J. Am. Chem. Soc. 1991, 113, 631-636

Reaction of Bu$_2$CuLi·LiI with Alkyl Iodides: Evidence for Free Radicals and Electron Transfer[1]

Steven H. Bertz,* G. Dabbagh, and A. M. Mujsce

Contribution from AT&T Bell Laboratories, Murray Hill, New Jersey 07974.
Received May 21, 1990

Abstract: Treatment of iodocyclohexane with Bu$_2$CuLi·LiI yields substantial amounts of butylcyclohexane, cyclohexane, cyclohexene, bicyclohexyl, and octane. Trapping experiments demonstrate that the bulk of these products derive from cyclohexyl radicals, indicating that an electron-transfer mechanism is operative. Some of the cyclohexane and bicyclohexyl is traced to transmetalation. Likewise, 1-methyl-1-cyclohexyl iodide and 2-heptyl iodide react via electron transfer, whereas cyclohexyl bromide, 1-heptyl iodide, and 1-heptyl bromide do not. These results are in harmony with House's hypothesis that electron transfer from organocuprates occurs when the reduction potentials of the substrates are more positive than −2.35 V.

The structures of organocuprates[2] in solution and the mechanisms of organocuprate reactions are poorly understood,[3] in spite of the fact that they are among the most important reagents of organic chemistry. Mechanistic investigations to date have focused on such aspects as reduction potential,[4] rearrangements,[4-6] and degree of racemization of optically active substrates.[7-9] While some progress has been made recently,[10] major issues remain to be resolved, e.g., the occurrence of electron transfer, radicals, and Cu(II) or Cu(III) intermediates; the origins of selective coupling; and the differences between cuprates prepared from a lithium reagent and various different Cu(I) salts.[2,11] More than a decade ago, House suggested that organocuprates react with α-enones via an electron-transfer pathway, on the basis of the correlation of conjugate addition with reduction potential.[4] While electron transfer has yet to be verified in the case of α-enones,[10] we have developed evidence that electron transfer to alkyl iodides does occur when their reduction potentials are in the range proposed by House. For example, in the Bu$_2$CuLi·LiI–iodocyclohexane system we observe the product (octane) of oxidatively induced reductive elimination from the copper center and the products of a radical intermediate (cyclohexyl) from the substrate.

Results and Discussion

Table I summarizes the product distributions from the reactions of Bu$_2$CuLi prepared from various Cu(I) precursors and 1 equiv of iodocyclohexane (**1**) after 1 h at −78 °C. The yields of butylcyclohexane (**2**) decrease in the series Bu$_2$CuLi·LiCN > Bu$_2$CuLi·LiBr ≈ Bu$_2$CuLi·LiOTf > Bu$_2$CuLi·LiI. In addition to **2**, cyclohexane (**3**), cyclohexene (**4**), bicyclohexyl (**5**), and octane (**6**) are produced, especially in the case of Bu$_2$CuLi·LiI. The amounts of **3** and **4** are comparable in the case of Bu$_2$CuLi·LiI, but for the other butyl cuprates studied **3** ≫ **4**. The amounts of **5** and **6** from **1** and Bu$_2$CuLi·LiI are much higher than the amounts from the other cuprates; nevertheless, the amounts from Bu$_2$CuLi·LiBr, Bu$_2$CuLi·LiOTf, and Bu$_2$CuLi·LiCN are significant.

Table I. Reaction of Bu$_2$CuLi with Iodocyclohexane[a]

precursor	% **2**[b,c]	% **3**[b,d]	% **4**[b,e]	% **5**[b,f,g]	% **6**[b,h]	2[**4**]/[**5**]
CuI	28.9	18.5	17.0	29.2	30.4	1.16
	32.4	18.4	15.4	27.9	33.1	1.10
CuBr[i]	52.6	6.7	1.4	5.1	8.9	0.55
	47.4	10.9	2.0	7.4	13.4	0.54
CuOTf[j]	50.2	8.2	1.0	4.5	2.9	0.44
	44.2	8.8	1.8	6.5	11.9	0.55
CuCN	81.2	5.5	0.7	5.1	5.5	0.25
	70.8	10.6	1.3	9.9	17.8	0.26

[a] Experimental conditions: 1.00 mmol/2.5 mL of THF and 0.8 mL of hexane (from BuLi), stirred at −78 °C for 1 h. [b] Yields were determined by GLC calibrated with authentic products and internal standard. Mass balances, 100 ± 5%. [c] Butylcyclohexane. [d] Cyclohexane. [e] Cyclohexene. [f] Bicyclohexyl. [g] 100 × millimoles of **5**/0.5 mmol of **1**. [h] Octane. [i] Dimethyl sulfide complex. [j] Benzene complex.

The presence of **3**–**5** in substantial amounts in the case of Bu$_2$CuLi·LiI is suggestive of the intermediacy of cyclohexyl radicals (Cy$^\bullet$), and our values for the ratio of disproportionation to combination,[12] $k_d/k_c = 2[\mathbf{4}]/[\mathbf{5}]$, fall within the range (1.1–1.5) reported for cyclohexyl radicals in the liquid phase.[13] We calculate 2[**4**]/[**5**] rather than ([**3**] + [**4**])/[**5**], since in all our reactions [**3**] > [**4**].[12] Quenching reaction mixtures with D$_2$O rather than H$_2$O shows that the excess of **3** is due to **3**-d_1, indicating that transmetalation is occurring to some extent in all the reaction mixtures. The excess of **3** is relatively small for Bu$_2$CuLi·LiI but becomes significant for the other reagents. The **5** that results upon treatment of **1** with cuprates prepared from CuBr, CuOTf, or CuCN can be attributed mainly to the reaction of **1** with a cyclohexylcopper(I) species from transmetalation. Thus, the values of 2[**4**]/[**5**] are a sensitive function of the competing paths to **5**. Warming the reaction mixtures from any of the precursors to 0 °C results in the appearance of additional amounts of **5**. We do not detect **3**–**5** when **1** is treated with Me$_2$CuLi·LiI or Ph$_2$CuLi·LiI under the same conditions.

