Evidence for Single Electron Transfer in the Reactions of Lithium Dimethylcuprate with Alkyl Halides

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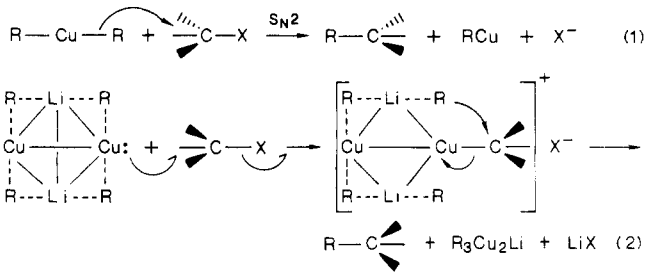
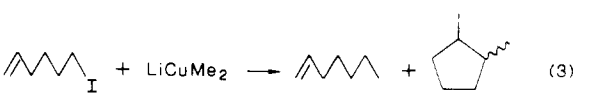
A variety of methods have been utilized to explore the occurrence of radical intermediates and free-radical chain processes initiated by electron transfer in the reactions of lithium dimethylcuprate with alkyl halides. The effect of leaving group, nature of the cuprate species, and ratio of cuprate to substrate, solvent, hydrogen atom donor, and other additives on the rate of and product distribution were investigated by using a cyclooctenyl radical probe. The presence of significant amounts of radicals strongly supports single electron transfer (SET) as a major pathway for the reaction of secondary iodides with $LiCuMe_2$. There is some evidence of single electron transfer also occurring with secondary bromides, but tosylates appear to be reacting entirely by a S_N2-like pathway. The role of dicyclohexylphosphine (DCPH) as an additive in the reaction was investigated with the result that it was shown to be capable of behaving in a unique manner depending on whether the substrate is an alkyl iodide or bromide. The product distribution, rate, and effect of *p*-dinitrobenzene on the reaction of 5-iodo-1-cyclooctene were compared with three other probes and the results demonstrate that at least three reaction pathways are involved to varying degrees. These pathways could involve the initiation of free radicals or radical anion ($S_{RN}1$) chain processes. These studies also demonstrate how changes in the substrate can alter the predominant reaction pathways that are followed.

Introduction

The substitution reaction of lithium diorganocuprates ($LiCuR_2$) with alkyl halides and tosylates is an important reaction synthetically,[1] but the exact mechanism (or mechanisms) of this reaction is still not thoroughly understood. Although it has been suggested that single electron transfer occurs between cuprates and enones or aromatic ketones,[2] stereochemical studies of the substitution reaction have shown that the reaction of optically active 2-bromobutane and 2-butyltosylate with lithium diphenylcuprate proceeds with predominant inversion of configuration.[3,4] On the other hand, lithium dialkenylcuprates and lithium di-*endo*-2-norbornylcuprates have been shown to couple with various substrates with retention of configuration of the R group transferred.[4,5] The order of reactivity of the transferred group is 1° > 2° > 3° and the rate law of the coupling reaction generally has been found to be first order in substrate and first order in organocuprate.[3,6] All of these points, plus the lack of any significant effect of the radical trap, Ph_3CH, in typical reactions of cuprates with alkyl halides, have been used as an argument against an electron-transfer/free-radical process and in favor of a S_N2-like reaction pathway. Two reaction mechanisms with several variations have been proposed to account for these results: (1) nucleophilic displacement by the carbanion of the cuprate[6] (eq 1) and (2) oxidative addition of the alkyl substrate followed by reductive elimination to form coupled product (eq 2).[7] The direct displacement mechanism (eq 1) generally has been discounted because it fails to explain the difference in nucleophilicity between cuprates, Grignard reagents, and organolithium compounds and because the groups on the cuprates most capable of providing carbanions are generally the least reactive.[7,8] The second S_N2-like mechanism (eq 2) requires that the alkyl group of the substrate be differentiated from the R groups of the cuprate. A further requirement is that either a very unstable transient Cu(III) species is involved or the dimeric (Et_2O or THF) mixed copper species. The intermediate species also has been described as a copper(II)-radical complex.[9]



Recently, evidence has accumulated that a S_N2-like reaction mechanism may not be valid in at least some reactions. We reported recently that when 6-iodo-1-heptene was allowed to react with $LiCuMe_2$, cyclized substitution product was produced in 65% yield (eq 3), indicating the



formation of a radical intermediate.[10] Later Lipshutz showed that the reaction of (*R*)-(−)-2-iodooctane and (*S*)-(+)-2-iodobutane with cuprates occurs with almost complete racemization of the substitution product.[11] These results are inconsistent with the S_N2-like mechanisms (eq 1 and 2) and suggest that the reaction of alkyl iodides (or at least secondary alkyl iodides) react with $LiCuMe_2$ predominantly via a reaction pathway different from the other halides and tosylates.

The reason for these results may be explained by Lipshutz's study of the electrochemical reduction of alkyl halides and tosylates in which alkyl iodides gave two waves at potentials considerably more positive than the corre-

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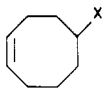
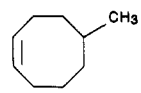
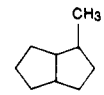
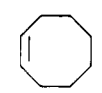
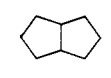
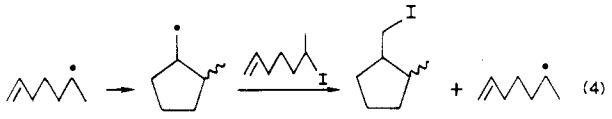
Table I. Reactions of 5-Substituted 1-Cyclooctenes with $LiCuMe_2$ at 0 °C in THF

			% yield						
									
expt	X=	time	recovered substrate	4	5	6	7	diene	other
1	I (1)	23 h	0	13.1	4.4	16.7	23.4	0	a
2	Br (2)	20 days	69.6	3.9	0	2.9	12.1	0	0
3	OTs (3)	10 days	0	56.4	0	0	0	30.4	0

[a] 17.4% dimer and 4.4% 1-hydridene (8).

sponding bromides which gave only a single wave.[12] Tosylates reductively cleaved at the S–O bond, not at the C–O bond. These results suggest that alkyl iodides are much more inclined to undergo SET than the corresponding bromides or especially the tosylates. The stereochemical and radical probe studies of secondary iodides are also consistent with a radical chain process that we described earlier[13] in which iodine atom abstraction is involved (eq 4).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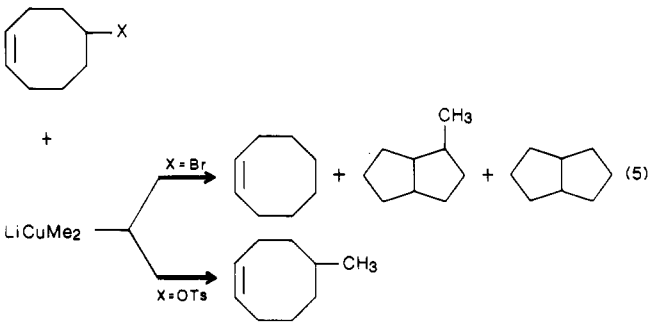
The reactions of several secondary as well as primary cyclizable radical probes, especially 5-substituted-1-cyclooctenes, were studied by determining the nature of the products formed and the effect of reaction conditions and additives on the product distribution and reaction rate in order to explore the phenomena of radical involvement in the reaction of $LiCuMe_2$ with alkyl halides.

Results and Discussion

The cyclization of the 4-cyclooctenyl radical has been shown by a number of authors to be a quite facile rearrangement.[14-16] In most of the studies, free-radical addition to a double bond of *cis,cis*-1,5-cyclooctadiene was used to form the 5-cyclooctenyl radical which then cyclized to form 2-substituted bicyclo[3.3.0]octanes. Posner allowed 5-bromo-1-cyclooctene and the tosylate of 5-hydroxy-1-cyclooctene to react with $LiCuMe_2$ in diethyl ether at 25 °C and found that in the case of the bromide, considerable cyclized substitution and reduction products were observed (eq 5).[16] No cyclized products were observed in the tosylate case. Since the integrity of the cuprate at 25 °C is questionable, and because the reactions were not explored further, this radical probe system was selected for more detailed study at a lower temperature (0 °C) particularly with the iodide substrate for comparison. All reactions were carried out in duplicate and the average value of products was recorded. If significant variation existed between the two runs, additional runs were carried out until consistent results were obtained.


(5)

Effect of Leaving Group. The order of reactivity normally seen in S_N2 reactions and which also is seen in reactions of cuprates with primary halides and tosylates is tosylates ≥ iodides > bromides > chlorides.[3,17] In the reaction of secondary alkyl halides or tosylates with cuprates, the order of reactivity between iodide and tosylates is reversed, with the iodide much more reactive than the tosylate.[18] This reactivity reversal can be seen in Table I for the cyclooctenyl system where the reaction of 5-iodo-1-cyclooctene (1) with $LiCuMe_2$ is over in less than 24 h, whereas over a week is necessary for complete reaction of the tosylate of 5-hydroxy-1-cyclooctene (3). A possible explanation is that the reduction potential of the iodide favors a SET pathway while the higher reduction potential of the tosylate 3 does not and a slower S_N2-like reaction takes place instead. In addition, the radical chain process (eq 4) reported earlier[13] is more significant when the 5-substituent is iodide rather than tosylate. The product distribution supports a radical pathway for reaction of the iodide 1 since more than half of the products isolated are either bicyclo[3.3.0]octane derivatives or dimers. On the other hand, the tosylate reaction yields only uncyclized substitution and elimination products (dienes). The sluggishness of the bromide 2 reaction (30% reaction after 20 days) suggests that neither the electron-transfer pathway (perhaps due to the higher reduction potential of the bromide) nor the direct substitution pathway (perhaps due to the poorer leaving group ability of bromide) is particularly favorable. Nonetheless, the formation of significant amounts of cyclized bicyclo[3.3.0]octane (7) in the reaction of the bromide suggests that radicals are involved in product formation.

