*n*-butylcuprate. The relative rates of reaction of the two halides was taken to be proportional to the yields of the coupled products derived from each halide. The relative rates obtained from these experiments are represented in Figure 1; individual rate data are summarized in the Experimental Section. Figure 1 compares these relative rates with "typical" rates for these alkyl groups in S<sub>N</sub>2 displacement reactions,<sup>18</sup> and with rates of displacement of bromide ion from alkyl bromides by tributylphosphine-cobaloxime anion.<sup>19</sup> The agreement between these structure-reactivity profiles is sufficient to indicate that the transition state for the nucleophilic coupling reaction between alkyl halides and lithium di-*n*-butylcuprate closely resembles that for an unexceptional S<sub>N</sub>2 reaction, and to confirm previous suggestions to this effect.<sup>20</sup> These data do not, of course, distinguish between mechanisms for the coupling in which C-1 of the *n*-butyl acts as the nucleophile and those in which the copper atom is the nucleophile.<sup>21</sup>



**Figure 1.** Comparison of rate-structure profiles for reactions of lithium di-*n*-butylcuprates (●) and tributylphosphine-cobaloxime anion<sup>19</sup> (○) with alkyl bromides with the rate-structure profile for "typical" S<sub>N</sub>2 reactions<sup>18</sup> (□) indicates that the transition state for the coupling reaction between alkyl halide and cuprate is that expected for an S<sub>N</sub>2 reaction.

### Conclusions

The selectivity exhibited by mixed ate complexes "R<sub>1</sub>R<sub>2</sub>CuLi" in the transfer of R<sub>1</sub> to the other reaction component is in general most pronounced when the copper(I) derivative of the remaining group, R<sub>2</sub>Cu(I), is particularly stable, *viz.*, when R<sub>2</sub> is an acetylenic, alkoxy, or aryl group. Although these groups appear to offer the greatest selectivity, limited data suggest that they may in certain instances form the basis of mixed ate complexes of low reactivity. Practical utilization of mixed ate complexes thus requires a balancing of selectivity against reactivity. For most purposes, alkoxy, acetylenic, or possibly aryl groups seem to be most useful in encouraging reaction of the second component of mixed cuprates; for sluggish reactions, mixed complexes incorporating more basic alkyl groups, particularly *tert*-butyl, should be more useful. Mixed ate complexes appear to offer significant advantages over symmetrical complexes in efficient utilization of valuable organolithium reagents.

The structural and mechanistic basis for the selectivities observed in these reactions is not known. Selectivities follow the same general pattern for reactions of mixed cuprates with 1-bromopentane and methyl vinyl ketone, that is, in each of the mixed cuprates examined with these two substrates, the same organic group of the pair composing the cuprate was the more reactive. However, details of these selectivities varied markedly between the reactions. The yield data obtained from the oxidative coupling reactions are difficult to compare directly with these reactions; however, it is qualitatively evident that the acetylenic moiety shows low reactivity in all three reaction types. Without more information concerning details of the composition of these reaction mixtures, particularly the structure of the ate complexes present in each, it is pointless to speculate about possible bases for these selectivities.

### Experimental Section

**General Methods.** Tetrahydrofuran, dimethoxyethane, pentane, and hexamethylphosphoramide were purified by distillation

from disodium benzophenone dianion under an atmosphere of prepurified nitrogen. Diethyl ether was distilled from calcium hydride under nitrogen. All solvents were transferred using hypodermic syringes or stainless steel cannulas and were stored under an atmosphere of prepurified nitrogen. Alkyl halides were distilled and stored over 3A molecular sieves. Methyl vinyl ketone and nitrobenzene were dried over 3A molecular sieves but were not distilled. Mesityl oxide was distilled on a 10-cm platinum spinning band column and stored over 3A molecular sieves. Tris(*N,N*-dimethylamino)phosphine was distilled at reduced pressure under nitrogen in a flame-dried apparatus.<sup>22</sup>

Solutions of *n*-butyllithium in hexane were obtained from the Foote Mineral Co. and from Alfa Inorganics, Inc. Solutions of *sec*-butyllithium in hexane were obtained from the Foote Mineral Co. and solutions of *tert*-butyllithium in pentane were obtained from the Foote Mineral Co. and from Matheson Coleman and Bell. Phenyllithium was prepared by metal-halogen exchange between iodobenzene and *n*-butyllithium in pentane.<sup>23</sup> Organolithium reagents were assayed using the Gilman double titration procedure.<sup>24</sup> Manipulations of organometallic reagents were carried out using standard procedures.<sup>25</sup> Tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] was prepared by the procedure of Kaufman and Teter.<sup>26</sup> 1-Pentynylcopper(I) was prepared by the method of Stephens and Castro<sup>27</sup> and also by the method of House and Umen.<sup>9</sup> Authentic samples of products were obtained from the following sources: 2-octanone was obtained from the Aldrich Chemical Co., 3-methyloctane, 2,2-dimethylheptane, 3-methylheptane, 3,4-dimethylhexane, 2,2,3-trimethylpentane, 2,2,3,3-tetramethylbutane, 2,2-dimethylhexane, 4-nonyne, 1-phenyl-1-pentyne, 4,6-decadiyne, 5-methyl-2-heptanone, and 4-phenyl-2-butanone were obtained from Chemical Samples Co., and *n*-butylbenzene and 2-phenylbutane were obtained from the Eastman Chemical Co.

