Reactions of Lithium Diorganocuprates(I) with Tosylates. I. Synthetic Aspects

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Abstract: The coupling reactions of a wide variety of lithium diorganocuprates(I) with primary tosylates have been found to proceed in high yield (70–100% isolated). Because of competition of elimination reactions, secondary tosylates gave lower yields (10–75%) of substitution products. The coupling reactions of cuprates and tosylates were found to proceed at lower temperatures than those of cuprates and halides. The tosylate–cuprate reactions were found to be faster in diethyl ether than in tetrahydrofuran; the opposite case was obtained in the halide–cuprate reactions. Coupling reactions to yield alkylarenes do not occur with cuprates and aryl tosylates. Using difunctional substrates the cuprates were found to react preferentially at the tosylate in a keto tosylate, faster at the tosylate in a bromo tosylate, and with little selectivity in an epoxy tosylate.

Substitution reactions on substrates containing carbon-bound leaving groups by organometallic reagents are conceptionally among the most straightforward operations for the production of new carbon–carbon σ bonds. Such reactions are notably successful when the organometallic reagents are derived from charge-delocalized carbanions (*e.g.*, allyllithium[2,3] or lithium enolates[4]). In the more general cases, expressed by eq 1, with highly reactive organometallics

$$\mathrm{RM} + \mathrm{R'X} \longrightarrow \mathrm{R\text{-}R'} + \mathrm{MX} \qquad (1)$$

one often finds unruly competition by side reactions such as α- and β-eliminations, metal–halogen exchange, α-metalation, and extraneous coupling reactions whereas less reactive organometallic reagents often fail to react at all.[5] The circumvention of these problems has been strikingly achieved in many cases by the use of organometallic compounds containing carbon–copper(I) bonds.[7]

Various classes of organocopper(I) species[5,7–9] have been investigated as reagents in substitution reactions. The insolubility of the monoorganocopper reagents (**1**)

RCu **1** $\qquad$ RCuL **2** $\qquad$ $\mathrm{R_2CuLi}$ **3**

$\mathrm{R_2CuLiL}$ **4** $\qquad$ $\mathrm{R_3CuLi_2}$ **5**

L = ligand

and the work-up complications due to the presence of ligands in reagents **2** and **4** severely limit the usefulness of these reagents. Reagents of stoichiometry **5** have been investigated only briefly.[10] The lithium diorganocuprates(I) (**3**) are highly reactive and have proven to be of exceptional value in a host of substitution reactions[11] on the following types of substrates: alkyl,[6,9] alkenyl,[6,9] aryl[6,9] and acyl halides,[12] epoxides,[13–15] allylic[15,16] and propargylic acetates,[17] and tosylates.

Reports of the reactions of tosylates with organocuprates have been very few; in fact only three reactions have appeared in the literature. Whitesides, House, and coworkers published a detailed paper on the reactions of organocuprates with aryl halides, vinyl halides, and alkyl halides.[6] In their study of the reactions of lithium di-*n*-butylcuprate, they found that the cuprate reacted with almost equal facility with *n*-amyl iodide, bromide, chloride, and tosylate to yield nonane. The second example of a tosylate reaction came in an elegant study of the mode of decomposition of organocopper(I) compounds.[18] An *endo*-norbornyl cuprate was reacted with methyl tosylate at −78° to yield 2-methylnorborane (98% endo, 2% exo); the results obtained from this work established the fact that cuprates "transfer" organic group with greater than 98% retention of configuration. The other example of the reaction of a tosylate with an organocuprate involved the displacement of a sterically hindered primary tosylate with lithium dimethylcuprate.[19] The objective of the study described in the present paper was to explore the synthetic utility of the reaction of lithium dialkylcuprates with tosylates.

Results and Discussion

The coupling reaction of alkyl halides and lithium diorganocuprates are generally run in tetrahydrofuran at

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temperatures around 25°.[6,9] At this temperature many cuprates are unstable; thus there is need for use of large excesses of the cuprate or the use of more stable cuprates such as those complexed with tri-*n*-butylphosphine. The ligand, as noted above, complicates work-up. These problems could be avoided by a modification of the reaction so that coupling takes place at a temperature where the lithium diorganocuprates are stable. We have found that changing the leaving group from a halide to a tosylate and the solvent from tetrahydrofuran to diethyl ether produced dramatic changes in the rates of coupling reactions. For instance, a 99% yield of nonane was obtained when *n*-octyl tosylate was reacted with 2 equiv of lithium dimethylcuprate in ether for 40 min at −40°. On the other hand, the reaction of *n*-octyl iodide required 5 equiv of the cuprate in ether at 0° for 10 hr to proceed to 90% completion. The effect observed on changing the solvent from tetrahydrofuran to diethyl ether is very interesting; the reactions of halides with lithium di-*n*-butylcuprate have been observed to proceed more rapidly in THF than in ether.[9] Our results show that the reactions of tosylates with lithium di-*n*-butylcuprate proceed faster in ether than in THF (Table I).