Reaction of $LiCuMe_2$ with 5-Iodo-1-cyclooctene. A more detailed study of the reaction of the cyclooctenyl iodide 1 with $LiCuMe_2$ over a period of time revealed that very early in the reaction 1 was converted to 2-iodobicyclo[3.3.0]octane (9) (Table II). It is evident that most if not all of the cyclized products bicyclo[3.3.0]octane (7), 2-methylbicyclo[3.3.0]octane (5), and bicyclo[3.3.0]oct-2-ene (8) were produced from the reaction of the cuprate with 9 rather than from the starting iodide 1. It is important to note that significant amounts of cyclized

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Table II. Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ in THF at 0 °C

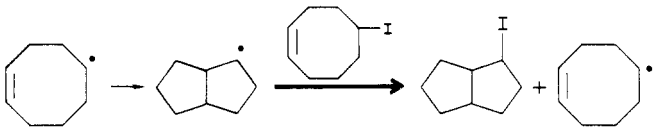
	% yield							
								
time, min	1	9	4	5	6	7	8	dimers
15	49.9	29.7	8.0	trace	8.3	trace	0	5.5
31	24.3	34.1	11.4	1.7	13.0	2.1	2.3	7.8
47	11.7	34.8	11.5	1.4	14.4	2.2	1.6	14.7
65	6.4	34.3	11.6	2.6	14.7	3.1	2.7	15.0
124	0	29.7	12.0	3.3	15.7	4.7	3.1	13.2
1380	0	0	13.1	4.4	16.7	23.4	4.4	17.4

Table III. Effect of Radical Traps on the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ in THF at 0 °C

			% yield							
expt	additive	time	6	7	4	5	1	9	8	dimers
1	none	23 h	16.7	23.4	13.1	4.4	0	0	4.4	17.4
2	1,4-cyclohexadiene	24 h	63.6	6.5	15.1	1.4	0	0	trace	0
3	DCPD (0.15 M)	24 h	83.9 (87)[a]	3.5 (100)[a]	2.4	0	0	0	trace	0
4	t-$BuNH_2$ (0.15 M)	26 h	13.6	20.2	7.6	2.8	0	9.0	4.7	12.0
5	none	5 min	3.1	0	2.4	0	83.2	11.6	0	2.7
		16 min	5.3	0	3.9	0	62.5	21.6	0	5.5
6	1,4-dinitrobenzene (0.006 M)	5 min	3.9	0	2.9	0	75.1	16.2	0	4.8
		15 min	6.5	0	4.2	0	59.0	23.9	0	6.0
7	di-*tert*-butylnitroxyl radical (0.006 M)	5 min	3.0	0	2.3	0	75.4	13.1	0	6.0
		16 min	5.5	0	4.3	0	60.4	21.1	0	7.8

[a] Deuterium incorporation in parentheses.

products formed only after **9** was formed in large amount. According to the data in Table II (1380 min), the reaction of $LiCuMe_2$ with the bicyclo iodide **9** produced mainly the reduction product **7** and not the substitution product **5**. The significant increase in the amount of dimer formed (13.2% to 17.4%) during the time period 124–1380 min is indicative of a radical intermediate in the reaction of the bicyclo iodide **9** with $LiCuMe_2$. Maybe more significant is the probability that the bicyclo iodide **9** is the result of a radical chain process initiated by electron transfer from the cuprate to **1** (eq 6).[13,19]



(6)

Effect of Radical Traps. A series of experiments using radical traps were conducted (Table III) to explore how nonsubstitution products arose in the reaction of **1** with $LiCuMe_2$. Experiment 1 shows the product distribution in the absence of any radical trap for comparison purposes. In experiments 2 and 3, the hydrogen atom donors, 1,4-cyclohexadiene[20,21] and dicyclohexyldeuteriophosphine (DCPD),[20,21a,22] were present in fivefold excess with respect to **1**. A much greater yield of the reduction product (cyclooctene (**6**)) was observed in both cases, as well as a decrease in cyclized products **5**, **7**, and **8** and the complete elimination of dimers. DCPD traps more of the initial radical than cyclohexadiene as can be seen by comparison of the amount of bicyclooctane **7**, normal substitution product **4**, and cyclized substitution product **5** formed in experiments 2 and 3. No cyclized iodide was seen during the reaction in the presence of cyclohexadiene or DCPD. The deuterium content of the reduction products **6** and **7** were found by mass spectral analysis to be 87% and 100%, respectively. Since the only deuterium source was DCPD (>99% d_1), it is clear that DCPD is trapping the radical intermediates to form the reduction products. A method used by Kuivila[22c] for comparing the product distribution using dicyclohexylphosphine with that of *tert*-butylamine (t-$BuNH_2$) was used to insure that dicyclohexylphosphine(D), a poor Lewis acid with a pK_a of 35, was not trapping anions rather than radicals. The pK_a of t-$BuNH_2$ is similar to DCPH(D) but it is a poor hydrogen atom donor compared to DCPH(D). If anions are being trapped, t-$BuNH_2$ should trap them as effectively as DCPH(D), but if radicals are being trapped, there should be quite a difference in the product distribution. Experiment 4 of Table III shows that DCPH(D) is not trapping anions but radicals, since the product distribution is similar to that of the reaction with no additive (compare experiments 1 and 4). Very significant is the presence of dimer and cyclized iodide **9** which is in contrast to the results using hydrogen atom donors which produce none of these products! The explanation for the lower reactivity in the presence of t-$BuNH_2$ could be that the amine complexes the lithium or copper atom of the cuprate, thus lowering the reactivity of the cuprate as a one-electron donor.

Experiments 5, 6, and 7 (Table III) were conducted in order to determine if any inhibiting effects early in the reaction could be observed in the presence of *p*-dinitrobenzene, a good radical anion chain ($S_{RN}1$) inhibitor,[23] or di-*tert*-butylnitroxyl radical, a good free-radical chain process inhibitor. As is evident from the data, no effect

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Table IV. Effect of Radical Traps on the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ in THF at 0 °C

		% yield							
additive	time, min	1	9	4	5	6	7	8	dimer
none	15	49.9	29.7	8.0	1	8.3	1	0	5.5
1,4-cyclohexadiene	15	54.7	6.6	8.7	0	14.7	1	0	0
DCPH	17	0	0	6.4	0	83.9	1.4	0	0
none	31	24.3	34.1	11.4	1.7	13.0	2.1	2.3	7.8
1,4-cyclohexadiene	37	38.6	6.7	12.0	0	30.5	1	0	0
DCPH	34	0	0	6.6	0	84.9	1.2	0	0
t-$BuNH_2$	34	54.3	23.5	4.1	0	8.0	1.2	2.2	7.4

Scheme I. Two Possible Chain Reactions Involving DCP•

initiation: $R^\bullet + DCPH \rightarrow RH + DCP^\bullet$

$S_{RN}1$ propagation:
$DCP^\bullet + Nuc^- \rightarrow DCPNuc^{\bullet-}$
$DCPNuc^{\bullet-} + RX \rightarrow DCPNuc + [RX]^{\bullet-}$
$[RX]^{\bullet-} \rightarrow R^\bullet + X^-$
$R^\bullet + DCPH \rightarrow RH + DCP^\bullet$

free-radical chain propagation:
$DCP^\bullet + RI \rightarrow DCPI + R^\bullet$
$R^\bullet + DCPH \rightarrow RH + DCP^\bullet$

was seen in either case. This was initially puzzling in the case of the free-radical trap since the cyclization of the iodide 1 to 9 was believed to proceed by a free-radical chain process; however, the free-radical trap was shown by ESR to react almost instantaneously with the cuprate to form nonradical species. Evidently the free-radical trap is not present long enough to have an effect. Most important in these trapping studies were the results of experiment 2 showing a profound effect in the trapping of the initial radical to produce the hydrocarbon 6 and benzene. The interpretation of the data from dicyclohexylphosphine trapping is more complicated.

Effect of DCPH(D) on the Reaction Pathway. The question arose as to why the direct substitution product 4 decreased dramatically when the reaction was carried out in the presence of DCPD. It would be expected that 4 would be formed primarily in the solvent cage even if radical intermediates from SET were involved, and so DCPD would not be expected to be able to trap these intermediates. When the reaction was studied early in its progress (Table IV), it was found that the reaction was greatly accelerated in the presence of DCPH. For example, in the presence of DCPH the reaction is over in less than 17 min as compared to less than 50% reaction in its absence. 1,4-Cyclohexadiene seems to be trapping the initial radical at the expense of iodine atom abstraction to form 9 or dimer formation and it does not accelerate the reaction as does DCPH. The inclusion of t-$BuNH_2$ was made as comparison of the product distribution in its presence compared to the hydrogen atom donors. The data show that t-$BuNH_2$ has little effect on the reaction (compare experiment at 31 min using no additive and 34 min using t-$BuNH_2$).