An authentic sample of 4,4-dimethyl-2-octanone was prepared by the addition of di-*n*-butylcuprate to mesityl oxide. The product was distilled, bp 42–43° (1.3 Torr), and had  $\nu$  (CCl<sub>4</sub>) 2930 (s), 2870 (s), 1705 (s), 1465 (s), 1385 (m), 1360 (s), 1160 cm<sup>-1</sup> (m); nmr (CCl<sub>4</sub>)  $\delta$  0.95 (s, 3 H), 0.97 (s, 6 H), 1.23 (m, 4 H), 2.04 (s, 3 H), 2.22 (s, 2 H).

Anal. Calcd for C<sub>10</sub>H<sub>20</sub>O: C, 76.86; H, 12.90. Found: C, 77.09; H, 12.88.

Product mixtures were analyzed by glpc using unexceptional internal standard techniques; *n*-nonane was normally used as the standard except for the couplings with *n*-C<sub>5</sub>H<sub>11</sub>Br. In which experiments decane was used as the standard. Products were identified by comparison of their retention times with those of authentic samples on three columns (5% Carbowax 2M on Chromosorb P, 10% SE-30 on Chromosorb W, and 3% Apiezon N on alumina). Peak areas were obtained using a Disc integrator.

**Lithium (*n*-Butyl)(*sec*-butyl)cuprate (Typical Procedure).** Tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] [0.393 g, 0.25 mmol, 1.00 mmol of Cu(I)] was placed in a flame-dried, 40-ml centrifuge tube equipped with a No-air stopper. The tube was flushed with nitrogen, and 5 ml of tetrahydrofuran, freshly distilled from disodium benzophenone dianion under nitrogen, was added using a hypodermic syringe. The resulting colorless solution was cooled to -78° under a positive nitrogen pressure, and *n*-butyllithium (1.00 mmol, ca. 0.65 ml) in hexane solution was added *via* hypodermic syringe. *sec*-Butyllithium (1.00 mmol, ca. 0.85 ml) in hexane solution was then added *via* hypodermic syringe and the tube was shaken vigorously for about 10 sec to ensure complete formation of the cuprate. Normally a pale yellow solution resulted, but light pink, light purple, and colorless solutions have been observed. Other mixed and unmixed cuprates containing alkyl and phenyl groups were prepared by analogous procedures.

**Lithium (*n*-Butyl)(1-pentynyl)cuprate (Typical Procedure).** 1-Pentynylcopper (0.131 g, 1.00 mmol) was placed in a flame-dried, 40-ml centrifuge tube equipped with a No-air stopper and magnetic stirring bar. The tube was flushed with nitrogen, and 5 ml of tetrahydrofuran, freshly distilled from disodium benzophenone dianion under nitrogen, was added *via* hypodermic syringe. The resulting slurry was cooled to -78° under a positive nitrogen pressure, and *n*-butyllithium (1.00 mmol, ca. 0.65 ml) in hexane solution was added *via* hypodermic syringe. The resulting mixture was stirred at -78° for about 30 min. Not all of the pentynylcopper dissolved. Other mixed and unmixed cuprates containing alkyl and phenyl groups were prepared by analogous procedures.

**Reaction of Lithium (*n*-Butyl)(*sec*-butyl)cuprate with 1-Bromopentane (Typical Procedure).** 1-Bromopentane (0.15 g, 1.00 mmol), freshly distilled under nitrogen, was added to a cold (-78°) solution of lithium (*n*-butyl)(*sec*-butyl)cuprate (1.00 mmol) prepared as described previously. The resulting solution

was shaken vigorously for approximately 10 sec and allowed to warm to 0°, at which temperature it gradually turned dark green and a copper mirror formed on the centrifuge tube. The tube was held at 0° for 2 hr and then diluted to 40 ml with tetrahydrofuran. The products were identified and yields were determined by glpc. Other mixed and unmixed cuprates were allowed to react with alkyl bromides using an analogous procedure. Studies of the influence of leaving group and solvent on the selectivity of organic group transfer were carried out using analogous procedures.