Table I. Effect of Solvent and Temperature on the Reaction of Lithium Di-*n*-butylcuprate with Alkyl Tosylates[a]

$$\text{R–OTs} + (n\text{-Bu})_2\text{CuLi}^d \longrightarrow \text{R–}(n\text{-Bu}) + n\text{-BuCu}$$

R	Concn, *M*	Equiv of cuprate	Temp, °C	Time, hr	Solvent	R-(*n*-Bu)[b] yield, %
n-C_5H_{11}[c]	0.0446	5	−78	0.5	THF	10
				2.5		17
				6		28
n-C_5H_{11}	0.0446	5	−78	0.5	Et_2O	98
n-C_5H_{11}	0.0446	2	−78	0.5	Et_2O	87
				1		90
				5		99
n-C_5H_{11}	0.0446	2	−20	1	THF	52
				2		62
				3		74
				6		98
n-C_5H_{11}	0.0446	2	−20	1	Et_2O	96
				2		98
n-C_5H_{11}	0.0446	5	−20	1	THF	98
n-C_5H_{11}	0.0446	5	0	1	THF	91
				3		95
n-C_5H_{11}	0.0446	5	0	0.5	Pentane	25
				1		25
				3		25
2-C_8H_{17}	0.0446	2	−78	1	Et_2O	11
				3		21
				8		30
				20		32
2-C_8H_{17}	0.0446	2	−20	0.5	Et_2O	63
				8		63
2-C_8H_{17}	0.0446	5	−20	1	Et_2O	59
				4		59
2-C_8H_{17}	0.0446	5	−20	1	THF	13
				4		33
			Warm to RT[e]	6		36
				24		60

[a] Yields are based on the tosylate; reactions were run under an atmosphere of N_2. Aliquots were removed at the stated time intervals and immediately quenched in a saturated ammonium chloride solution. [b] Yields were determined by use of an internal standard (mesitylene). [c] Upon warming the reaction mixture to 0° a 77% yield of nonane could be observed. [d] Lithium di-*n*-butylcuprate was prepared from 2 equiv of *n*-butyllithium and 1 equiv of cuprous iodide. All the solutions contain 1.6 ml of pentane/equiv of cuprate. [e] RT = room temperature.

The difference in the rates of reaction run in THF and those in diethyl ether can be seen in the following examples. *n*-Amyl tosylate reacted with 2 equiv of lithium di-*n*-butylcuprate in ether (−78°, 5 hr), yielding nonane (98%). A similar reaction using 5 equiv of the cuprate proceeded to only 20% completion (−78°, 24 hr) when THF was used as the solvent. In order for the reaction to go to completion in THF, the temperature had to be raised to −20°. No noticeable reaction could be observed at 0° when pentane was used as the solvent. For high yield preparative purposes it was found to be impractical to use less than 2 equiv of cuprate.

The temperatures required for these reactions are quite low (Table I). In fact, all the tosylates studied, with the exception of neopentyl tosylate, reacted readily at temperatures where the cuprates were stable. This results in very little decomposition of the cuprate and smaller amounts could be used; generally only 2 equiv of the cuprate were necessary. Since the reactions could be run at low temperatures, the cuprates could be prepared by simple addition of 2 equiv of the organolithium reagent to an ether slurry of cuprous iodide. Lithium dimethylcuprate and lithium diphenylcuprate were best prepared at 0° while the other alkylcuprates studied were best prepared at −40°. When higher temperatures were employed during the preparation, decomposition of the cuprates was observed, and at lower temperatures formation of the cuprate was very slow.

The reactions of primary tosylates with organocuprates are summarized in Table II. These reactions always proceeded in high yields (70–100% isolated). The lower yields, 70–75%, were due only to mechanical losses and volatility of the products. These yields have not been optimized.

Table II. Reactions of Primary Tosylates with Organocuprates

$$\text{R–OTs} + \text{R}'_2\text{CuLi} \longrightarrow \text{R–R}'$$

R	Concn, *M*	R′	Equiv of cuprate	Temp, °C	Time, hr	R–R′[a] yield, %
n-C_8H_{17}	0.05	CH_3	2	0	1	95
n-C_8H_{17}	1.3	C_2H_5	3	0	5	96.5
n-C_8H_{17}	0.064	*t*-C_4H_9	5	−15	16	90
n-C_8H_{17}	0.064	*sec*-C_4H_9	5	−15	16	85
n-C_8H_{17}	0.064	Ph	2	0	24	81
n-C_5H_{11}	0.045	*n*-C_4H_9	2	−20	2	98
$PhCH_2CH_2$	0.14	*n*-C_4H_9	2	−20	18	72.5
$PhCH_2CH_2$	0.10	*t*-C_4H_9	5	−20	18	70
$PhCH_2CH_2$	0.14	Ph	2	−20	18	100
Allyl	0.40	Ph	2	−20	6	89
Neopentyl	0.135	Ph	3	RT[c]	72	80
Cinnamyl	0.122	CH_3	3	0	7	45[b]

[a] Isolated yields based on the tosylate. Reactions were run in diethyl ether under an atmosphere of N_2. [b] Yield is based on cinnamyl alcohol, since the tosylate was too reactive to isolate. [c] RT = room temperature.