Earlier studies have shown that DCPH(D) often does more than simply trap radicals, and two reaction pathways have been proposed to explain the additional role that DCPH(D) is playing in this reaction (Scheme I).[20,24] Several experiments were conducted in order to determine which reaction pathway is more probable. The reaction of the iodide 1 with $LiCuMe_2$ in the presence of 5 equiv of DCPH was carried out in the presence and absence of p-dinitrobenzene (p-DNB) (Table V). The effect of p-DNB was negligible. The reaction of iodide 1 in the presence of dicyclohexylphosphine also was carried out

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Table V. Effect of p-Dinitrobenzene on the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ in the Presence of DCPH[a]

		% yield			
added p-DNB[b]	time, min	1	4	6	7
no	8	4.2	7.1	76.1	2.0
yes	8	8.0	7.6	76.3	2.4
no	25	0.6	7.2	88.6	3.5
yes	24	3.5	7.0	86.8	2.8

[a] Ratio of $LiCuMe_2$/DCPH/iodide was 10:5:1. Reactions were run in THF at 0 °C. [b] p-Dinitrobenzene (p-DNB) concentration is 5% relative to $LiCuMe_2$.

Table VI. Effect of CuI Salt on the Reactions of 5-Iodo-1-cyclooctene (1) with Cuprates in THF at 0 °C

	% yield					
	0.5 h			24 h		
	CuI	$CuBr{\cdot}SMe_2$	CuCN	CuI	$CuBr{\cdot}SMe_2$	CuCN
4	11.4	8.9	22.2	13.1	10.8	20.4
5	1.7	0.8	1.8	4.4	4.1	1.8
6	13.0	9.7	11.9	16.7	13.2	12.0
7	2.1	1.0	2.6	23.4	21.2	5.2
1	24.3	34.0	0	0	0	0
9	34.1	21.2	5.4	0	0	0
8	2.3	1.3	2.1	4.4	4.9	3.8
dimer	7.8	10.7	27.2	17.4	11.0	26.4

[a] Salts were allowed to react with 2 equiv of MeLi.

with insufficient cuprate (20% relative to iodide) calculated for a stoichiometric reaction to take place (Table VIII, last two entries). The reaction proceeded past the stoichiometric amount of cuprate to yield between 40% to 60% hydrocarbon product. A $S_{RN}1$ process is unlikely for the following reasons: (1) p-DNB is a very good $S_{RN}1$ chain process inhibitor; however, no decrease in reaction rate took place. (2) $S_{RN}1$ reactions require a stoichiometric amount of nucleophile, yet more than the stoichiometric amount of hydrocarbon products were produced. (3) No DCPH substitution products were observed. A free-radical chain process is consistent with the results reported herein and therefore is proposed as a reasonable mechanism.

Since the radical probe, 5-iodo-1-cyclooctene (1), forms a number of products and has at least two competing pathways on reaction with $LiCuMe_2$ (the free-radical chain process to form cyclized iodide 9 and the reaction of iodide with cuprate to produce free radicals and substitution products), it appeared that this probe could be very sensitive to changes in the cuprate reagent (source of Cu(I), ratio of MeLi to Cu(I)), ratio of cuprate to halide, and solvent. A series of experiments were undertaken and the reaction rates and product distributions were studied in order to explore whether such changes could yield information as to what factors are important in the course of the reaction.

Effect of Changes in the Cuprate Reagent. Lipshutz has shown that cuprates made from CuCN with 2 equiv of organolithium compound (so called higher order organocuprates) often are superior in effecting substitution at

Table VII. Effect of Varying the MeLi to CuI Ratio on the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ in THF at 0 °C

	% yield at MeLi/CuI								
	0.5 h			2 h			15 h		
product	1.8	2.0	2.2	1.8	2.0	2.2	1.8	2.0	2.2
4	0.8	6.4	10.7	2.2	9.2	13.2	3.2	9.2	15.0
5	0	0.6	1.4	0	1.9	2.6	0.2	2.9	5.2
6	2.2	9.9	11.0	8.1	16.7	14.8	18.4	17.2	17.4
7	0.2	1.1	1.3	1.2	2.9	4.2	5.9	17.4	19.3
1	83.6	43.7	24.3	53.1	4.7	0	0	0	0
9	11.5	23.2	21.2	30.6	33.1	24.5	61.9	15.7	3.4
8	0.4	1.4	2.2	2.4	2.1	2.7	2.0	3.6	4.8
dimer	1.3	7.8	6.3	3.1	9.6	7.4	1.4	10.0	11.3

Table VIII. Effect of the Ratio of 5-Iodo-1-cyclooctene (1) to $LiCuMe_2$ on the Reaction in THF at 0 °C[a]

			% yield					
time, h	iodide/cuprate	additive	1	9	4	5	6	dimers
23	0.1	none	0	0	13.1	16.7	23.4	17.4
36	0.9	none	14.0	57.8	1.9	20.7	2.9	trace
89	0.9	none	0.2	61.1	2.2	23.2	6.5	trace
26	0.9		5.7	49.3	7.2	22.8	9.2	5.6
14	5	none	80.1	13.9	0.7	4.2	0	1.6
154	5	none	58.0	24.9	1.5	8.1	0.2	2.4
11	5	DCPH (0.15 M)	58.5	0	0	41.5	trace	0
89	5	DCPD (0.15 M)	42.2	0	0	53.9	4.2	0

[a] 4.4% of 5 and 8 were formed in the first experiment whereas in all of the other experiments, only traces of 5 and 8 were detected. [b] CuCN used instead of CuI to prepare the cuprate.

secondary halides.[18] Since $CuBr{\cdot}SMe_2$ is often used in place of CuI or CuBr, it also was studied for comparison purposes. The comparison of these three Cu(I) salts is shown in Table VI. The product ratios are similar, the main difference being that the more reactive cuprate produced more of the normal substitution product 4 and less of the cyclic products 5, 7, and 8 after 24 h. This result is due to the competition between cyclization of the starting iodide and the direct reaction. If the direct reaction is fast, then cyclization competes less favorably with the formation of the normal substitution product.

The ratio of MeLi to Cu(I) salt was studied in order to determine how sensitive the exact ratio of reactants is on the reaction course. The results in Table VII show that when the ratio was altered (MeLi:CuI, 1.8–2.2), the only significant change was the reactivity of the species. As the ratio of MeLi:Cu(I) increased, the reactivity of the copper species increased, producing more 5-methylcyclooctene (4) and less overall cyclized products. Although the cyclized substitution product 5 and the reduction product 7 appear to be greater for the 2.2 to 1 ratio after 15 h, this result is due to the incomplete reaction of the cyclized iodide 9. The total amount of cyclized products increases as the ratio of MeLi:CuI decreases. This trend of greater normal substitution product and less cyclized products with increased reactivity is the same as seen for the effect of Cu(I) salts, and so the reaction is very sensitive to MeLi:CuI ratios in a predictable manner related to the reactivity of the cuprate species ($LiCu_2Me_3$ vs. $(LiCuMe_2)_2$). When the ratio MeLi:CuI dropped below 1.8, e.g., 1.5, the reaction became very slow compared to the higher ratios. Also there appeared to be little effect when LiI-free cuprate reagent was used in placed of the normal reagent generated from MeLi and CuI which contains 1 mol of LiI per mol of $LiCuMe_2$.

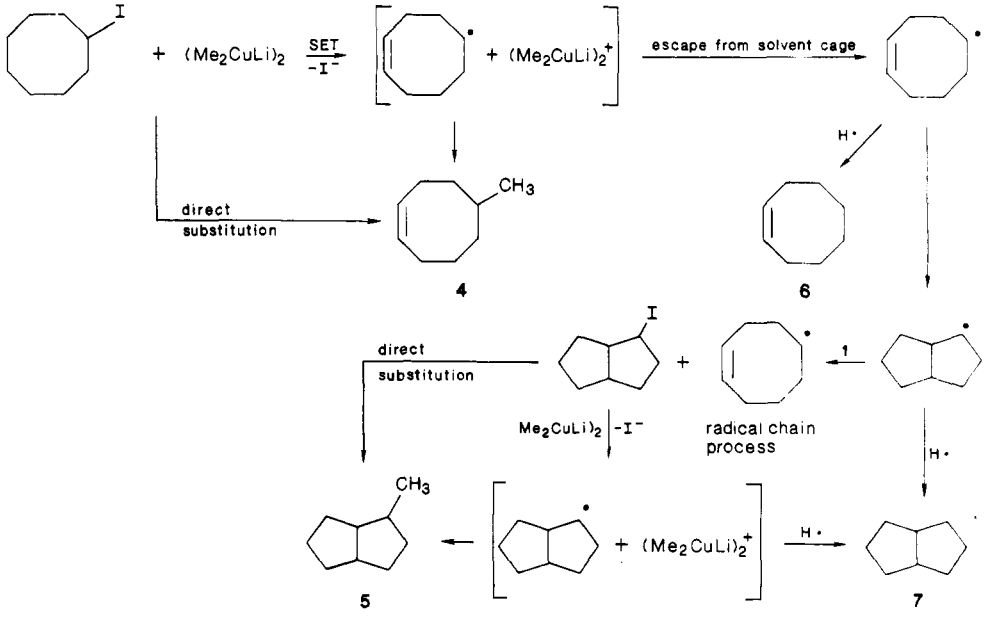
Effect of Ratio of Cuprate to Iodide. The reactions of cuprates with alkyl halides and tosylates has always suffered from the fact that excess cuprate normally is needed to obtain reasonable yields in short time periods. The reactions reported herein have all been carried out at a 10:1 cuprate/iodide ratio in order to insure that the reagent had not appreciably changed during the course of the reaction. At lower ratios the cuprate reagent at the beginning of the reaction could have a different composition from the reagent at the conclusion of the reaction. The methyl/copper ratio would be expected to decrease as methyl groups are transferred to the alkyl halide and the copper species redistribute. The first four reactions in Table VIII explore how the product distribution is altered by going from a large excess of cuprate (0.1 iodide/cuprate) to only a slight excess (0.9) relative to the iodide present. The main product in the 0.9:1 reactions is the cyclized iodide 9 with the formation of very little of the other cyclized products or dimer. By lowering the concentration of $LiCuMe_2$ relative to iodide, the rate of the direct reaction is decreased and this allows the free-radical cyclization of iodide 1 to 9 to become more competitive. The use of CuCN as the source of Cu(I) accelerates the reaction, but the product ratios are similar to those obtained by using CuI as the source of Cu(1). The final four reactions in Table VIII were carried out in order to explore whether a chain process was occuring in the presence or absence of DCPH. Since these reactions with a ratio of 5:1 alkyl iodide/cuprate have only 20% cuprate relative to iodide, any reaction that proceeds further than 20% is indicative of a chain process of some sort. All of these reactions proceeded further than 40% relative to starting alkyl iodide. The main product without DCPH is the cyclized iodide 9 and with DCPH is cyclooctene 6. A chain process therefore is supported for both the cyclization of the iodide and the reaction in the presence of DCPH.