**Reaction of Lithium (*n*-Butyl)(*sec*-butyl)cuprate with Methyl Vinyl Ketone (Typical Procedure).** Methyl vinyl ketone was deoxygenated by bubbling a vigorous stream of nitrogen through the liquid and dried over 3A molecular sieves. A sample of ketone (0.105 g, 1.50 mmol) was added *via* hypodermic syringe to a cold (-78°) solution of lithium (*n*-butyl)(*sec*-butyl)cuprate (1.00 mmol) prepared as described previously. The resulting dark red solution was shaken vigorously for approximately 10 sec and allowed to warm to 0°. The solution was allowed to stand for 1 hr and was then diluted to 40 ml with tetrahydrofuran. Yields were determined by glpc. Other mixed and unmixed cuprates were allowed to react with methyl vinyl ketone using an analogous procedure.

**Oxidation of Lithium (*n*-Butyl)(*sec*-butyl)cuprate with Nitrobenzene (Typical Procedure).** Dry nitrobenzene (0.5 ml, 5 mmol) was added to a cold (-78°) solution of lithium (*n*-butyl)(*sec*-butyl)cuprate (1.00 mmol) prepared as described previously. The resulting dark red solution was shaken vigorously for about 10 sec and held at -78° for 30 min. The solution was warmed to 0° for 30 min, then warmed to room temperature and diluted to 40 ml with diethyl ether. The products were analyzed as described previously. Other mixed and unmixed cuprates were oxidized with nitrobenzene using analogous procedures.

**Reaction of Lithium (*n*-Butyl)(pentynyl)cuprate with Mesityl Oxide.** 1-Pentynylcopper (0.131 g, 1.00 mmol) was placed in a flame-dried, 40-ml centrifuge tube equipped with a Teflon coated magnetic stirring bar and No-air stopper. The tube was flushed with nitrogen, and 5 ml of THF, freshly distilled from disodium benzophenone dianion under nitrogen, was added. Tris(dimethylamino)phosphine (0.37 ml, 2.0 mmol) was added and the mixture was stirred at room temperature until all the solid was dissolved (ca. 20 min). The solution was cooled to -78° and *n*-butyllithium (0.55 ml, 1.8 M in hexane, 1.0 mmol) was added. Mesityl oxide (0.15 ml, 1.3 mmol) was added and the solution was warmed to 0° and stirred for 2 hr. The yield was determined by glpc.

**Reaction of Lithium (*n*-Butyl)(*tert*-butoxy)cuprate with Mesityl Oxide.**<sup>28</sup> Copper(I) iodide (0.194 g, 1.00 mmol) was placed in a flame-dried, 40-ml centrifuge tube equipped with a Teflon-coated magnetic stirring bar and a No-air stopper. The tube was flushed with nitrogen, and 5 ml of THF, freshly distilled from disodium benzophenone dianion under nitrogen, was added. The tube was cooled to -78° and methyllithium (0.63 ml, 1.6 M, 1.0 mmol) was added with stirring. Bright yellow methylcopper precipitated immediately and stirring was continued for 30 min. *tert*-Butyl alcohol (0.094 ml, 1.0 mmol) was added and the mixture was stirred at 0° for 3 hr under nitrogen. The yellow suspension was then cooled to -78°, *n*-butyllithium (0.55 ml, 1.8 M, 1.0 mmol) was added, and the mixture was stirred at -78° for 1 hr. Mesityl oxide (0.15 ml, 1.3 mmol) was added and the solution was stirred at -78° for 2 hr and then was warmed to -20° and stirred for an additional 2 hr. The yield was determined by glpc.

**Reaction of Lithium (*n*-Butyl)(cyano)cuprate with Mesityl Oxide.** Copper(I) cyanide (0.090 g, 1.0 mmol) was placed in a flame-dried, 40-ml centrifuge tube equipped with a Teflon-coated magnetic stirring bar and a No-air stopper. The tube was flushed with nitrogen, and THF, freshly distilled from disodium benzophenone dianion under nitrogen, was added. The tube was cooled to -78° and *n*-butyllithium (1.00 mmol, ca. 0.65 ml) in hexane was added with stirring *via* hypodermic syringe. All the cuprous cyanide dissolved after stirring for about 30 min. Mesityl oxide (0.15 ml, 1.3 mmol) was added and the solution was warmed to 0° and stirred for 2 hr. The solution was then warmed to 25° and held for 8 hr. The yields were determined by glpc.