A few of the reactions in Table II deserve comment. The reactions of allyl tosylate with the cuprates were very fast and went to completion in less than 1 hr at −20°. Neopentyl tosylate reacted very sluggishly with lithium diphenylcuprate at 25°. This is typical of neopentyl groups in S_N2 displacement reactions.

Cinnamyl tosylate was very difficult to prepare;[20] each time the solvent was removed from the tosylate, rapid decomposition took place. This problem was circumvented by not removing the solvent and using ether solutions of the freshly prepared tosylate. Cinnamyl tosylate reacted with lithium dimethylcuprate to yield 1-phenyl-1-butene (45%), but some 3-phenyl-1-butene (1%) could also be detected.

During this study large differences in reactivity between the various cuprates were observed. Lithium dimethylcuprate and lithium diphenylcuprate react a great deal slower than all the other cuprates investigated. This noticeable change in reactivity could be ascribed to the difference in the stability of the cuprates themselves: the less stable cuprates react faster than the more stable ones.[9] It was found that alkylcuprates, other than methyl, could displace primary tosylates at −78° in several hours, whereas lithium dimethylcuprate and lithium diphenylcuprate required temperatures of −40 to 0°. In most cases the tosylates reacted with the cuprates at temperatures of 0° and below.

When secondary tosylates were reacted with cuprates there was competition between substitution and elimination reactions. The ratio of substitution product to elimination product varied with the tosylate and in some cases with the cuprate. For instance, 2-octyl tosylate reacted with lithium dimethylcuprate to give an 87% yield of 2-methyloctane and a 13% yield of 2-octene. When lithium diphenylcuprate was used, a 60% yield of 2-phenyloctane was obtained; with lithium di-*n*-butylcuprate a 65% yield of 5-methylundecane was isolated. The elimination products probably arise from an E2 reaction with the cuprate acting as the base.

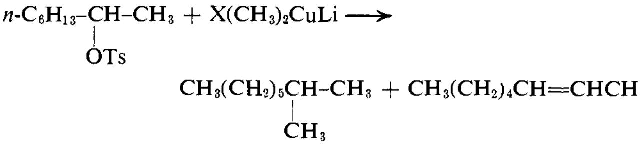
Cyclohexyl tosylate reacts with lithium dimethylcuprate to yield methylcyclohexane (20%) and cyclohexene (80%). A wide variety of conditions were tried; however, the amount of substitution product could not be increased. The formation of cyclohexene can readily be explained, since the ring can easily "flip" the tosylate group into an axial position for an E2 reaction. This postulate can be tested by switching to the cyclopentane ring system where substitution reactions are more facile. Acceptable yields of methylcyclopentane (60%) and phenylcyclopentane (60%) were obtained. The major side reaction was elimination to yield cyclopentene (30%). Another minor product was obtained in low yields (5–10%). This product could never be obtained in a high state of purity, but the ir and vpc data were indicative of dicyclopentyl ether. This compound could be formed by attack of the cuprate at the sulfur atom of the tosylate group, yielding the corresponding sulfone and an alkoxide.[21] This alkoxide could then displace the tosylate of another molecule (eq 2). This type of reaction is not without precedent, and it has been observed during the reaction of norbornyl brosylates with strong bases to yield dinorbornyl ethers.[22]

$$\text{R-O-SO}_2\text{-}p\text{-tolyl} + \text{R}'\text{-Cu}^-\text{-R Li}^+ \longrightarrow \text{R-O}^- + \text{R}'\text{-SO}_2\text{-}p\text{-tolyl} \quad (2)$$

$$\text{R-O}^- + \text{R-OTs} \longrightarrow \text{R-O-R} + {}^-\text{OTs}$$

The amount of elimination product obtained appeared to be the limiting factor in the synthetic utility of these reactions. An investigation of the reaction of 2-octyl tosylate with lithium dimethylcuprate to yield 2-methyloctane and 2-octene was undertaken. It was hoped that by varying the reactions conditions, the amount of substitution product could be increased. The temperature of the reaction, varied from −78 to 25°, did not significantly affect the amount of substitution product. The concentration of the reactants, both the tosylate and the cuprate, was varied and again only a slight change in yield of substitution product was observed. Finally, the mode of addition was changed by adding the cuprate to the tosylate and again, only a slight increase in the amount of substitution product was observed. These results are listed in Table III.

Table III. Reaction of 2-Octyl Tosylate with Lithium Dimethylcuprate[a]



$$n\text{-C}_6\text{H}_{13}\text{-}\underset{\text{OTs}}{\underset{|}{\text{CH}}}\text{-CH}_3 + \text{X(CH}_3)_2\text{CuLi} \longrightarrow \text{CH}_3(\text{CH}_2)_5\underset{\text{CH}_3}{\underset{|}{\text{CH}}}\text{-CH}_3 + \text{CH}_3(\text{CH}_2)_4\text{CH=CHCH}$$

2-Octyl tosylate concn, *M*	X[b]	Temp, °C	Time, hr	Substitution, %[c]	Elimination, %[c]
0.0446	2	0	3	81	19
0.125	2	0	3	80	20
0.0170	2	0	8	80	20
0.0437	1.1	0	8	No reaction	
0.0233	6	0	3	84	16
0.0379[d]	2	0	3	84	16
0.0446	2	−20	3	80	20
0.0446	2	−20	18	87	13
0.0471	2[e]	0	3	0	100
0.0471	2[e]	−60	3	0	100

[a] Reactions were run in diethyl ether under an atmosphere of dry N_2. [b] The letter X refers to the number of equivalents of cuprate used. [c] Yields were calculated from the relative peak heights obtained by vpc. [d] Inverse addition of the cuprate to the tosylate. [e] Only methyllithium was used, no cuprous iodide.