Effect of Solvent. The final study involving the radical probe 5-iodo-1-cyclooctene (1) was the determination of the effect of solvent on the product distribution and reaction rate. Table IX presents the results of the reaction of 1 with $LiCuMe_2$ in Et_2O, THF, and 20% HMPA/THF. Once again, the more reactive the system, the greater the yield of direct substitution product 4 compared to the cyclized products derived from the bicyclooctyl iodide 9. Diethyl ether, as has been noted in the literature, is a poor solvent for the reaction of alkyl halides with cuprates, and the trend is that the more polar the solvent system, the more reactive the cuprate in the substitution reaction.[1,5b,25]

Table IX. Effect of Solvent on the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$ at 0 °C

		% yield							
time, h	solvent	1	9	4	5	6	7	8	dimers
1	20% HMPA/THF	0	15.4	23.0	5.1	18.7	6.5	3.1	16.2
	THF	4.1	31.8	11.4	1.7	17.5	4.4	2.6	11.9
	Et_2O	63.0	24.6	3.1	0	5.5	trace	0	3.3
4	20% HMPA/THF	0	4.3	21.7	5.9	17.0	12.2	3.5	13.1
	THF	0	20.3	11.5	2.4	17.9	11.0	2.1	11.1
	Et_2O	13.1	51.2	5.2	0	11.9	1.7	0	6.4
23	20% HMPA/THF	0	0	21.7	6.5	17.6	16.1	3.3	14.3
	THF	0	0.9	11.9	3.9	18.3	26.2	2.9	11.4
	Et_2O	0	46.4	6.5	2.5	14.9	9.7	3.1	8.6

Scheme II. Proposed Mechanism of the Reaction of 5-Iodo-1-cyclooctene (1) with $LiCuMe_2$



Lipshutz has shown that solvent plays an important role in the reduction potential of an alkyl halide and that the reduction potential is a lower negative value in the order DMF > CH_3CN > THF.[12] Therefore, the more polar the solvent, the more favorable electron transfer should be, and hence this result is consistent with electron transfer as the rate-determining step of the reaction.

All of the data obtained for the reaction of 5-iodo-1-cyclooctene (1) with $LiCuMe_2$ lead to the mechanism postulated in Scheme II. The substitution products, 5-methyl-1-cyclooctene (4) and 2-methylbicyclo[3.3.0]octene (5), could arise either from a direct oxidative addition–reductive elimination to give a S_N2-like reaction or could proceed by a three-step pathway involving initial electron transfer followed by rapid coupling in the solvent cage of the cuprate species with the alkyl radical from the iodide. Reductive elimination of this copper species yields substitution products. The cyclized iodide arises from the abstraction of iodine from the starting substrate 1 by the free radical of bicyclo[3.3.0]octane. The new free radical of cyclooctene 6 cyclizes and continues this chain process while also abstracting a hydrogen atom from some source. The reduction products 6 and 7 are therefore formed by the respective free-radical abstraction of hydrogen from some source, such as the solvent, added hydrogen donor, the alkyl halide, or the cuprate itself. Dimer arises from the coupling of two free radicals and is not shown in the scheme. The source of the free radicals in all of these reactions is escape from the solvent cage of radicals formed from electron transfer between the cuprate and iodide or free radicals formed in the radical chain process (eq 6). The electron-poor dimeric cuprate species that remains then could transfer a second electron followed by reductive elimination of ethane to form methyl copper(I) as in eq 7.[2b]

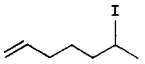
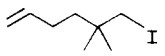
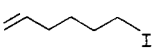
$$Me_4Cu_2Li_2 \xrightarrow{-e^-} [Me_4Cu_2Li_2]^+ \xrightarrow{-e^-} [Me_4Cu_2Li_2]^{+2} \rightarrow Me\text{–}Me + 2MeCu + 2Li^+ \quad (7)$$

Cuprate Reactions of 5-Bromo-1-cyclooctene (2) in the Presence and Absence of Radical Probes. The study of the reaction of 5-bromo-1-cyclooctene (2) with $LiCuMe_2$ provides some interesting contrasts with respect to the corresponding iodide. As noted earlier, the bromide reaction is quite sluggish at 0 °C in THF and is only about 30% complete in 20 days (Table X). During the course of the reaction, cyclized bromide 2, cyclized substitution product 5, and dimer are not observed at any time during the reaction. Interestingly, the ratio of cyclized to uncyclized reduction products is greater for the bromide compared to the iodide. This is to be expected since the bicyclo radical precursor to 7 should not participate as readily in a radical chain process (eq 6) with the bromide 2 as the iodide 1. Thus the bicyclo radical competes more favorably in hydrogen atom abstraction to form 7.

The effect of the radical scavengers *p*-dinitrobenzene (PDNB) and DCPH on the reaction of 5-bromo-1-cyclooctene (2) with $LiCuMe_2$ in THF at 0 °C was studied. *p*-DNB does slow down the reaction rate (4% reaction in 10 days), inhibits the formation of the cyclized reduction product 7, and slightly increases the amount of cyclized substitution product 5 formed. The presence of DCPD

(25) (a) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443. (b) House, H. O.; Lee, T. V. *J. Org. Chem.* **1978**, *43*, 4369.

Table X. Comparison of the Reactivity and Product Distribution of Several Iodide Radical Probes with $LiCuMe_2$ at 0 °C in THF

			% yield						
			reduction product		substitution product		iodide		
iodide probe	cuprate/iodide	reactn time	uncycl.	cycl.	uncycl.	cycl.	uncycl.	cycl.	other
1	10	23 h	16.7	23.4	13.1	4.4	0	0	21.8
	0.2	6 days	8.1	0.2	1.5	0	58.0	24.9	2.4
 10	10	14 min	0	7.5	19.9	61.3	0	0	0
	0.2	21 days	0	5.9	trace	trace	26.8	58.8	0
 11	10	2 days	0	24.4	15.8	57.4	2.4	0	0
	0.2	21 days	0	3.7	4.7	6.5	81.5	0	0
 12	2.0	3 min	0	0	98.8	0	0	0	0

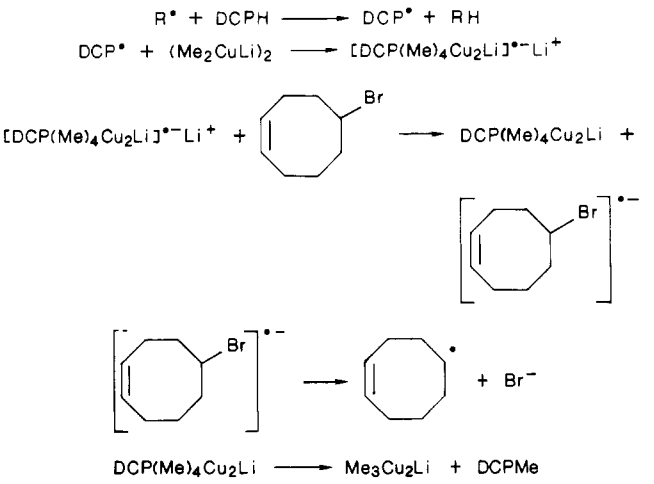
[a] 17.4% dimer and 4.4% 8. [b] Dimer.

accelerates the rate of reaction (30% reaction in 1.5 days) in the presence of DCPD as compared to 30% reaction in 20 days in the absence of DCPD. Again high deuterium incorporation (90–96%) was observed in the reduction products **6** and **7**. Another product, dicyclohexylmethylphosphine (DCPMe), was observed in the bromide reactions in the presence of DCPH(D). This product is not observed in the iodide case, even in trace amounts. This result strongly suggests a difference in the rate-determining step of the reaction mechanism of the bromide **2** reaction with DCPH(D) as compared to the iodide **1** reaction.