The intermediacy of cyclohexyl in the formation of **3**–**5** from **1** and Bu$_2$CuLi·LiI is supported by trapping experiments in which dicyclohexylphosphine[14] (Cy$_2$PH) was included in the reaction mixtures. Upon addition of 4 equiv of Cy$_2$PH, the yields of **4** and **5** were decreased from 24% and 32% to 9% and 4%, respectively,

---

[1] New Copper Chemistry. 19. Part 18: Bertz, S. H.; Smith, R. A. J. *Tetrahedron* **1990**, *46*, 4091.

[2] (a) Bertz, S. H.; Dabbagh, G. *J. Am. Chem. Soc.* **1988**, *110*, 3668. (b) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031.

[3] (a) Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980; pp 544–565. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley-Interscience: New York, 1980.

[4] House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

[5] Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251.

[6] Bertz, S. H.; Dabbagh, G.; Cook, J. M.; Honkan, V. *J. Org. Chem.* **1984**, *49*, 1739.

[7] Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

[8] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

[9] Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696.

[10] Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133. Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276.

[11] Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251.

[12] Calculated as $k_d/k_c = 2[\mathbf{4}]/[\mathbf{5}]$, in accord with the following: Bennett, J. E.; Gale, L. H.; Hayward, E. J.; Mile, B. *J. Chem. Soc., Faraday Trans. 1* **1973**, *69*, 1655. The factor of 2 in the denominator of Bennet et al.'s equation for k_d/k_c is incorporated into our calculation of yields; see Table I.

[13] Cramer, W. A. *J. Phys. Chem.* **1967**, *71*, 1171. Falconer, J. W.; Burton, M. *J. Phys. Chem.* **1963**, *67*, 1743.

[14] Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833.

0002-7863/91/1513-631$02.50/0

Scheme I

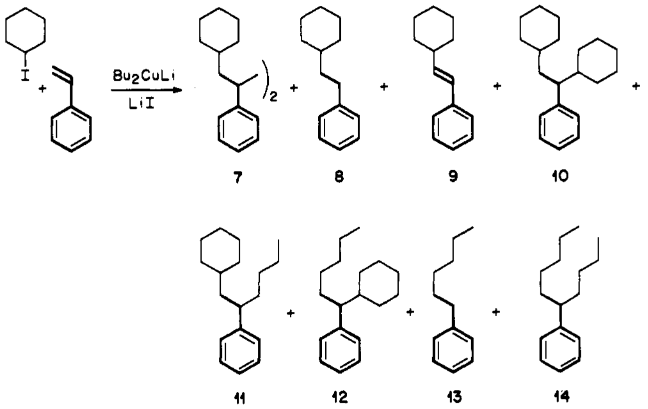


Table II. Yields[a] as a Function of Time

time (s)	% 2[b]	% 3[c]	% 4[d]	% 5[e]	2[4]/[5]
2	22.5	7.0	4.2	6.9	1.22
6	27.4	7.8	4.7	7.3	1.29
12	30.9	7.6	4.2	7.0	1.20
31	35.5	8.0	4.1	7.5	1.09
58	39.1	7.5	3.6	6.6	1.09
120	39.2	7.2	3.6	7.7	0.94
360	45.7	8.1	3.9	8.1	0.96
3601	54.8	9.7	4.7	10.2	0.92

[a] Measured in triplicate by GLC calibrated with authentic products and internal standards. Experimental conditions: 1.00 mmol/6.0 mL of THF solution at −78 °C for each time. [b] Butylcyclohexane. [c] Cyclohexane. [d] Cyclohexene. [e] Bicyclohexyl.

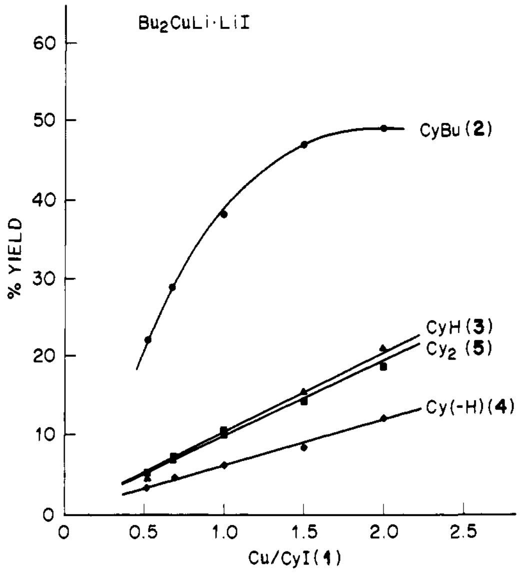


Figure 1. Percent yield vs reactant ratio, $Bu_2CuLi\cdot LiI/1$. Experimental conditions: 1.00 mmol of cuprate/6.0 mL of THF solution at −78 °C for 0.1 h.

and the yield of 3 was increased from 23% to 82%. When the reaction run in the presence of Cy_2PH was quenched with D_2O, only 4% *d* incorporation into product 3 was measured by MS. The use of Cy_2PD (4 equiv) as the trapping agent (H_2O quench) yielded 57% of 3 (76% d_1 by MS analysis), 18% of 4, and 15% of 5. The presence of 14% of unlabeled 3 (24% of 57%) with the Cy_2PD trap may be attributed to the disproportion of cyclohexyl (cf. 18% of 4 present). The yield of 2 is reduced from 21% to 5% by Cy_2PH (4 equiv) and to 10% by Cy_2PD (4 equiv). The yields of **2–5** reported here for the reaction without phosphine were from a third experiment run simultaneously with the phosphine-containing reaction mixtures (see Table V). Ashby et al. have also observed that Cy_2PD is a less efficient radical trap than Cy_2PH.[15] We have ruled out a radical chain reaction between Cy_2PH and **1** in our study by generating $Cy_2P^\bullet$ (from Cy_2PH with benzoyl peroxide or AIBN) in the presence of **1** and measuring a quantitative recovery of **1**.