It was concluded that the best conditions for substitution reactions of secondary tosylates with cuprates are low temperatures and long reaction times.

In general, the reaction of organocuprates with secondary tosylates is a fair reaction with substitution products being obtained in about 60% yield, the major exception being the cyclohexyl systems where yields of 6–34% were obtained. Several of the reactions of secondary tosylates are outlined in Table IV. The one major drawback to the reactions of secondary tosylates occurs when *sec*-alkyl- and *tert*-alkylcuprates are used. Substitution products from these reactions are obtained in 40–60% yields along with the elimination product and several other unidentified products which were difficult to separate.

We have examined the possibility of coupling between aryl tosylates and lithium dialkylcuprates; in all cases the reaction failed to yield the desired alkylarenes.

The mild conditions required for the reaction of the organocuprates with both oxiranes[13] and tosylates, combined with the observation that dialkylcuprates are relatively inert toward saturated carbonyl moieties, suggested the possibility of selective reactions with these

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Table IV. Reactions of Secondary Tosylates with Organocuprates[a]

Tosylate R-OTs	Concn, *M*	Cuprate R'_2CuLi	Equiv of cuprate	Temp, °C	Time, hr	R-R', % yield[b]
$2\text{-}C_8H_{17}$	0.138	Methyl	2	0	3	81
$2\text{-}C_8H_{17}$	0.138	Methyl	2	−20	4	87
$2\text{-}C_8H_{17}$	0.048	*n*-Butyl	3	0	3	65
$2\text{-}C_8H_{17}$	0.0463	Phenyl	2	−20	3	60
$Ph(CH_3)CH$	0.060	Ethyl	5	−20	5	33
$c\text{-}C_5H_9$	0.0718	Methyl	2	0	5	65[c]
$c\text{-}C_5H_9$	0.145	Phenyl	2	0	12	61
$c\text{-}C_6H_{11}$	0.0718	Methyl	2	0	5	20[d]

[a] Reactions were run in diethyl ether under an atmosphere of dry N_2. [b] Isolated yields based on the starting tosylate. [c] Yield was a vpc yield with cyclohexane used as an internal standard. [d] Yield was calculated from the relative areas of the peaks obtained by vpc.

functional groups in the presence of an unprotected carbonyl group. The reactions of oxiranes in the presence of the carbonyl group have been reported.[13a]

At low temperatures the tosylate group could be displaced by the alkyl or aryl group of the organocuprate in the presence of other functional groups. To a solution of lithium dimethylcuprate at −78°, 3-phenyl-3-oxopropyl *p*-toluenesulfonate was added; an 83% (isolated) yield of butyrophenone was obtained (eq 3).

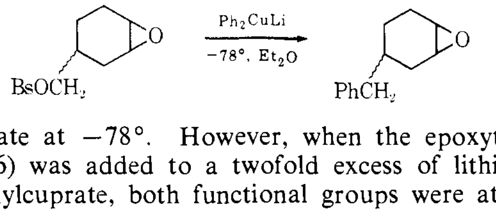
$$PhCCH_2CH_2OTs + Me_2CuLi \longrightarrow PhCCH_2CH_2Me \qquad (3)$$

The tosylate was insoluble in diethyl ether at −78°; this problem was easily remedied by using either toluene or dry dimethoxyethane as a cosolvent.

A more challenging problem was the investigation of reactions of the cuprates with molecules that contained two functional groups that normally react with cuprates. The reactions of alkyl halides with the cuprates were considerably slower than the reactions with tosylates. The difunctional 2-bromoethyl tosylate was prepared and allowed to react with lithium di-*n*-butylcuprate (3 equiv). After 1 hr at −78°, a 90% yield of 1-bromohexane was obtained (eq 4). A temperature of −78° was required for this displacement, for when the reaction mixture was warmed to −20°, the excess of lithium di-*n*-butylcuprate reacted with the 1-bromohexane and a 90% yield of decane was obtained.

$$BrCH_2CH_2OTs \xrightarrow[-78^\circ]{(n\text{-}Bu)_2CuLi} BrCH_2CH_2\text{-}n\text{-}Bu \xrightarrow[-20^\circ]{(n\text{-}Bu)_2CuLi} n\text{-}BuCH_2CH_2\text{-}n\text{-}Bu \qquad (4)$$

The reaction with tosylates in the presence of oxiranes is even more difficult since the cuprates react with oxiranes at low temperatures.[13] The primary brosylate group was preferentially displaced when the epoxybrosylate (eq 5) was reacted with lithium diphenylcuprate at −78°. However, when the epoxytosylate (eq 6) was added to a twofold excess of lithium dimethylcuprate, both functional groups were attacked. If only 1 equiv of cuprate was used, a mixture of the three possible products and starting material was obtained. From these results it can be suggested that the relative reactivity of substrates with lithium diorganocuprates is tosylates ≃ epoxides > halides > ketocarbonyl.