Experimental tests for the $S_{RN}1$ mechanistic pathway in the reaction of 5-bromo-1-cyclooctene (**2**) with $LiCuMe_2$ in the presence of DCPH were carried out. It was observed that PDNB clearly retards the rate of reaction and shows a complete absence of reduction products as compared to nearly 10% reduction product formation after 24 h without *p*-DNB present. This result strongly suggests that a $S_{RN}1$ mechanism (Scheme I) is involved. In order to investigate this matter further, an entrainment experiment was performed in which the cyclooctenyl iodide **1** was added to the reaction of the cyclooctenyl bromide **2** with $LiCuMe_2$ in the presence of DCPH after the reaction had proceeded for 2 (experiment 5). An entrainment effect often is seen in $S_{RN}1$ chain processes and is explained by the assumption that once the chain process is in effect, the difference between electron transfer from the radical anion to an iodide or bromide is not that significant so that either will react with about the same ease.[23] By adding a small amount of iodide **1** relative to bromide **2**, iodide initiated the radical anion chain process and a dramatic acceleration in reaction rate was observed. The reaction with added iodide was complete in less than 24 h, as compared to less than 20% reaction in the absence of added iodide. A catalytic amount of $LiCuMe_2$, 20% relative to bromide, was allowed to react with cyclooctenyl bromide **2** in the presence of DCPH for 20 days. The fact that less than 1% reaction took place suggests that a free-radical chain process is not likely but rather supports a $S_{RN}1$ chain process since a $S_{RN}1$ pathway requires a stoichiometric amount of cuprate.

Scheme III outlines the proposed $S_{RN}1$ chain process that occurs in the reaction of the bromide **2** with $LiCuMe_2$ in the presence of DCPH. The last step in the scheme demonstrates why DCPMe is seen as a byproduct of the reaction with the bromide **2** but not with the iodide **1**, namely, because the reaction with the iodide **1** occurs by

Scheme III. Reaction Pathway of 5-Bromo-1-cyclooctene (2) with $LiCuMe_2$ in the Presence of DCPH



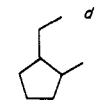
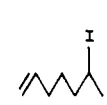
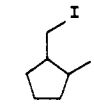
a free-radical chain process. Unlike the bromide reaction, the iodide reaction is not affected by the addition of *p*-DNB.[26] The difference in reaction pathways of iodide vs. bromide in the presence of DCPH appears to be due to the much faster rate that the iodine atom is abstracted by free radicals compared to the bromine atom from the corresponding alkyl halide (eq 6).[19]

The proposed mechanism suggested for the reaction of the bromide **2** with $LiCuMe_2$ in the absence of additives is identical with that proposed for the iodide (Scheme II) except that the radical precursor to **7** does not react with **2** to produce the cyclized bromide in a radical chain process as takes place in the case of the corresponding iodide. The reason for this appears to be the same as for the reactions with DCPH; i.e., bromine atoms are extracted by radicals at a much slower rate, and therefore, the free radicals primarily abstract hydrogen from some source in the reaction to give reduction products. The overall slowness of the reaction is due to the poorer ability of the bromide **2** to accept an electron from $LiCuMe_2$ as compared to iodide **1**.

Reaction of $LiCuMe_2$ with Other Radical Probe Alkyl Iodides. In order to determine how general the reaction pathway found for 5-iodo-1-cyclooctene (**1**) is,

(26) Crandall, J. K.; Banks, P. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423.

Table XI. Effect of *p*-Dinitrobenzene on the Reaction of 6-Iodo-1-heptene (10) with $LiCuMe_2$[a]

		% yield					
							
additive[b]	time		15	14	13	10	16
none	10 min		5.5[c]	10.3	25.0 (4.2)	56.8	
p-DNB	11 min					100.0	
none	32 min		10.3 (4.4)	16.3	37.9 (4.5)	23.6	3.2[c]
p-DNB	32 min			0.9		99.1	
none	66 min	1.3	12.2 (3.2)	17.3	39.9 (4.8)	10.1	6.2[c]
p-DNB	66 min			2.4		93.7	6.3[c]
none	24 h	0.7	14.7 (4.6)	25.5	50.9 (4.7)		
p-DNB	24 h		6.9 (5.3)	19.5	27.6 (3.5)	29.6	15.6 (6.4)

[a] Reaction at 0 °C in THF with a 4:1 ratio of $LiCuMe_2$/alkyl. [b] *p*-DNB is *p*-dinitrobenzene. [c] Cis isomer predominates. [d] cis/trans ratio in parentheses.

6-iodo-1-heptene (**10**), 5,5-dimethyl-6-iodo-1-hexene (**11**), and 6-iodo-1-hexene (**12**) were allowed to react with $LiCuMe_2$. The secondary iodide probe 6-iodo-1-heptene (**10**) had been studied earlier and was observed to yield 65% of 2-ethyl-1-methylcyclopentane (**13**), the cyclized substitution product.[10] Since **10** is a secondary iodide like the cyclooctenyl iodide **1**, it was expected that these iodides would behave similarly. This was not the case when the reaction was explored in detail. At a 10 to 1 ratio of $LiCuMe_2$ to **10** in THF at 0 °C (similar conditions under which most of the reactions of **1** were performed), the reaction was very fast and was over in less than 14 min as compared to nearly 24 h required for the reaction of the cyclooctenyl iodide. The major products were 61% cyclized substitution product 1-ethyl-2-methylcyclopentane (**13**), 19.9% uncyclized substitution product 6-methyl-1-heptene (**14**), and 7.5% cyclized reduction product 1,2-dimethylcyclopentane (**15**) (Table 10). The results of these reactions will be discussed in more detail later.

The reaction of 6-iodo-1-heptene (**10**) was investigated at a 4:1 ratio of $LiCuMe_2$ to alkyl iodide in the absence and presence of *p*-DNB (Table XI) in order to carry out a more thorough study. A dramatic inhibiting effect was observed for the reactions containing *p*-DNB. After 10 min, over 40% reaction had occurred with no additive present; on the other hand, no discernible reaction was observed in the presence of *p*-DNB after 11 min. After 66 min, more than 90% of the starting iodide remained with *p*-DNB present and only about 10% without it. In the early part of the reaction, the only product with the additive *p*-DNB present was uncyclized substitution product **14**, and this was in a reduced yield (2.4%, 66 min) compared to the normal reaction (17.3%, 66 min). The reaction began to return to normal after the inhibiting effect was overcome as seen at the 24-h reaction time which indicated that over 70% of the starting alkyl iodide had reacted. It is evident that the cyclization of the iodide **10** to yield 1-(iodomethyl)-2-methylcyclopentane (**16**) is not as inhibited as the formation of the other products in the reaction in the presence of *p*-DNB.

All of the reactions with and without *p*-DNB after 24 h produced predominantly cyclized products which have cis and trans isomers. The cis to trans isomer ratio in all cases was 3.5–4.8 at 0 °C. Garst has shown[27] that cis to trans ratios of ~4 at 0 °C are indicative of radical cyclization and ratios of less than 1 are typical of anion cyclization. The results in Table XIII are consistent with free-radical cyclization.

(27) Garst, J. F.; Hines, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 6443.

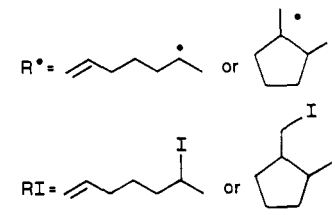
Scheme IV. $S_{RN}1$ Pathway of the Reaction of 6-Iodo-1-heptene (10) with $LiCuMe_2$

$$[Me_2CuLi]_2 + R^\bullet \longrightarrow [RMe_4Cu_2Li]^{\bullet-}Li^+$$

$$[RMe_4Cu_2Li]^{\bullet-}Li^+ + RI \longrightarrow [RMe_4Cu_2Li] + [RI]^{\bullet-}Li^+$$

$$[RI]^{\bullet-}Li^+ \longrightarrow R^\bullet + LiI$$

$$[RMe_4Cu_2Li] \longrightarrow MeR + Me_3Cu_2Li$$



The effect of a good $S_{RN}1$ chain inhibitor such as *p*-DNB and the evidence of substantial radical products support the reaction pathway in Scheme IV. The $S_{RN}1$ chain process probably is initiatied by electron transfer between the radical probe iodide **10** and $LiCuMe_2$ to produce free radicals. These free radicals couple with another dimeric cuprate species to form the radical anion $[RMe_4Cu_2Li]^{\bullet-}$. This new cuprate species transfers an electron to the alkyl iodide (either **10** or **16**) to give the neutral cuprate species $[RMe_4Cu_2Li]$ and the radical anion of the iodide. The radical anion of the radical probe iodide very rapidly dissociates to form iodide ion and the free-radical probe which continues the chain. The cuprate species $[RMe_4Cu_2Li]$ decomposes to give methyl-substituted product and Me_3Cu_2Li.