The presence of cyclohexyl radicals in the reaction of **1** with $Bu_2CuLi\cdot LiI$ is further supported by experiments in which styrene (2.5 equiv) was added as a radical trap in reaction mixtures (0.18 M, −78 °C, 1 h) prepared from each of the four cuprates. Only in the one prepared from $Bu_2CuLi\cdot LiI$ was 1,4-dicyclohexyl-2,3-diphenylbutane (**7**) present. This product of cyclohexyl radical addition to the β-position of styrene followed by dimerization at the α-position occurred as a 1/1 mixture of stereoisomers in ~8% total yield (see Scheme I). No 6,7-diphenyldodecane, the corresponding product of butyl addition to styrene, was detected. The absence of this compound supports a nonradical pathway for the production of the octane observed (vide infra). Also present in the reaction mixture prepared from CuI (but not in those from CuBr, CuOTf, or CuCN) were 1-cyclohexyl-2-phenylethane (**8**, 1%), 1-cyclohexyl-2-phenylethene (**9**, 1%), 1,2-dicyclohexyl-1-phenylethane (**10**, 7%), 1-cyclohexyl-2-phenylhexane (**11**, 5%), 1-cyclohexyl-1-phenylhexane (**12**, 0.5%), 1-phenylhexane (**13**, 3%), and 5-phenyldecane (**14**, 3%). No **13** or **14** was observed in control reactions that contained no **1**. Also present were 10% of **2**, 5% of **3**, 11% of **4**, 7% of **5**, and 13% of **6**. In the control experiment without styrene, the yields of **2–6** were 16%, 16%, 19%, 35%, and 49%, respectively.

Previous investigators have reported that $Bu_2CuLi\cdot LiI$ and **1** afford only cyclohexene[16] or that they afford **2** in quantitative yield.[17] We have used CuI from two suppliers (Aldrich and Alfa), both as received and after purification.[18] Further, we have investigated the reaction as a function of temperature from −78 to +25 °C and as a function of reactant ratio (Cu/**1**) from 0.5–4, and we have not been able to obtain either result. Lipshutz et al. reported the yield of **2** from **1** and $Bu_2CuLi\cdot LiCN$ to be quantitative;[19] however, the best yield we have been able to obtain by quenching with H_2O is 81%. When the reaction mixture was quenched with 1-iodobutane, the yield was increased to 91%, since the cyclohexylcuprate formed by transmetalation (vide supra) was trapped under these conditions.[7]

Substantial octane (30–33%, see Table I) above that which results from cuprate preparation (1–10%) was observed upon treatment of **1** with $Bu_2CuLi\cdot LiI$. Smaller amounts of octane (3–18%) were produced upon treatment of **1** with the other cuprates. Whitesides et al. showed that octane is not formed during the thermal decomposition of $BuCuPBu_3$.[20] Likewise, we find that octane is not produced when Bu_2CuLi (prepared from any of the four precursors) is aged at −78 °C, 0 °C, or even 25 °C (sampled after 1 h at each temperature). The octane in our system is best explained by reductive elimination from an oxidized Cu center (see Mechanistic Discussion).

The product distributions from $Bu_2CuLi\cdot LiI$ and 1 equiv of **1** as a function of time are given in Table II, from which it may be noted that ~90% of the **4** present after 1 h is also present after 2 s, whereas only ~40% of the final **2** is present after 2 s. The operation of a transmetalation process accounts for the increase in **3** and **5** at long times and is reflected in a slow decrease in 2[**4**]/[**5**]. The yield of **2** rises smoothly and begins to level off at ca. 40% after ~1 min, followed by a subsequent slower increase.

The yields of products as a function of the reactant ratio for $Bu_2CuLi\cdot LiI/1$ and $Bu_2CuLi\cdot LiCN/1$ are plotted in Figures 1 and 2, respectively. Of importance to synthetic applications, the yields of **2** level off with increasing excesses of cuprate whereas

---

(15) Ashby, E. C.; DePriest, R. N.; Su, W.-Y. *Organometallics* **1984**, *3*, 1718.

(16) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615.

(17) See ref 9, footnote 24.

(18) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 10.

(19) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

(20) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

Table III. Reaction of Bu_2CuLi with Cyclohexyl Tosylate and Bromocyclohexane

precursor[a]	substrate	temp (°C)	time (h)	% **2**[b,c]	% **3**[b,d]	% **4**[b,e]	% **5**[b,f]
CuI	CyI	-50	1	25.1	35.5	22.0	22.4
		25	2	32.1	35.5	22.5	27.0
	CyBr	-50	1	<0.1	0.8	1.2	<0.1
		25	2	11.4	67.3	11.3	2.7
	CyOTs	-50	1	<0.1	5.6	18.2	<0.1
		25	2	0.8	46.6	23.9	<0.1
CuCN	CyI	-50	1	41.4	19.2	7.7	3.5
		25	2	43.1	24.1	19.0	7.6
	CyBr	-50	1	<0.1	5.2	0.9	<0.1
		25	2	1.6	3.0	10.4	<0.1
	CyOTs	-50	1	<0.1	<0.1	25.4	<0.1
		25	2	<0.1	2.7	25.9	<0.1

[a] Experimental conditions: 1.00 mmol/10 mL of THF solution. [b] Yields were determined by GLC calibrated with authentic products and internal standards. [c] Butylcyclohexane. [d] Cyclohexane. [e] Cyclohexene. [f] Bicyclohexyl.