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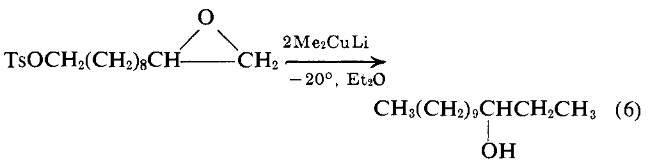

$$TsOCH_2(CH_2)_8CH\text{—}CH_2 \xrightarrow[-20^\circ,\ Et_2O]{2Me_2CuLi} CH_3(CH_2)_9CHCH_2CH_3 \qquad (6)$$

In the paper immediately following we discuss stereochemistry, kinetics, and mechanism of these tosylate–cuprate reactions.[23]

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points were determined during distillation or by the inverted capillary tube method and are uncorrected. Refractive indices were determined with a Bausch and Lomb refractometer and are corrected to the temperatures given in the literature. Infrared spectra were measured with a Perkin-Elmer Model 137B infracord. Nuclear magnetic resonance spectra were obtained on a Varian T-60 spectrometer. Mass spectra were determined on an AEI Model MS-9 with an ionization potential of 70 eV, 100 mA. Microanalyses were performed by Midwest Microlabs, Ltd., Indianapolis, Ind. A Hewlett-Packard Research Chromatograph Model 5750 with a thermal conductivity detector and a 6 ft × 0.25 in. SE-30 column was used for most of the routine work. The nonroutine work employed the use of the Perkin-Elmer Model F-11 with a flame ionization detector and 50 ft × $^1/_{16}$ in. Carbowax 20M capaillary columns. The following organolithiums were purchased: methyllithium (Foote), ethyllithium (Foote), *n*-butyllithium (Lithcoa and Foote), *sec*-butyllithium (Lithcoa), *tert*-butyllithium (Lithcoa), and phenyllithium (Foote). Cuprous iodide was purchased from either Ventron or Matheson and purified.[24] Diethyl ether and tetrahydrofuran were reagent grade and distilled from sodium dispersion. Pentane was stirred over concentrated sulfuric acid overnight and then distilled from calcium hydride. The procedure of Schleyer[25] was used unless stated otherwise for the preparation of tosylates (Table V). The tosyl chloride (mp 66–67°) (Matheson) was used without further purification. In the preparation of the organocuprates a three-necked round bottom flask was fitted with two addition funnels and a magnetic stirring bar. A positive pressure of dry nitrogen was started; the glassware was then flame dried.

Lithium Dimethylcuprate. To a suspension of cuprous iodide at 0° (3.8 g, 0.02 mol) in 10 ml of ether was added methyllithium (24 ml, 0.04 mol) dropwise over 30 min. The suspension immediately turned bright yellow (methylcopper), and then as more methyllithium was added, turned into a colorless or light tan solution. This end point could be easily detected.

Lithium Diethylcuprate. To a suspension of cuprous iodide (0.190 g, 1 mmol), stirred at −30°, was added ethyllithium (1.77 ml 2 mmol). A black suspension immediately formed, and after the addition of 2 equiv of ethyllithium, a black solution resulted. The end point was very difficult to detect.

Lithium Di-*n*-butylcuprate. To a suspension of cuprous iodide (1.37 g, 7.25 mmol) in 10 ml of ether stirred at −30° was added dropwise *n*-butyllithium (6 ml, 14.5 mmol). The initial bright yellow color lasted until about half of the butyllithium had been added. This then changed to a dark blue solution and the end point could be detected when the solution turned a dark red-brown color.

Lithium Di-*sec*-butylcuprate. To a suspension of cuprous iodide (1.7 g, 8.8 mmol) in 10 ml of ether at −20° *sec*-butyllithium (14.7 ml, 17.6 mmol) was added dropwise over a 30-min period. The solution turned black immediately, and the end point could not be detected after the addition of 2 equiv of *sec*-butyllithium. The final solution of the cuprate was black and appeared to be homogeneous.

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Table V. Tosylates

Name	Mp, °C	Lit. mp, °C	Ref
2-Phenylethyl	38.5–39.5	37.5–38.2	*d*
1-Phenylethyl	Dec at RT[c]	Dec at RT[c]	*e*
Neopentyl	45–46.5	47–48	*f*
Benzyl	53–53.5	55–57.8	*g*
Cinnamyl	Dec at RT[c]	18–20	20
Cyclohexyl	43–45	44.8–45.4	*h*
Cyclopentyl	28–29	29	*i*
2-Bromoethyl	12–13	11.9	*j*
3-Keto-3-phenylpropyl	103–105		
3-Cyclohexenylmethyl[a]	38–38.5	34.5–35	*k*
3,4-Epoxycyclohexylmethyl[a,b]	38–54		
10,11-Epoxyundecyl	25–27		