The fact that **10** produced a primary alkyl compound upon cyclization was considered to be a possible explanation for the difference in reactivity and product distribution between **10** and **1**. The reaction of $LiCuMe_2$ with 2-iodooctane was compared to the same reaction with **10** to test this hypothesis. The results shown in Table XII indicate that *p*-DNB inhibits the reaction of 2-iodooctane with $LiCuMe_2$ as well as **10**, although not as dramatically. These results suggest a similarity of mechanisms for the reaction of $LiCuMe_2$ with **10** and 2-iodooctane and leave open the question of the differences between the two secondary probes **10** and **1**. It is evident that the cyclization of **10** does occur during the course of the reaction to some extent and is known to be the dominant reaction when insufficient $LiCuMe_2$ is present (Table X, 0.2 cuprate to iodide ratio). However, the formation of **16** is not necessary as a precursor for the formation of cyclized products since 2-iodooctane appears to react in a similar manner and cyclized products are not formed in the

Table XII. Comparison of the Reaction of 2-Iodooctane and 6-Iodo-1-heptene (10) with $LiCuMe_2$ in the Presence or Absence of *p*-Dinitrobenzene at 0 °C in THF

alkyl iodide	additive[a]	time	% yield[b] starting iodide	reduction products	substitution products	cyclized iodide
2-heptenyl	none	10 min	56.8	5.5	35.3	0
2-octyl	none	11 min	60.5	0.8	37.2	NA
2-heptenyl	*p*-DNB	11 min	100.0	0	0	0
2-octyl	*p*-DNB	10 min	90.3	0	8.8	NA
2-heptenyl	none	66 min	10.1	6.2	57.2	6.2
2-octyl	none	60 min	15.3	4.2	80.5	NA
2-heptenyl	*p*-DNB	66 min	93.7	6.3	2.4	6.3
2-octyl	*p*-DNB	59 min	61.5	0	24.6	NA
2-heptenyl	none	24 h	0	15.4	76.4	0
2-octyl	none	48 h	0	3.7	96.2	NA
2-heptenyl	*p*-DNB	24 h	29.6	6.9	47.1	15.6
2-octyl	*p*-DNB	24 h	13.0	2.8	84.2	NA

[a] *p*-DNB is *p*-dinitrobenzene. [b] NA = not available.

Table XIII. Reactions of 5,5-Dimethyl-6-iodo-1-hexene (11) with $LiCuMe_2$ in the Presence or Absence of *p*-Dinitrobenzene at 0 °C in THF

ratio of $LiCuMe_2$:(11)	additive[a]	time	% yield 18	20	17	11	19
10.0	none	10 min	8.3	8.9	32.1	44.8	0
	none	65 min	24.4	15.8	57.4	2.4	0
2.0	none	12 min	3.0	4.2	15.3	75.2	0
	p-DNB	14 min	0	7.5	2.6	87.3	0
	none	64 min	5.7	10.1	39.5	35.9	0
	p-DNB	60 min	2.0	19.1	16.6	63.7	0
	none	1 day	12.6	22.7	54.6	9.0	0
	p-DNB	1 day	5.2	51.2	29.2	15.5	0
0.2	none	1 day	1.6	3.3	3.0	89.3	0
	none	21 days	3.7	4.7	6.5	81.5	0

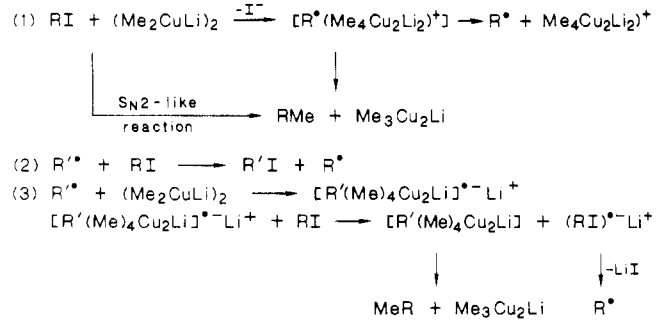
[a] *p*-DNB is *p*-dinitrobenzene.

presence of *p*-DNB even when cyclized alkyl iodide **16** is present (Table XI).

The primary probe, 5,5-dimethyl-6-iodo-1-hexene (**11**) (neooctenyl iodide), is quite hindered, and therefore S_N2-like substitutions would be expected to be slowed compared to radical pathways. This indeed appears to be the case since a considerable amount of cyclized substitution product 1,1-dimethyl-3-ethylcyclopentane (**17**) and cyclized reduction product 1,1,3-trimethylcyclopentane (**18**) were observed in the reaction with $LiCuMe_2$ (Table XIII). In none of the experiments, including the reactions with insufficient cuprate, was any cyclized iodide **19** observed. Although iodide **19**, being a 1° iodide, could react so fast that no appreciable concentration builds up during the reaction, it seems unlikely that when insufficient $LiCuMe_2$ was present not even a trace was detected. In addition, the reaction failed to proceed past a stoichiometric reaction, i.e., when the $LiCuMe_2$/alkyl iodide ratio was 0.2:1, only ~20% reaction occurred. It appears that, unlike secondary iodides, iodide **11** does not participate in a free-radical cyclization process to form the cyclized iodide **19** in the presence of $LiCuMe_2$.

The effect of *p*-DNB on the reaction of $LiCuMe_2$ with alkyl iodide **11** in a 2:1 ratio was explored. The reaction in the presence of *p*-DNB is slowed somewhat, but the most striking change is in the ratio of cyclized substitution product **17** to uncyclized substitution product **20**. The ratio of **17**:**20** after 24 h without *p*-DNB added is 2.4 and with *p*-DNB added is 0.57, almost a reverse in the product ratio. The cyclized reduction product **18** also is reduced in the presence of *p*-DNB. These results, coupled with the evident stoichiometric reactivity observed, support a $S_{RN}1$ process for the formation of cyclic products; however, when this pathway is inhibited, the direct reaction with **11** is sufficiently fast to allow the formation of uncyclized product **20** to predominate.

Scheme V. Three Reaction Pathways Observed in the Reaction of Alkyl Iodides with $LiCuMe_2$



The unhindered primary probe, 6-iodo-1-hexene (**12**), seems to behave in a quite straightforward manner. After only 3 min (2:1 ratio of $LiCuMe_2$/alkyl iodide), the alkyl iodide had completely reacted to give 1-heptene essentially quantitatively. In the presence of *p*-DNB, the reaction was slightly slower, but whether this is significant is unclear. If SET is ocurring in this reaction, very rapid coupling in the solvent cage must follow, and there is no way to differentiate between this possibility and an S_N2-like reaction.

As Table X demonstrates, there are a number of similarities and differences in the reactions of these four

probes. All of the iodides followed at least one of the three reaction pathways summarized in Scheme V. It is evident that a number of factors such as primary vs. secondary alkyl iodide and steric hindrance determine which reaction pathways are followed. It is clear that in all of the radical probe reactions studied except for 6-iodo-1-hexene (**12**) free radicals are involved. In the case of the two secondary iodide probes **1** and **10**, radical abstraction of iodine to form cyclized iodides **9** and **16** occurs, but perhaps due to the greater reactivity of the primary iodides, no evidence of the cyclization of primary iodide probe **11** was seen. The free radicals also initiate the $S_{RN}1$ chain process when iodides **10** and **11** are allowed to react with $LiCuMe_2$; however, this is not the case for **1** and **12**. Although the direct reaction to form substitution product could be due to a S_N2-like reaction, it is equally possible that both the coupled product produced by direct reaction, as opposed to a $S_{RN}1$ pathway, and the free radicals which initiate pathways 2 and 3 in Schene V arise from the same initial step, i.e., SET between $LiCuM_2$ and the alkyl halide.

Summary

The reactions of $LiCuMe_2$ with the radical probe system, 5-substituted cyclooctene, were studied. In the case of the corresponding iodide, considerable amounts of cyclized products were observed. These cyclized products were shown to be formed from 2-iodo-*cis*-bicyclo[3.3.0]octene which was produced from the starting iodide by a free-radical chain process. Extensive trapping of the free radicals by hydrogen atom donors indicated that a substantial concentration of free radicals was produced in the reaction. These free radicals are believed to be produced by SET between the cuprate and the iodide. In the bromide case the reaction was quite slow; however, free-radical cyclization still was detected. When DCPH was added to the reaction mixture, a $S_{RN}1$ chain reaction was initiated, accelerating the reaction and producing dicyclohexylmethylphosphine as a byproduct.

Another secondary iodide probe, 6-iodo-1-heptene, was shown to react differently with $LiCuMe_2$. This probe reacted much faster and produced considerably more cyclized substitution products. It was shown that *p*-dinitrobenzene dramatically inhibits the reaction, and this suggests that a $S_{RN}1$ reaction pathway is operating which is catalyzed by free radicals produced by SET involving the cuprate and the iodide. The primary iodide probe, 5,5-dimethyl-6-iodo-1-hexene, was shown also to have a $S_{RN}1$ reaction component, but the direct substitution is more competitive and becomes the dominant reaction pathway when *p*-dinitrobenzene is present as an additive.

Experimental Section

Materials. Solvent-grade pentane and hexane were stirred over concentrated H_2SO_4, washed with water, dried over $MgSO_4$, and distilled from $NaAlH_4$ under nitrogen. Reagent-grade diethyl ether and tetrahydrofuran (THF), both from Fisher, were distilled under nitrogen from deep purple solutions of sodium benzophenone ketyl. Hexamethylphosphoramide, HMPA, from Aldrich was fractionally distilled from sodium under reduced pressure. Samples of 1-heptene, *n*-decane, cuprous bromide–dimethyl sulfide, and *p*-dinitrobenzene were obtained from Aldrich; 1,1,3-trimethylcyclopentane, 6-methyl-1-heptene, 2-methyloctane, and 1-ethyl-2-methylcyclopentane were obtained from Wiley Organics; *cis*- and *trans*-1,2-dimethylcyclopentane were obtained from Chem Samples; *n*-octane was obtained from Eastman; cuprous cyanide was obtained from Fischer; and di-*tert*-butylnitroxyl radical was obtained from Alfa. All of the above were used as received.