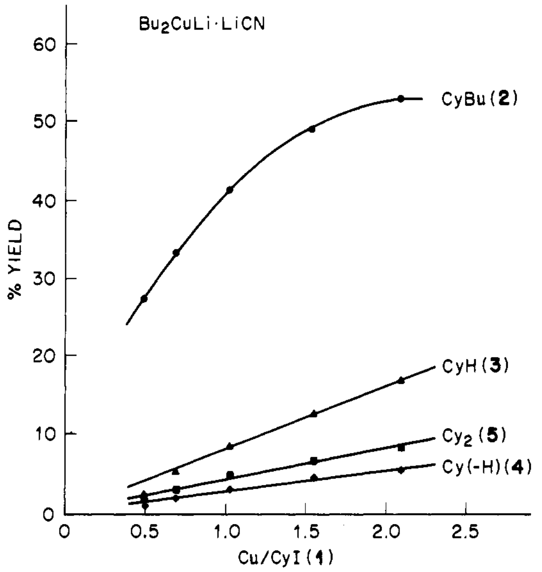


Figure 2. Percent yield vs reactant ratio, $Bu_2CuLi{\cdot}LiCN$/**1**. Experimental conditions: 1.00 mmol of cuprate/6.0 mL of THF solution at -78 °C for 0.1 h.

Table IV. Effects of Added Salt

precursor[a]	% **2**[b]	% **3**[c]	% **4**[d]	% **5**[e,f]	2[**4**]/[**5**]
CuI	49	9.7	5.3	11.2	0.95
CuI + LiI	48	5.3	0.41	2.4	0.34
CuI + LiBr	53[g]	5.0	0.55	2.6	0.42
CuI + LiOTf	14[h,i]	1.3	0.18	0.32	1.12
CuI + LiCN	40	8.8	3.0	8.3	0.72
CuCN	76	4.4	0.40	3.2	0.25
CuCN + LiI	79	4.2	0.084	2.1	0.08
CuCN + LiBr	75[g]	8.4	1.0	7.1	0.28
CuCN + LiOTf	30[i,j]	1.3	0.20	0.40	1.00
CuCN + LiCN	79	6.0	0.28	4.1	0.14

[a] Experimental conditions: 2.0 mmol/11 mL of THF solution, stirred at -78 °C for 1 h. The cuprates were prepared at -50 °C and then stirred at 0 °C for 30 min before **1** was added at -78 °C. [b] Butylcyclohexane, determined by GLC calibrated with authentic material and internal standard. [c] Cyclohexane, measured as in *b*. [d] Cyclohexene, measured as in *b*. [e] Bicyclohexyl, measured as in *b*. [f] 100 × millimoles of **5**/0.5 mmol of **1**. [g] The yield from $Bu_2CuLi{\cdot}LiBr$ was 44%. [h] Upon warming to 0 °C for 1 h, the yield became 40%. [i] The yield from $Bu_2CuLi{\cdot}LiOTf$ was 61%. [j] Upon warming to 0 °C for 1 h, the yield became 51%.

the yields of side products do not. Therefore, the common practice of using large excesses of organocuprates (2-10 equiv has not been uncommon) may not be warranted and may even be deleterious. Of course, every substrate and cuprate must be examined individually: Our point is simply that one should not start with a large excess. The yields of **2** are slightly higher for the cyanocuprate at a given reactant ratio, whereas the yields of **3**-**5** are higher for the iodocuprate. Considering all the products, the iodocuprate appears to be slightly more reactive at each reactant ratio. For example, at a reactant ratio of 1, the total yields of **2**-**5** are 65% for the iodocuprate and 58% for the cyanocuprate. It is not correct to say that the cyanocuprate is more reactive than the iodocuprate;[19] it is simply reactive in a different way.

A comparison of the reactivities of $Bu_2CuLi{\cdot}LiI$ and $Bu_2CuLi{\cdot}LiCN$ with **1**, bromocyclohexane, and cyclohexyl tosylate can be made with the data in Table III. No **2** is detected from bromocyclohexane or cyclohexyl tosylate and either cuprate after 1 h at -50 °C, conditions under which substantial amounts of **2** are produced from **1**. Allowing the $Bu_2CuLi{\cdot}LiI$ reaction mixtures to warm to 25 °C results in some **2** from both the bromide and the tosylate, significantly more from the former. The reactivity profile is clearly CyI ≫ CyBr > CyOTs. The cyanocuprate appears to be less reactive toward both the bromide and the tosylate than the iodocuprate.

In order to ascertain whether or not the I^- liberated from **1** as the reaction proceeds has an influence on further reaction, we examined the effects of added salts upon the product distributions. Table IV lists the yields of **2**-**5** obtained after 1 h at -78 °C, with use of 0.18 M reaction mixtures rather than the 0.3 M ones used to obtain the data in Table I. The more dilute solutions were necessary so that the reagents would be homogeneous. Under these more dilute conditions, the yield of **2** from $Bu_2CuLi{\cdot}LiI$ is higher and the yields of **3**-**5** are lower. When an additional 1 equiv of LiI or LiBr is included in the $Bu_2CuLi{\cdot}LiI$ reaction mixture, the production of **3**-**5** is suppressed; however, the yield of **2** is not increased. The addition of LiCN or LiOTf to $Bu_2CuLi{\cdot}LiI$ does not suppress the radical reaction nearly as much as the halide salts. With the exception of LiOTf, the addition of the various salts to $Bu_2CuLi{\cdot}LiCN$ did not have a dramatic effect.

As in the case of **1**, the reactions of 2-heptyl iodide and 1-methyl-1-cyclohexyl iodide with $Bu_2CuLi{\cdot}LiI$ yield substantial amounts of disproportionation and combination products and they are affected by Cy_2PH in the same way (see Table V). Again, the intermediacy of radicals (2-heptyl and 1-methyl-1-cyclohexyl, respectively) is indicated.