[a] *p*-Bromobenzenesulfonate. [b] Mixture of diastereomers. [c] RT = room temperature. [d] E. L. Eliel and T. J. Prosser, *J. Amer. Chem. Soc.*, **78**, 4045 (1956); W. H. Saunders, S. Asperger, and D. H. Edison, *ibid.*, **80**, 2421 (1958). [e] H. M. R. Hoffmann, *J. Chem. Soc.*, 6748 (1965). [f] M. S. Silver, *J. Amer. Chem. Soc.*, **83**, 3482 (1961). [g] S. Winstein, E. Grunwald, and W. Jones, *ibid.*, **73**, 2700 (1951); R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944). [h] W. Hueckel, R. Bross, O. Fechtig, H. Feltkamp, S. Geiger, M. Hanack, M. Heinzel, A. Hubele, J. Kurx, M. Maier, D. Maucher, G. Naeher, R. Neidlein, and R. Rashingkar, *Justus Liebigs Ann. Chem.*, **624**, 142 (1959). [i] W. Hückel and R. Bross, *ibid.*, **664**, 1 (1963). [j] W. F. Edgell and L. Parts, *J. Amer. Chem. Soc.*, **77**, 4899 (1955). [k] G. L. Ny and M. M. Delepine, *C. R. Acad. Sci.*, **251**, 1526 (1960).

Lithium Di-*tert*-butylcuprate. To a suspension of cuprous iodide (4.0 g, 0.0209 mol) in 20 ml of ether at −40° was added *tert*-butyllithium (0.0418 mol) dropwise over 30 min. The initial suspension turned black but at the end point a dark red-brown color could be detected.

Lithium Diphenylcuprate. To a suspension of cuprous iodide (9.35 g, 0.0492 mol) in 30 ml of ether at 0° was added phenyllithium (55 ml, 0.0984 mol) dropwise over 1 hr. The suspension initially turned bright yellow, and then turned a red-brown color until 1 equiv of phenyllithium had been added. The solution then started turning green, and the end point could be detected by the formation of a clear green solution. The intensity of the color appeared to be dependent on the quality of the phenyllithium used.

Work-up of Organocuprate Coupling Reactions. Upon completion of the reaction, a saturated solution of ammonium chloride was added to the reaction mixture at 0° or below and stirred for at least 10 min. The layers were separated, and the ether layer was washed two times with a saturated solution of sodium chloride, separated, and dried over magnesium sulfate. The solvents were generally removed by distillation (6-in. Vigreux).

Reaction of 2-Phenylethyl Tosylate with Lithium Di-*tert*-butylcuprate. To an ether solution of the cuprate (18.1 mmol in 10 ml) at −20° was added an ether solution of the tosylate (1.0 g, 3.62 mmol in 10 ml) over a 30-min period. The reaction was run for 19 hr at this temperature and was worked up in the usual manner to yield, after chromatography on silica gel, a colorless liquid (0.41 g, 70% yield); ir, nmr, and vpc data were consistent with the structure of 1-phenyl-3,3-dimethylbutane.

Reaction of Cyclopentyl Tosylate with Lithium Dimethylcuprate. To an ethereal solution of the cuprate (3.52 mmol in 10 ml) at 0° was added an ether solution of the tosylate (0.423 g, 1.76 mmol, in 10 ml) with cyclohexane added as an internal standard. After reacting for 5 hr, the mixture was worked up in the usual manner and methylcyclopentane (63%) and cyclopentene (32%) were obtained (vpc yields).

Reaction of Cyclopenty Tosylate with Lithium Diphenylcuprate. To an ether solution of the cuprate (8.32 mmol in 10 ml) at 0° was added an ether solution of the tosylate (1.0 g, 4.16 mmol, in 10 ml). The reaction was run for 22 hr, and after work-up and chromatography, a colorless oil (0.433 g) was obtained. This oil turned black upon standing overnight at room temperature. Nmr analyses showed the mixture to be mostly cyclopentylbenzene and another product having very similar spectral characteristics to dicyclopentyl ether. The compounds were separated by preparative gas chromatography; cyclopentylbenzene, $n^{20}\mathrm{D}$ 1.5289 (lit.[26] $n^{20}\mathrm{D}$ 1.5281). was obtained. A pure sample of the cyclopentyl ether could not be obtained. It was identified by vpc retention time and comparison of nmr and ir spectra with an authentic sample. A 50% yield of pure cyclopentylbenzene was isolated.

Reaction of Cyclohexyl Tosylate with Lithium Dimethylcuprate. To an ether solution of the cuprate (3.52 mmol) at 0° was added an ether solution of the tosylate (0.44 g, 1.76 mmol, in 10 ml). After 3 hr, the reaction was worked up to yield methylcyclohexane (20%) and cyclohexane (80%).

Preparation of Allyl Tosylate. Following the procedure of Sendega,[20] allyl alcohol (0.58 g, 0.01 mol) and tosyl chloride (2.0 g, 0.011 mol) were dissolved in diethyl ether and cooled in −20°. Sodium hydroxide (1.5 g), freshly ground with a mortar and pestle to a fine powder, was added to this solution over a 30-min period. After allowing the solution to stir for an additional hour, it was poured into ice–water, washed two times with cold water (0°), and while being kept cold, it was dried over sodium sulfate, and filtered and the ether removed on the rotary evaporator at 0°. A 90% yield of allyl tosylate was obtained free from any contaminants (nmr and ir). Care must be taken to keep the tosylate at 0° or below for upon warming, it turns dark. The storage life in a sealed ampoule is at least 2 months.