Cyclooctene was obtained from Chem Samples; 1,5-cyclooctadiene, 1,4-cyclohexadiene and *tert*-butylamine were obtained from Aldrich and were distilled from CaH_2 under nitrogen before use. DCPH was obtained from Aldrich and was distilled (bp 68–70 °C at 0.04 mmHg) before use. Deuteriated DCPH was prepared by a previously described method.[28] An authentic sample of *cis*-bicyclo[3.3.0]octane was obtained by preparative GLC (column B) of a hydrolyzed sample from the reaction of 5-iodo-1-cyclooctene with $LiAlH_4$ and exhibited the following: ^1H NMR ($CDCl_3$) δ 1.0–2.0 (m, 12 H), 2.4–2.8 (m, 2 H); mass spectrum, *m/e* (relative intensity) 110 (M^+, 3.9). Anal. Calcd for C_8H_{14}: C, 87.17; H, 12.83. Found: C, 86.95; H, 12.87.[28] A sample of 2-iodo-*cis*-bicyclo-[3.3.0]octane was obtained by preparative HPLC (benzene as an eluent) of a hydrolyzed sample from the reaction of 5-iodo-1-cyclooctene with $LiAlH_4$ and exhibited the following: ^1H NMR ($CDCl_3$) δ 1.1–2.45 (m, 10 H), 2.5–2.6 (m, 2 H), 3.76–3.9 (m, 1 H); mass spectrum, *m/e* (relative intensity) 235 (M^+, 30.8). Anal. Calcd for $C_8H_{13}I$: C, 40.69; H, 5.56. Found: C, 40.70; H, 5.57. A sample of 5-methyl-1-cyclooctene was obtained by preparative GLC (column C) from a hydrolyzed sample of the reaction of 5-iodo-1-cyclooctene with $LiCuMe_2$ and showed the following: ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H), 1.1–1.25 (m, 1 H), 1.3–1.5 (m, 3 H), 1.5–1.7 (m, 3 H), 2.0–2.4 (m, 4 H), 5.55–5.70 (m, 2 H); mass spectrum, *m/e* (relative intensity) 124 (M^+, 3.2); chemical ionization mass spectrum, *m/e* 125 ($M^+ + 1$). Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.21; H, 12.73. A sample of 5,5-dimethyl-1-heptene was obtained by preparative GLC (column C) from a hydrolyzed sample of the reaction of 5,5-dimethyl-6-iodo-1-hexene with $LiCuMe_2$ and exhibited the following: ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 0.95 (s, 6 H), 1.15–1.45 (m, 4 H), 1.95–2.05 (m, 2 H), 4.85–5.05 (m, 2 H), 5.75–5.90 (m, 1 H); mass spectrum, *m/e* (relative intensity) 126 (M^+, 2.5); chemical ionization mass spectrum, *m/e* 127 ($M^+ + 1$). Anal. Calcd for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.63; H 14.34. A sample of 1,1-dimethyl-3-ethylcyclopentane was obtained by preparative GLC (column C) from a hydrolyzed sample of the reaction of 5,5-dimethyl-6-iodo-1-hexene with $LiCuMe_2$ and exhibited the following: ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 0.86 (t, 3 H), 1.00 (s, 3 H), 1.15–1.95 (m, 9 H); mass spectrum, *m/e* (relative intensity) 126 (M^+, 5.8); chemical ionization mass spectrum, *m/e* 125 ($M^+ - 1$). Anal. Calcd for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.71; H, 14.23. Fischer purified copper(I) iodide was repurified by being dissolved in saturated aqueous KI, treated with decolorizing charcoal, and filtered. After precipitation by dilution with deoxygenated water, the CuI was collected by filtration and washed with absolute ethyl alcohol followed by anhydrous ether and dried overnight under high vacuum.[29] Methyllithium was purchased from Aldrich, filtered, using oven-dried Celite filter aid, and standardized by both Eastham-Watson titration and total base titration. The standardization agreed to ±5%.

General Procedures. All glassware and syringes were oven-dried at 150 °C, and the glassware was additionally flame-dried under high vacuum and then flushed with nitrogen. Syringes were flushed with nitrogen and kept under positive nitrogen pressure while cooling until used. Transfer of reagents was performed by using calibrated syringes equipped with stainless steel needles. Reactions were carried out in round-bottom flasks equipped with T-bore stopcocks attacked to male 24/40 standard taper joints and were stirred with Teflon-coated magnetic stirring bars. Storage and transfer of CuI and $CuBr{\cdot}SMe_2$ took place in a glovebox equipped with a recirculating system consisting of manganese oxide columns to remove oxygen and liquid nitrogen traps to remove solvent vapors.

Proton NMR spectra were recorded on either a Varian T-60A or Bruker WM-300 instrument with chemical shifts reported relative to tetramethylsilane (TMS). Mass spectral analyses were performed on a Varian MAT-112S spectrometer. IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. Elemental compositions were determined either by microanalysis (Atlantic Microlabs, Inc. of Atlanta, GA) or by high resolution mass spectrometry.

Quantitative gas-liquid chromatographic (GLC) analyses were conducted on a Varian Model 3700 instrument equipped with a flame ionization detector using a 100-m DB-1 capillary column

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(column A). GLC yields were determined by using internal standards and comparing peak areas which were corrected for response factors. Preparative GLC separations were performed on a F&M Model 720 instrument equipped with a thermal conductivity detector using either a 6 ft × $^1/_4$ in., 10% Apiezon L on S720U (column B) or a 25 ft × $^1/_4$ in., 10% Apiezon L on Chromosorb P (column C). For quantitative GLC analyses, the following conditions were used for the various reaction systems studied (retention times are given relative to the internal standard used): for the analysis of 5-iodo-1-cyclooctene, 5-bromo-1-cyclooctene, and the tosylate of 5-hydroxy-1-cyclooctene and their products, 60 °C for 8 min, followed by 10°/min to 250 °C, bicyclo[3.3.0]oct-2-ene (0.45), bicyclo[3.3.0]octane (0.49), 1,3-cyclooctadiene (0.56), cyclooctene (0.57), 2-methylbicyclo-[3.3.0]octane (0.66), 5-methylcyclooctene (0.80), *n*-decane (1.00, internal standard), 5-bromo-1-cyclooctene (1.43), 2-iodobicyclo-[3.3.0]octane (1.51), 5-iodo-1-cyclooctene (1.59), and dimers (2.1 to 2.2); for the analysis of 6-iodo-1-heptene and its products, 35 °C for 7 min, followed by 15°/min to 160 °C, then held for 5 min, *trans*-1,2-dimethylcyclopentane (0.62), 1-heptene (0.64), *cis*-1,2-dimethylcyclopentane (0.73), 6-methyl-1-heptene (0.86), *trans*-1-ethyl-2-methylcyclopentane (0.96), octane (1.00, internal standard), *cis*-1-ethyl-2-methylcyclopentane (1.04), 6-iodo-1-heptene (1.54), *trans*-2-methyl-1-iodomethylcyclopentane (1.64), *cis*-2-methyl-1-iodomethylcyclopentane (1.69); for the analysis of 5,5-dimethyl-6-iodo-1-hexene and its products, 30 °C for 6 min, followed by 10°/min to 160 °C, then held for 5 min, 1,3,3-trimethylcyclopentane (0.47), 3,3-dimethyl-1-ethylcyclopentane (0.75), 5,5-dimethyl-1-heptene (0.76), *n*-decane (1.00, internal standard), 5,5-dimethyl-6-iodo-1-hexene (1.11); for the analysis of 2-iodooctane and its products, 35 °C for 7 min, followed by 15°/min to 160 °C, then held for 5 min, *n*-octane (0.69), 2-methyloctane (0.81), *n*-decane (1.00, internal standard); and for the analysis of 6-iodo-1-hexene and its products, 30 °C for 6 min, followed by 10°/min to 160 °C, 1-heptene (0.45), *n*-decane (1.00, internal standard), 6-iodo-1-hexene (1.01).

Preparations. 5-Hydroxy-1-cyclooctene (the Tosylate of 5-Hydroxy-1-cyclooctene). The alcohol was prepared by the method of Crandall[26] and exhibited the following: ^{1}H NMR (neat) δ 1.0–2.6 (m, 10 H), 3.35–3.9 (br, 1 H), 4.5–4.95 (m, 2 H), 5.2–5.9 (m, 2 H); mass spectrum, *m/e* (relative intensity) 108 ($M^+ - H_2O$, 11.1); chemical ionization mass spectrum, *m/e* 127 ($M^+ + 1$). From the alcohol, the tosylate was prepared by allowing it to react with 1 equiv of tosyl chloride at 0 °C in dry pyridine for 5 days. After filtration, the solution was diluted with hexane, washed with dilute HCl and water, and dried with $MgSO_4$. After removal of solvent, the crude material (>90% yield) was twice recrystallized from hexane/ethanol to provide analytically pure tosylate which exhibited the following: mp 45.5–46.0 °C (lit.[30] mp 47–48 °C); ^{1}H NMR ($CDCl_3$) δ 1.0–2.5 (m, 10 H), 2.3 (s, 3 H), 4.25–4.75 (m, 1 H), 5.35–5.7 (m, 2 H), 7.1–7.9 (m, 4 H); mass spectrum, *m/e* (relative intensity) 280 (M^+, 0.5). Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 64.19; H, 7.21.

5-Iodo-1-cyclooctene. To a solution of 20 g of the recrystallized tosylate of 5-hydroxy-1-cyclooctene in 200 mL of dry acetone was added 60 g of NaI, and the reaction mixture was refluxed for 24 h. After standard workup and removal of solvent, the iodide formed was fractionally distilled to yield 9 g (53% yield) which exhibited the following: bp 38 °C (2.3 mmHg); n^{25}_D 1.5655; ^{1}H NMR (neat) δ 0.75–3.0 (m, 10 H), 4.25–4.75 (m, 1 H), 5.35–5.95 (m, 2 H); mass spectrum, *m/e* (relative intensity) 109 ($M^+ - I$, 77), chemical ionization mass spectrum, *m/e* 236 (M^+, 100). Anal. Calcd for $C_8H_{13}I$: C, 40.70; H, 5.55. Found: C, 40.82; H, 5.61.