On the other hand, 1-heptyl iodide does not yield a significant amount of 1-heptene when treated with $Bu_2CuLi{\cdot}LiI$; therefore, the heptane and tetradecane produced are not the progeny of the 1-heptyl radical. Instead, they indicate transmetalation. Furthermore, this reaction is not significantly affected by Cy_2PH. Radical products are also absent from the reaction of $Bu_2CuLi{\cdot}LiI$ and 1-heptyl bromide. Under the conditions used for the substrates in Table V, 1-heptyl bromide yielded 21% undecane, 2% heptane, and <1% 1-heptene or tetradecane.

Mechanistic Discussion

A conceptual framework useful for discussing our results is presented in Scheme II, which shows a radical-cage mechanism (paths A and B) involving Cu(II) intermediate **15** and a two-step nucleophilic oxidative addition[21] (paths C and D) via Cu(III) intermediates **16** and **17**. Cyclohexyl radicals that escape from the cage give rise to products **3**-**5**, and the combination of Cy•

---

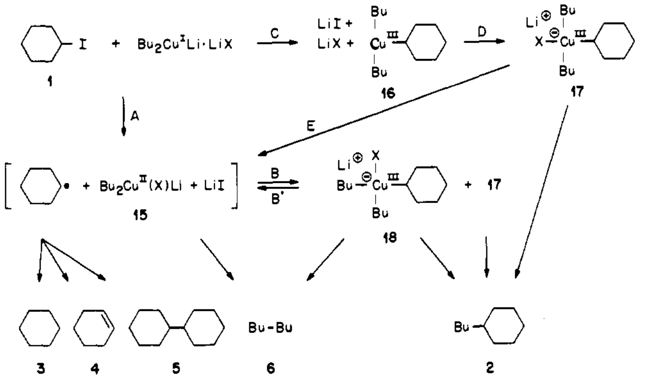
(21) See ref 3a, p 184-189.

Table V. Reaction of Alkyl Iodides with $Bu_2CuLi{\cdot}LiI$

		yields (%)[a]					
RI, R	Cy_2PH (equiv)	BuR	RH	R(−H)	R(−H)′	R(−H)‴	R–R
1-methylcyclohexyl	0	3	23	41[b]	14[c]		1
	4	2	88	20[b]	5[c]		0.3
cyclohexyl	0	21	23	24			32
	4	5	82	9			4
2-heptyl	0	15	28	19[d]	2[e]	9[f]	8[g]
	4	11	71	16[d]	2[e]	7[f]	4[g]
1-heptyl	0	35	26	0.6			20
	4	34	52	0.2			14

[a] Measured by GLC calibrated with authentic products (internal standard method), unless otherwise noted. Experimental conditions: 1.00 mmol/2.5 mL of THF and 0.7 mL of hexane (from BuLi) stirred at −78 °C for 1 h. [b] Methylcyclohexene. [c] Methylenecyclohexane. [d] 1-Heptene. [e] *cis*-2-Heptene. [f] *trans*-2-Heptene. [g] No authentic product available.

Scheme II



and **15** gives Cu(III) intermediates **17** and **18** that undergo reductive elimination to **2**. Reductive elimination of two butyls from **15** or **18** yields **6**. The elimination of **6** from **18** also yields CyCu, which affords the transmetalation products. For oxidative additions to transition metals forming metal–carbon bonds, the following has been observed: "There is a delicate balance between a polar, two-step, 'S_N2' path, a radical chain path, and a radical cage path."[21]

An alternative source of cyclohexyl would be the homolysis of the Cy–Cu bond in **17** (path E) or **18** (path B′). If homolysis of the Cy–Cu bond in **17** were the source of the radical intermediate Cy•, then the radical products **3–5** and the substitution product **2** would appear together throughout the course of the reaction and the yields of **2** would be independent of the presence of a radical trap; however, such is not the case.

Copper(III), like copper(II), has a square-planar ligand field.[22] The trans disposition of the groups in **17** originally from the cuprate has been invoked to explain the selective coupling that is observed for cuprate reactions in general,[23] as reductive elimination only occurs when groups are cis. While a Cu(III) intermediate is commonly assumed for organocuprate reactions, other possibilities have also been mentioned. For example, if the Cu(III) remains part of a cluster of Cu and Li atoms, two Cu(II) sites would be equivalent to a single Cu(III) site.[3a] Selective coupling of a bridging alkyl group from the cuprate with the nonbridging alkyl group from the alkyl halide would then complete the process.

The Buxton,[24] Cohen,[25] and Kochi[26] groups have shown that alkyl radicals react with Cu(II) compounds, and Meyerstein[27] has observed some of the resulting Cu(III) intermediates spectroscopically. A Cu(II) intermediate from the reaction of alkyl radicals with Cu(I) has also been observed spectroscopically.[24]

Scheme III

Initiation

$$R_2Cu^{I}Li + X\cdot \rightarrow R_2Cu^{II}(X)Li$$

$$R_2Cu^{II}(X)Li + \mathbf{1} \rightarrow R_2Cu^{III}(X)(I)Li + Cy\cdot$$

Propagation

$$R_2Cu^{I}Li + Cy\cdot \rightarrow R_2Cu^{II}(Cy)Li$$

$$R_2Cu^{II}(Cy)Li + \mathbf{1} \rightarrow R_2Cu^{III}(Cy)(I)Li + Cy\cdot$$

Unlike most of the cases studied to date, the initial product of oxidative addition to Cu(I) in our system is not stable enough to be observed directly, making a definitive study of the mechanism difficult if not impossible.