Reaction of Allyl Tosylate with Lithium Diphenylcuprate. To an ether solution of the cuprate (0.02 mol) at −20° was added an ether solution of the tosylate (2.12 g, 0.01 mol). The reaction was allowed to run for 6 hr and then was worked up to yield allylbenzene (1.04 g, 88% yield); $n^{26}\mathrm{D}$ 1.5202.

Reaction of Neopentyl Tosylate with Lithium Diphenylcuprate. To a stirred ether solution (10 ml) of the cuprate (0.015 mol) at room temperature was added an ether solution (10 ml) of the tosylate (1.21 g, 5 mmol). After 5 hr, the reaction was less than 10% complete; after 24 hr it was 27% complete. After 72 hr, the reaction was worked up and, after chromatography, on silica gel, yielded 1-phenyl-2,2-dimethylpropane (0.59 g, 80%), bp 180–181°, $n^{20}\mathrm{D}$ 1.4864 (lit.[27] bp 180–180.5, $n^{20}\mathrm{D}$ 1.4862), which showed no impurities by vpc and nmr.

Preparation of Cinnamyl Tosylate. Following the procedure of Sendega,[20] cinnamyl alcohol (1.3 g, 0.01 mol) and tosyl chloride (2.0 g, 0.011 mol) were dissolved in diethyl ether (25 ml) and cooled to −20°. Sodium hydroxide (1.5 g), freshly ground with a mortar and pestle to a fine powder, was added to this solution over a 30-min period. After allowing the ether mixture to stir for an additional hour, it was poured into ice–water. The ether layer was washed two times with cold water (0°), and while being kept cold, it was dried over sodium sulfate and filtered. This ether solution was used in the reaction with the cuprate. All attempts to evaporate the ether resulted in formation of a white solid which was extremely sensitive to air, heat, and moisture. This compound rapidly turned pink, then dark red when the solvent was removed.

Reaction of Cinnamyl Tosylate with Lithium Dimethylcuprate. The ether solution obtained above containing 0.01 mol of cinnamyl tosylate was added to an ether solution of the cuprate (0.03 mol, in 10 ml) at 0° and the mixture was allowed to stir for 7 hr. Work-up in the usual manner resulted in an oil which was chromatographed, yielding 1-phenyl-1-butene (0.59 g, 45% yield from the alcohol): bp 192°; $n^{23.5}\mathrm{D}$ 1.5374. Nmr shows a slight impurity due to 2-phenyl-1-butene (less than 3% of the product).

Reaction of 2-Octyl Tosylate with Lithium Dimethylcuprate. The usual procedure was followed using 1.18 g (4.16 mmol) of tosylate in 10 ml of ether and 8.32 mmol of cuprate in 10 ml of ether. The reaction was run at 0° for 3 hr and worked up to yield 2-methyloctane (0.41 g, 80% yield), bp 148–150° (lit.[28] bp 148.2°), $n^{20}\mathrm{D}$ 1.4032 (lit.[28] $n^{20}\mathrm{D}$ 1.4029); and 2-octene (0.047 g, 10% yield), >95% trans by ir and nmr.

Preparation of 1-Phenylethyl Tosylate. Following the procedure described for cinnamyl and allyl tosylates,[20] 1-phenylethanol (1.22 g, 0.01 mol) was converted to the tosylate (1.0 g of a white solid) which had to be kept at 0° or below to prevent decomposition. Attempts to record the melting point failed due to the presence of decomposed tosylate. The nmr was acceptable and the material was used as is in the following reaction. All attempts at purification resulted in decomposition.

Reaction of 1-Phenylethyl Tosylate with Lithium Diethylcuprate. To an ether–benzene solution (the ethyllithium was in benzene) of the cuprate (0.0181 mol in 10 ml of ether and 30 ml of benzene) was

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added an ether solution of the tosylate (1.0 g, 3.62 mmol in 20 ml of ether) at −20° The reaction was stirred for 5 hr and then worked up in the usual manner, and after chromatography, yielded 2-phenylbutane (0.159 g, 33%).

Preparation of the Ethylene Glycol Ketal of Ethyl Benzoylacetate. Ethyl benzoylacetate (19.2 g, 0.1 mol), ethylene glycol (40 g, 0.5 mol), toluenesulfonic acid (100 mg), and 100 ml of benzene were placed in a 500-ml, round-bottomed flask fitted with a Dean-Stark trap, a condensor, and a magnetic stirring bar, and refluxed with vigorous stirring overnight. The solution was allowed to cool, the layers were separated, and the benzene layer then was washed successively with water, a saturated bicarbonate solution, water, and a saturated sodium chloride solution. It was dried and the benzene removed on the rotary evaporator. Infrared analysis showed complete disappearance of the benzoyl carbonyl absorption, and the material was used without further purification.