5-Bromo-1-cyclooctene. To 45 g of 34% HBr/glacial acetic acid was added 25 mL of freshly distilled 1,5-cyclooctadiene, and the mixture was vigorously stirred overnight. The reaction mixture was poured into an ice/water mixture, extracted with Et_2O, washed with $NaHCO_3$ solution, and dried over $CaCl_2$, and the solvent removed and fractionally distilled under vacuum to give 29 g (76% yield) of >90% pure bromide.[31] This was chromatographed on silica gel by using hexane/benzene as the eluent to yield 20 g (52% yield) of analytically pure bromide which exhibited the following: bp 65–66 °C at 0.1 mmHg; n^{25}_D 1.5216; ^{1}H NMR (neat) δ 1.3–2.9 (m, 10 H), 4.0–4.55 (m, 1 H), 5.3–5.9 (m, 2 H); mass spectrum, *m/e* (relative intensity) 188 (M^+, 3.76), 190 (M^+, 3.72). Anal. Calcd for $C_8H_{13}Br$: C, 50.81; H, 6.93. Found: C, 50.90; H, 6.96.

5,5-Dimethyl-6-iodo-1-hexene. The iodide was prepared from the corresponding alcohol, 2,2-dimethyl-5-hexen-1-ol. The alcohol was prepared according to the method of Beckwith,[32] and the iodide was prepared according to a previously described method.[33] The NMR, IR, and mass spectra agreed with those previously reported.

6-Iodo-1-heptene. This compound was prepared from the tosylate of 6-heptene-1-ol by the reaction of the tosylate with NaI in refluxing acetone for 24 h. After standard workup and distillation at 77–79 °C (25 mmHg), the iodide exhibited NMR, IR, and mass spectra identical with those previously reported.[13] The alcohol 1-hepten-6-ol was prepared by the method of Ingold and Maeda[34b] and the tosylate by reaction of the alcohol with tosyl chloride in pyridine at 8 °C for 48 h.[13]

6-Iodo-1-hexene. This compound was prepared from the tosylate of 1-hexen-6-ol by reaction of the tosylate with NaI in refluxing acetone for several hours. The product exhibited NMR, IR, and mass spectra identical with those previously reported.[13]

2-Iodooctane. The iodide was prepared from 2-octanol by the method of San Filippo[35] and exhibited NMR, IR, and mass spectra consistent with those previously reported.

2-Methylbicyclo[3.3.0]octane. To a solution of 32.5 g of 1,5-cyclooctadiene in 300 mL of chloroform was added 1.46 g of benzoyl peroxide, and the solution was refluxed for 5 days. On four consecutive days an additional 0.73 g of benzoyl peroxide was added. The reaction was allowed to cool on the fifth day and the chloroform solution was washed with sodium bicarbonate three times and once with water and dried over $MgSO_4$. Upon fractional distillation, 18 g of 2-(trichloromethyl)bicyclo[3.3.0]octane (26%) was obtained which was >95% pure by GC and NMR.[14] Hydrogenation of 2-(trichloromethyl)bicyclo[3.3.0]octane was accomplished by the shaking of 2.7 g of the compound, 6 mL of methanol, 12 mL of triethylamine, and 1.2 mL of a basic aqueous slurry of Raney nickel under 50 psi hydrogen pressure for several hours after hydrogen uptake ceased. After standard workup the ether extractions were washed with water, dilute HCl, a saturated $NaHCO_3$ solution, and then water again. The completely reduced product was obtained by preparative GLC (column C) and exhibited the following: ^{1}H NMR ($CDCl_3$) δ 0.94–1.13 (m, 5 H), 1.27–1.93 (m, 10 H), 2.37–2.47 (m, 1 H); mass spectrum, *m/e* (relative intensity) 124 (M^+, 9.6). Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.28; H, 12.72.

Bicyclo[3.3.0]oct-2-ene. The mixture of 25 g of 1,5-cyclooctadiene and 7 g of 75% H_3PO_4 was refluxed overnight.[36] The reaction mixture was extracted with ether, washed with water, a saturated $NaHCO_3$ solution several times, and again with water and dried over $MgSO_4$ and the solvent removed. The title compound was obtained by preparative GLC (column B) and exhibited the following: ^{1}H NMR ($CDCl_3$) δ 1.28–1.53 (m, 4 H), 1.60–1.74 (m, 2 H), 1.96–2.03 (m, 1 H), 2.56–2.68 (m, 2 H), 3.12–3.16 (m, 1 H), 5.47–5.59 (m, 2 H); mass spectrum, *m/e* (relative intensity) 108 (M^+, 25); chemical ionization mass spectrum, *m/e* 109 ($M^+ + 1$, 78) and 107 ($M^+ - 1$, 100). Anal. Calcd for C_8H_{12}: C, 88.82; H, 11.18. Found: C, 88.95; H, 11.01.

Dicyclohexylmethylphosphine Oxide. By the procedure of Issleib,[37] dicyclohexylphosphinic chloride was obtained. To a solution of 0.5 g of the chloride in 3 mL of THF was added dropwise at room temperature 2.0 mL of 1.34 M MeMgBr, and the resulting mixture was allowed to stir overnight during which time a solid precipitated. The reaction mixture was quenched with water, washed with $NaHCO_3$, and filtered to remove the

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solids, and the solvent was removed. After sublimation at 100 °C, 0.5 mmHg,[38] the material exhibited the following: ^{1}H NMR ($CDCl_3$) δ 1.16–1.42 (m, 11 H), 1.65–1.96 (m, 14 H); mass spectrum, *m/e* (relative intensity) 228 (M^+, 11.4). Anal. Calcd for $C_{13}H_{25}PO$: M_r, 228.1643. Found: M_r, 228.1687.

General Procedures for Reaction of $LiCuMe_2$ with Alkyl Halide and Tosylate Probes. Copper iodide (1 equiv) was transferred to a 50-mL flask in an oxygen-free glovebox. Freshly distilled THF was added, and the slurry of CuI in THF was cooled to 0 °C in an ice bath. Two equivalents of MeLi were added dropwise by syringe while stirring, and a colorless solution was formed. To this solution was added a concentrated solution of the halide or tosylate in THF. For reaction profile studies, samples were taken by syringe and quenched immediately with stirred cold solutions of saturated NH_4Cl/NH_4OH (10 to 1) in glass vials which also contained the internal standard in hexane or pentane. After stirring for several minutes the water layer was removed and the nonaqueous layer washed with saturated NH_4Cl solution and then H_2O. The samples were then either immediately analyzed by GLC or stored in screw-top glass vials at <–10 °C until analysis could be made. In some cases the whole reaction mixture was quenched with cold saturated NH_4Cl solution under a nitrogen atmosphere at 0 °C and worked up similar to the above. New reactions were routinely submitted for analysis by GLC/mass spectroscopy to confirm product identification.

When additives were used, they were added as a concentrated THF solution immediately before the addition of the halide solution. In the solvent effect studies, the cuprate was formed as detailed above and the solvent removed by high vacuum in order to be replaced by the solvent mixtures to be studied. In the reactions using CuCN as the source of copper(I), the cuprates were prepared by the method used by Lipschutz.[18]

Control experiments by NMR using benzene as an internal standard showed that lithium dimethylcuprate was stable at 0 °C during the time periods studied and that DCPH and 1,4-cyclohexadiene were stable in the presence of cuprate during the time periods studied. It also was determined by GLC that DCPH and 1,4-cyclohexadiene do not react with the alkyl halides during the time periods of interest.

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Enzymes in Organic Synthesis. 39.[1] Preparations of Chiral Cyclic Acid-Esters and Bicyclic Lactones via Stereoselective Pig Liver Esterase Catalyzed Hydrolyses of Cyclic Meso Diesters

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Pig liver esterase catalyzed hydrolyses of *meso*-dimethyl cyclopropane-, cyclobutane-, and cyclohexane-1,2-dicarboxylates are enantiotopically specific, giving acid–ester products that are readily converted into γ-lactones of >97% ee that are of value as chiral synthons. There is a dramatic change of stereospecificity on going from the cyclopropane and cyclobutane diesters to the cyclohexane substrate, with the cyclopentane diester hydrolysis representing the changeover point within the series. This reversal of enzyme stereospecificity is explicable in terms of a two binding-pocket active-site model. Hydrolyses of dimethyl oxirane-2,3-dicarboxylate and of cyclopropane-1,2-diacetates are also stereoselective, giving product ee's of up to 30–70%.

Enzymes are now widely recognized as practical catalysts for asymmetric synthesis, with their abilities to induce stereospecific transformations on symmetrical substrates being of particular importance.[2] Esterases are attractive in this regard because they operate without requiring expensive coenzymes. One such enzyme that is commercially available, and whose potential for discriminating between enantiotopic ester groups of prochiral substrates such as meso diesters has already begun to be exploited in the preparation of useful chiral synthons,[3,4] is pig liver esterase (PLE, EC 3.1.1.1). The results detailed in this paper on the stereoselectivity of PLE-catalyzed hydrolysis of the monocyclic meso diesters **1**–**7**[4] extend further the asym-

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