Johnson and Dutra[8] showed that $Ph_2CuLi{\cdot}LiI$ alkylates (*S*)-2-butyl tosylate with complete inversion of stereochemistry, which is consistent with an S_N2-like reaction, and Whitesides et al.[7] found that it alkylates (*R*)-2-bromobutane with predominant inversion of configuration. In contrast, Lipshutz and Wilhelm[9] demonstrated that optically active 2-iodooctane gave only racemic products whether it was treated with organocuprates prepared from CuI or CuCN. This observation is consistent with a radical intermediate; however, as Collman and Hegedus point out, "the observation of a racemic product in oxidative additions should not necessarily be taken as evidence for a radical path, since racemization could occur after the initial metal-carbon bond is formed".[21] Ashby et al.[5] treated 6-iodo-1-heptene with $Me_2CuLi{\cdot}LiBr$ and obtained a 65% yield of the cyclized product, 1-ethyl-2-methylcyclopentane, along with the usual substitution product. They interpret this observation to mean that "the iodo compound reacts by a pathway involving predominantly electron transfer"; however, their data do not rule out oxidative addition–homolytic dissociation or a transition-metal-mediated insertion reaction of the double bond. Recent results by the Newcomb and Curran groups suggest that nucleophiles can react with mechanistic probes such as Ashby's via a sequence involving radical-chain isomerization of the alkyl halide probe (initiated by a small number of electron-transfer events), followed by nucleophilic attack on the rearranged halide.[28] It is suggested that, "in the case of alkyl iodide probes, the amount of rearranged product will probably be at least two orders of magnitude greater than the amount of radical initiation".[29] Consequently, we believe that we have the first bona fide evidence for electron transfer between organocuprates and alkyl halides. In light of our results, it is reasonable to conclude that radicals are, indeed, involved in Lipshutz's and Ashby's systems. The fact that Lipshutz observes racemization using cuprates prepared from CuCN as well as those

---

(22) Birker, P. J. M. W. L. *Inorg. Chem.* **1977**, *16*, 2478.
(23) See ref 3a, pp 194–197.
(24) Buxton, G. V.; Green, J. C. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 697.
(25) Cohen, T.; Lewarchik, R. J.; Tarino, J. Z. *J. Am. Chem. Soc.* **1974**, *96*, 7753.
(26) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843.
(27) Freiberg, M.; Meyerstein, D. *J. Chem. Soc., Faraday Trans. 1* **1980**, *76*, 1825.
(28) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.
(29) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195.

prepared from CuI suggests that radicals are also involved in our reaction of **1** with $Bu_2CuLi{\cdot}LiCN$. If this is indeed the case, the rate of scavenging of cyclohexyl by the Cu(II) intermediate **15** must be much greater than k_d or k_c in this case.

If a radical intermediate is involved, the alternative to the radical-cage reaction (Scheme II) is a radical-chain process (Scheme III) in which the starting Cu(I) complex is attacked by a radical (initiator) to give a Cu(II) complex, which then abstracts $I^{\bullet}$ from **1** to give a Cu(III) complex and cyclohexyl radical. The chain is propagated when the cyclohexyl radical attacks a starting Cu(I) complex to give a cyclohexylcopper(II) complex, which in turn abstracts $I^{\bullet}$ from **1** to yield a cyclohexylcopper(III) complex and cyclohexyl radical as the chain carrier. The cyclohexylcopper(III) complex reductively eliminates **2** and perhaps **6** (cf. **17** and **18**, Scheme II). The abstraction of $I^{\bullet}$ from **1** is best viewed as an inner-sphere electron transfer[30] in which I^- is transferred from a complexed **1** to Cu(II) with simultaneous transfer of an electron from Cu(II) to **1** to give Cu(III) and cyclohexyl radical. The reactions of radicals with both Cu(I) and Cu(II) have been found to be very fast, some approaching the diffusion-controlled limit.[24,31] This oxidation of Cu(II) to Cu(III) is considered to be energetically less favorable than the oxidation of Cu(I) to Cu(II) by **1** in the radical-cage mechanism of Scheme I, which is also possibly an inner-sphere electron transfer.

We believe that the best explanation for the octane observed from the reaction of $Bu_2CuLi{\cdot}LiI$ with **1** is "oxidatively-induced reductive elimination",[32] wherein an electron is removed from the Cu(I) reagent to give a Cu(II) intermediate (oxidation), which then decomposes to octane and Cu(0) (reductive elimination). Black "colloidal copper" is observed in these reaction mixtures. Whitesides et al.[33] obtained octane in high yield when they treated $Bu_2CuLi{\cdot}LiI$ with oxygen, nitrobenzene, or Cu(II), all good 1-electron oxidants. The facile reductive elimination of octane from Bu_2Cu^{II} mitigates against the radical-chain process of Scheme III, which requires Cu(II) intermediates with sufficient lifetimes for intermolecular reactions. The cage reaction of $Bu_2Cu(II)$ with $Cy^{\bullet}$ seems more reasonable. Another possible source of octane is reductive elimination from a Cu(III) intermediate such as **18**.

The usual radical traps (oxygen, galvinoxyl, disulfides, etc.) are not useful for probing organocuprate reactions because they react with organocuprates. We reasoned that styrene should be a useful radical scavenger, as it is not a good Michael acceptor for carbanions less nucleophilic than the lithium reagents used for its anionic polymerization and the free-radical polymerization of styrene is not an efficient process.[34] Indeed, we were rewarded with the plethora of products pictured in Scheme I. Product **7** is the most direct evidence for having trapped a radical, as it can be formed by the simple dimerization of two α-cyclohexylmethylbenzyl radicals. Products **8** and **9** are the disproportionation products of the cyclohexylmethyl-substituted benzyl radical. Like **7**, **10** is most likely a product of radical–radical coupling. Product **11** results from the interaction of the α-cyclohexylmethylbenzyl radical with a butylcopper species. Product **12** results from the coupling of a substituted benzylcopper species with cyclohexyl; the low yield is due to the fact that each of the partners has a higher probability of coupling with butyl (yielding **14** and **2**, respectively) than they have of coupling with each other. Products **13** and **14** are not attributable to reaction of styrene with $Bu_2CuLi{\cdot}LiI$, as they are not present in the control reaction run without **1**. Therefore, they result from the butylation of styrene by a product of the reaction of $Bu_2CuLi{\cdot}LiI$ with **1**. It is possible that some of the styrene is reacting via a Cu–olefin complex.[10]