Preparation of 3-Hydroxypropiophenone. Ethyl benzoylacetate ethylene glycol ketal (17.6 g, 0.0745 mol) was dissolved in 50 ml of dry ether and added dropwise to a suspension of lithium aluminum hydride (3.2 g, 0.080 mol) in 100 ml of ether at a rate that would maintain gentle boiling. The solution was stirred for an additional 3 hr at room temperature, and then worked up. The excess lithium aluminum hydride was destroyed, the resulting salts were filtered, the ether was dried over magnesium sulfate and filtered, and the solvent was removed on the rotary evaporator. The product obtained showed complete reduction of the ester group. The 3-hydroxypropiophenone ethylene glycol ketol obtained was stirred in 300 ml of 10% hydrochloric acid overnight at room temperature, ether was added, and the acid neutralized. The water layer was washed three times with ether. The combined ether layers were washed with a saturated solution of sodium chloride, dried over magnesium sulfate and filtered, and the ether was removed on the rotary evaporator. The nmr showed complete disappearance of the ketal and the material was used without further purification.

Reaction of 3-Keto-3-phenylpropyl *p*-Toluenesulfonate with Lithium Dimethylcuprate. To an ether solution of the cuprate (8.8 mmol in 20 ml) cooled to −78° was added a 50:50 ether–benzene solution of the tosylate (1.33 g, 4.3 mmol in 20 ml). The solution was stirred for 2 hr, then allowed to warm to 0° and was worked up in the usual manner, yielding butyrophenone (89%), which upon chromatography, gave an 80% yield of pure butyrophenone: bp 228–229°; $n^{20}\mathrm{D}$ 1.5203 (lit.[29] bp 228–229°; $n^{20}\mathrm{D}$ 1.5203).

Preparation of 3,4-Epoxycyclohexanemethyl *p*-Bromobenzenesulfonate. 3-Cyclohexenylmethyl *p*-bromobenzenesulfonate (5.0 g, 0.015 mol) was dissolved in 17 ml of benzene and the solution was added slowly to a benzene solution (170 ml) of *m*-chloroperoxybenzoic acid (90%, 3.45 g, 0.020 mol) and allowed to stir overnight. The solution was then washed three times with a 10% sodium hydroxide solution and three times with a saturated sodium chloride solution and dried. The solvent then was removed on the rotary evaporator, leaving a viscous oil which crystallized on standing, mp 38–54°.

Reaction of 3,4-Epoxycyclohexylmethyl *p*-Bromobenzenesulfonate with Lithium Diphenylcuprate. To an ether solution of the cuprate (0.0186 mol in 30 ml) cooled to −78° was added an ether–benzene solution of the epoxybrosylate (2.15 g, 6.2 mmol in 10 ml). The solution then was warmed to −20° and worked up after 4 hr to yield 4-benzylcyclohexene oxide (0.810 g, 70%). The nmr and ir of the product revealed the presence of the phenyl and epoxide groups and the absence of brosylate.

Reaction of 2-Bromoethyl Tosylate with Lithium Di-*n*-butylcuprate. To an ether solution of the cuprate (21.3 mmol in 36 ml) cooled to −78° was added an ether solution of the bromo tosylate (2.0 g, 7.1 mmol in 10 ml). After stirring for 1 hr an aliquot was taken which indicated that greater than 90% of the material was 1-bromohexane. After 4 hr, a considerable amount of decane was formed, and when allowed to warm to −20°, all the material was decane.

Preparation of 10-Undecen-1-ol. Undecylenic acid (9.2 g, 0.05 mol) (Aldrich) in ether (50 ml) was added to an ether solution of lithium aluminum hydride (2.7 g, 0.05 mol in 250 ml) at a rate that maintained a gentle boiling. The reaction was worked up after 2 hr, yielding 10-undecen-1-ol (6.19 g, 72% yield). No acid could be detected in the ir or nmr spectra.

Preparation of 10,11-Epoxyundecyl Alcohol. Methylene chloride solutions of 10-undecen-1-ol (6.19 g, 0.0362 mol in 50 ml) and *m*-chloroperbenzoic acid (7.0 g, 0.039 mol, 100 ml) were mixed together and refluxed for 48 hr. The reaction was worked up yielding 10,11-epoxyundecyl alcohol (6.0 g, 90%).

Reaction of 10,11-Epoxyundecyl Tosylate with Lithium Dimethylcuprate. To ether solutions of the cuprate (2.0 and 1.0 mmol) were added ether solutions of the tosylate (0.305 g, 0.9 mmol) at −40 and −20°, respectively. These solutions were allowed to react for 7 and 3 hr, and then worked up in the usual manner. The ir and nmr spectra show both the epoxide and the tosylate being attacked by the cuprate. The final product was a complex mixture, and no attempt was made to purify it.

Relative Rates of Reaction of Tosylates with Lithium Di-*n*-butylcuprate. The reaction of lithium di-*n*-butylcuprate with *n*-amyl tosylate and 2-octyl tosylate was studied. The amount of cuprate used was varied from a twofold excess to a fivefold excess. The temperature of the reaction was varied from −78° to −20°, to 0°, to room temperature. The solvents used in the study were diethyl ether, tetrahydrofuran, and pentane. The results are reported in Table I.

Acknowledgment. We thank Dr. Donald M. Wieland, Dr. R. W. Herr, and Mr. James P. Lockard for discussions and assistance.

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