**Reaction of Lithium Di-*n*-Butylcuprate with Mixed Alkyl Bromides (Typical Procedure for Halides of Similar Reactivity).** To a cold (-78°) solution of 1 mmol of lithium di-*n*-butylcuprate prepared as previously described was added approximately 20 mmol (ca. 10 ml) of a mixture of two alkyl bromides of known composition. The solution was allowed to warm to 0° and react for 2 hr. The resulting product mixture was diluted to 40 ml with tetrahydrofuran and analyzed by glpc. The products were con-

**Table VI**  
**Yields of Products R<sub>1</sub>C<sub>3</sub>H<sub>9</sub> and R<sub>2</sub>C<sub>4</sub>H<sub>9</sub> Obtained**  
**in Competitions of Pairs of Alkyl**  
**Halides for a Limiting Quantity (1 Mmol) of**  
**Lithium Di-*n*-butylcuprate**

Halide (mmol)		Yield, % <sup>a</sup>	
R <sub>1</sub> X	R <sub>2</sub> X	R <sub>1</sub> C <sub>3</sub> H <sub>9</sub>	R <sub>2</sub> C <sub>4</sub> H <sub>9</sub>
CH <sub>3</sub> Br (10)	PhCH <sub>2</sub> Br (10)	98	45
CH <sub>3</sub> Br (10)	C <sub>2</sub> H <sub>5</sub> Br (10)	190	0 <sup>b</sup>
<i>n</i> -C <sub>2</sub> H <sub>5</sub> Br (10)	<i>n</i> -C <sub>3</sub> H <sub>7</sub> Br (10)	51	45
<i>n</i> -C <sub>3</sub> H <sub>7</sub> Br (10)	<i>n</i> -C <sub>4</sub> H <sub>9</sub> Br (10)	50	47
<i>n</i> -C <sub>4</sub> H <sub>9</sub> Br (10)	<i>sec</i> -C <sub>4</sub> H <sub>9</sub> Br (10)	92	0 <sup>b</sup>
<i>sec</i> -C <sub>4</sub> H <sub>9</sub> Br (10)	<i>iso</i> -C <sub>4</sub> H <sub>9</sub> Br (10)	59	39
<i>iso</i> -C <sub>4</sub> H <sub>9</sub> Br (25)	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> Br	5	71
CH <sub>3</sub> Br (3)	<i>n</i> -C <sub>3</sub> H <sub>7</sub> I (300)	48	12
<i>n</i> -C <sub>3</sub> H <sub>7</sub> I (3)	C <sub>2</sub> H <sub>5</sub> Br (300)	84	13
C <sub>2</sub> H <sub>5</sub> Br (3)	<i>iso</i> -C <sub>4</sub> H <sub>9</sub> Br (150)	63	30
<i>iso</i> -C <sub>4</sub> H <sub>9</sub> Br (3)	<i>neo</i> -C <sub>4</sub> H <sub>9</sub> Br (57)	13	40

<sup>a</sup> Yields are calculated on the same basis as are those in Table I. Yields for R<sub>1</sub>C<sub>3</sub>H<sub>9</sub> and R<sub>2</sub>C<sub>4</sub>H<sub>9</sub> aggregating greater than 100% imply that non-ate-complexed alkylcopper(I) reagent is reacting with alkyl halide. <sup>b</sup> None detected (<1% would have been detected).

firmed by comparison of their retention times with those of authentic samples on two columns (3% Apiezon N on alumina and 10% SE-30 on Chromosorb W). Yields were determined using internal standard techniques.

**Reaction of Lithium Di-*n*-butylcuprate with a Mixture of Methyl Bromide and 1-Iodopropane (Typical Procedure for Halides of Greatly Differing Reactivities).** Tetrakis(iodotri-*n*-butylphosphine)copper [0.394 g, 0.25 mmol, 1.00 mmol of Cu(I)] was placed in a flame-dried, 100-ml, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a No-air stopper. The flask was flushed with nitrogen, and 50 ml of THF, freshly distilled from lithium aluminum hydride under nitrogen, was added. The flask was cooled to -78° and *n*-butyllithium (2.00 mmol, ca. 1.30 ml) in hexane solution was added with stirring *via* hypodermic syringe. A previously prepared mixture of methyl bromide (0.172 ml, 0.285 g, 3.0 mmol) and 1-iodopropane (29.2 ml, 51.0 g, 300 mmol) was added slowly *via* hypodermic syringe and the solution was warmed to 0° and stirred for 2 hr. Yields of *n*-pentane and *n*-heptane were determined by glpc.

The pairs of organic halides examined and the yields of products determined in these experiments are summarized in Table VI. The relative reactivities inferred from these data follow [alkyl group (*k<sub>r,1</sub>*): methyl (2520); ethyl (1); *n*-propyl (0.88); *n*-butyl (0.94); isopropyl (0.042); isobutyl (0.113); benzyl (1360); neopentyl (0.0068)]. These data are represented graphically in Figure 1.

**Registry No.** Methyl vinyl ketone, 78-94-4; mesityl oxide, 141-79-7; nitrobenzene, 98-95-3; 4,4-dimethyl-2-octanone, 49585-97-9.

### References and Notes

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