Finally, we note that the reduction potentials for 1-methyl-1-cyclohexyl, cyclohexyl, and 2-heptyl iodides are −1.8, −2.18, and −2.3 V, respectively, and they are −2.54, −3.01, and −3.47 V for 1-heptyl iodide, cyclohexyl bromide, and 1-heptyl bromide, respectively.[35] House hypothesized that organocuprates transfer an electron to α-enones with reduction potentials more positive than −2.35 V.[4] We have established that our substrates with reduction potentials ≥ -2.3 V react via electron transfer and those with reduction potentials ≤ -2.5 V do not. Thus, the threshold for electron transfer in our system (−2.4 ± 0.1 V) is very close to the value (−2.35 V) promulgated by House.[36]

In conclusion, we have presented evidence that $Bu_2CuLi{\cdot}LiI$ reacts with iodocyclohexane via electron transfer and cyclohexyl radical intermediates. The observation of radical-derived products from the substrate and the oxidatively induced reductive elimination product from the cuprate provides the first "smoking pistol" evidence for electron transfer in a typical cuprate reaction. By studying a series of alkyl halides, we have been able to confirm House's proposed threshold for electron transfer from organocuprates.

Experimental Section

Our procedure for cleaning and passivating glassware has been published.[37] Septa were purchased from Alrich Chemical Co. (We find their style Z12,743-4 to be superior to others we have tried.) Glassware was dried in an oven (120 °C) overnight or in a Bunsen burner flame. Flasks were charged with solids (and magnetic stir bars) and sealed with septa in a drybox (Ar atmosphere) containing an electronic balance. Liquids were dispensed by gas-tight microliter syringe into tared flasks that had been sealed with septa in the drybox. All septa were wired on to ensure the tightest possible fit.

Copper(I) iodide was purchased from Alrich (99.999%, Lots 4815CJ and 2212AK) and Alfa ("ultrapure", Lots 101680 and 111282). Aldrich Lot 4815CJ and Alfa Lot 111282 were purified by the standard procedure[18] and dried in a vacuum desiccator over a phosphorus pentoxide. Copper(I) bromide dimethyl sulfide (Aldrich), cuprous cyanide (Baker C.P.), and copper(I) triflate (benzene complex) (Strem) were used as received. Iodocyclohexane (Fluka or Aldrich) was distilled, immediately before use for important reactions, and stored in a brown bottle in a refrigerator. Bromocyclohexane (Aldrich) was used as received, and cyclohexyl tosylate was prepared according to a literature procedure,[38] as was 1-iodo-1-methylcyclohexane.[39] Tetrahydrofuran (Aldrich Gold Label) was distilled from Na/benzophenone immediately before use and transferred by syringe from the still to the reaction flasks, which were connected via rubber tubing fitted with syringe needles to a source of dry nitrogen (see ref 37 for details). When a number of reactions were run under nitrogen simultaneously, a Kontes manifold (No. K-216060) was used along with Y-tubes to further multiply the number of lines. Product analysis was carried out on a Hewlett-Packard 5880A gas chromatograph fitted with a 50-m Hewlett-Packard cross-linked methylsilicone column (0.2-mm i.d., 0.33-μm film). Split-mode injections (100/1 ratio) were made by automatic injector. Multiple injections were reproducible to within 5%. The ISTD mode of calibration was used with mixtures of authentic products and internal standards that mimicked the product mixtures as closely as possible. All products were characterized by GC-MS on a Hewlett-Packard 5985B quadrupole mass spectrometer.

Butyllithium. Butyllithium (Aldrich) was placed under reduced pressure in the drybox to remove the solvent and then on a diffusion pump to remove the last traces of octane. It was then dissolved in freshly distilled (CaH_2) hexane. Immediately before use, 1.00-mL aliquots were added to H_2O and 1,2-dibromoethane (1–2 mL of each, in separate 125-mL Erlenmeyer flasks capped with septa). The flask containing the dibromoethane (DBE) had been dried, and both had been purged with

---

(30) Taube, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 329.

(31) Jenkins, C. L.; Kochi, J. K. *J. Org. Chem.* **1971**, *36*, 3103.

(32) See ref 3a, pp 232–243.

(33) Whitesides, G. M.; San Filippo, J.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.

(34) Bowden, M. J. In *Macromolecules*; Bovey, F. A., Winslow, F. H., Eds.; Academic Press: New York, 1979; p 23.

(35) Lipshutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1983**, *48*, 3306. Strictly speaking, these are voltametric peak potentials; they only approximate the thermodynamic reduction potentials because they are not reversible (subsequent chemical reactions). The value for 2-iodoheptane is taken to be the same as the value for 2-iodooctane, which is a good assumption since the difference (H vs CH_3) is five carbons away from the C–I bond.

(36) A caveat: The reduction potentials we quote were measured in THF, the solvent we used for our reactions. House measured them for his enones in DMF, even though his reactions were run in ether or THF. Therefore, his threshold for electron transfer in THF might be different from −2.35 V; nevertheless, the important conclusion—verification that a threshold exists—remains valid regardless of the systematic error (DMF vs THF) in House's numerical values.

(37) Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119.

(38) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235.

(39) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

nitrogen. The reaction mixtures were titrated with 0.100 N HCl to a phenolphthalein end point. Near the end point, the DBE flask requires vigorous shaking (~10 s) between each drop in order to decolorize the DBE layer without overshooting the end point. The DBE layer should be decolorized with ~0.1 mL of 0.100 N HCl beyond the amount required to decolorize the water layer. The end point should be checked by back-titration with 0.100 N NaOH until the technique has been mastered. The DBE titration measures the residual base, and the difference between the H_2O and DBE titrations give the active butyllithium. About 2.5 M solutions were usually used in order to minimize the amount of hexane added but still allow accurate measurement. Aliquots were measured to the nearest 0.01 mL with gas-tight syringes (Hamilton) fitted with Chaney adapters when several reaction mixtures were set up simultaneously.

When butyllithium standardized in this way was used to initiate anionic polymerizations, molecular weights within 3% of the theoretical weights were obtained.[40]

Typical Experimental Procedures

0.3 M Reactions. To 1.10 mmol of Cu(I) salt in a septum-sealed 10-mL recovery flask also containing a magnetic stir bar was added 50 μL of nonane (weighed to the nearest 0.1 mg). The flask was cooled to 0 °C, and 2.2 mL of dry THF was added. The contents were stirred magnetically to dissolve the nonane and suspend the Cu(I) salt, and then the flask was cooled to -50 °C in a 2-propanol bath, the temperature of which was controlled by the occasional addition of powdered dry ice. A 0.85-mL aliquot of 2.60 M (0.12 M residual base) butyllithium (2.21 mmol) was added, and the reaction mixture was stirred for 15 min at -50 °C before being cooled to -78 °C (dry ice/2-propanol slurry). A 0.3-mL sample (10% of the total volume) was withdrawn with a cooled syringe and injected into a septum-sealed vial containing 1 mL of nitrogen-purged 3 M aqueous ammonium chloride solution. This "prequench" was used to measure the amount of octane formed during the preparation of the cuprate. After 10 min at -78 °C, 210 mg (1.00 mmol) of iodocyclohexane and 50 μL of dodecane (weighed to the nearest 0.1 mg) dissolved in 0.5 mL of THF at 0 °C were added. The reaction mixtures prepared this way were quenched after times ranging from 1 s to 3 h by adding 2 mL of nitrogen-purged 3 M ammonium chloride solution or D_2O (99.8% *d*, Aldrich). The quenched reaction mixtures were allowed to warm to room temperature, and 3 mL of ether was added. The organic phase was withdrawn with a disposable pipet and dried over anhydrous sodium sulfate. The products were analyzed by GLC calibrated with the dodecane internal standard.

0.18 M Reactions. These were carried out in the same manner as the 0.3 M reactions, but with 2.20 mmol of Cu(I) salt suspended in ~9 mL of dry THF in a 25-mL recovery flask, to which was added 4.40 mmol of BuLi (in ~2 mL of hexane) to form the cuprate in 11.0 mL of solution. Often, not all of the CuCN dissolved at -50 °C; these mixtures were stirred at 0 °C for 1-5 min, until they were homogeneous. A 1.0-mL prequench was removed at -78 °C with a cooled syringe. Unless otherwise noted, 1 equiv of substrate was added in 1.00 mL of THF cooled to 0 °C. Samples (1.0 mL) were withdrawn after various times at various temperatures with B-D disposable syringes cooled with dry ice. For the reaction mixtures that were quenched after short times, the procedure was carried out on half the above scale and the entire reaction mixture was quenched with 3 M ammonium chloride solution or D_2O. With $^1/_2$ in. × $^5/_8$ in. stir bars (Bel-Art No. F37110), it was possible to stir six flasks simultaneously with a Corning PC351 stirrer. PVC foam ice buckets (SGA No. P-1047-5) cut down to a depth of 6 cm were used for the cooling bath. Generally, two such sets of six reaction mixtures were run simultaneously, although on occasion three sets were run together.

Acknowledgment. S.H.B. thanks H. Taube, M. Newcomb, J. San Filippo, E. Ashby, and D. Peters for helpful discussions.

---

(40) Bates, F. Unpublished results.

Annulation via Alkylation–Alder Ene Cyclizations. Pd-Catalyzed Cycloisomerization of 1,6-Enynes

Barry M. Trost,* M. Lautens, C. Chan, D. J. Jebaratnam, and T. Mueller

Contribution from the Departments of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706, and Stanford University, Stanford, California 94305. *Received May 23, 1990*

Abstract: A Pd(0)-catalyzed alkylation of an allyl substrate with a nucleophile containing a double or triple bond to permit subsequent thermal Alder ene reactions constitutes a novel annulation protocol. In the case of a triple bond, a Pd(2+) complex catalyzes an equivalent of an Alder ene reaction. This new cyclization is probed in terms of the effect of substitution on the olefin, the acetylene, and the tether connecting the two. The reaction produces both 1,4-dienes (Alder ene-type products) and 1,3-dienes. Mechanisms to account for the diversity of products are presented. The Pd(2+)-catalyzed reaction shows an ability to interact with remote nonreactive parts of substrates to affect conformation and thereby selectivity. Several advantages accrue to the Pd(2+)-catalyzed reaction. First, the reaction normally proceeds at temperatures between 25 and 65 °C instead of the >250 °C (in static systems) to >500 °C (in flow systems) for the thermal reaction. Second, reactions that fail thermally succeed via the metal-catalyzed process. Third, complementary regioselectivity may be observed. Fourth, the ligating properties of the metal catalyst offer opportunities for exercising control not possible in a simple thermal process. A novel cyclopentannulation of allyl alcohols and related derivatives evolves in which Pd(0) catalyzes formation of the first bond and a simple electronic switch to Pd(2+) catalyzes formation of the second bond.

Carbametalations of carbonyl groups, i.e., the additions of main-group organometallics to the carbon–oxygen π bond, represent a major classical synthetic reaction. Carbametalations of less polarized π systems, especially olefins and acetylenes, have only relatively recently come to be recognized as a general reaction type with certain types of metals, in particular those having accessible d-orbitals. Two such reactions have achieved synthetic importance. Carbacupration of acetylenes rapidly became a major synthetic entry to olefins of defined geometry.[1] The Heck arylation and vinylation involves the relatively rare carbametalation (i.e., carbapalladation) of an unactivated olefin.[2] The feasibility of such processes greatly expands the possibility of using olefins and acetylenes as versatile functional groups for C–C bond formation.[3]

---

* Address correspondence to this author at Stanford University.

(1) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(2) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146; *Org. React.* **1982**, *27*, 345.

0002-7863/91/1513-636$02.50/0 © 1991 American Chemical Society