

Subtle factors are important: radical formation and transmetallation in reactions of butyl cuprates with cyclohexyl iodide†

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The reactions of $\text{Bu}_2\text{CuLi}\cdot\text{LiI}$ and $\text{Bu}_2\text{CuLi}\cdot\text{LiCN}$ with cyclohexyl iodide are critically dependent upon subtle factors such as the surface properties of the reaction vessel, nature of the solvent still and lot of ‘ultrapure’ copper salt in addition to major effects such as the Li counterion.

Butyl cuprates $\text{Bu}_2\text{CuLi}\cdot\text{LiI}$ **1a** and $\text{Bu}_2\text{CuLi}\cdot\text{LiCN}$ **1b** react with cyclohexyl iodide (CyI) in THF to give butylcyclohexane (BuCy) along with variable amounts of side products, cyclohexane (CyH), cyclohexene (Cy(-H)), dicyclohexyl (CyCy) and octane (BuBu).¹ The CyH, Cy(-H) and CyCy are the expected ‘radical products’ from the one-electron reduction of CyI; however, the amounts of CyH and CyCy are higher than predicted from the amount of Cy(-H) and the ratio of disproportionation to combination for cyclohexyl radical.²

The excess CyH and CyCy can be explained by transmetalation,³ and the balance between it and electron transfer depends not only on commonly recognized experimental variables such as the cuprate precursor and the temperature,¹ but also on subtle ones such as the surface properties of the reaction vessel (polypropylene vs. ‘virgin,’ ‘etched’ or ‘passivated’ glass), the kind of still used to dry the THF (‘aged’ Na/BP, BP = benzophenone, vs. ‘fresh’ Na/BP or K), and the lot of ‘ultrapure’ (99.999%) CuI.

Duplicate pairs of reactions of **1a** with CyI were run at concentrations of 0.12, 0.25 and 0.50 M in polypropylene tubes at -78°C with THF from an ‘aged’ Na/BP still, which had been in operation for ca. 3 months. Comparison (paired *t* test)⁴ of 1 h and 2 h yields at 0.12 M establishes that the reactions were complete after 1 h. All eight reactions form a homogeneous data set with a $59 \pm 1\%$ average yield of BuCy (Table 1, entries 1–8).⁴

Eight reactions of **1b**, run for 1 h at -78°C in THF from the same still, gave an $81 \pm 4\%$ average yield of BuCy (entries 9–16).

All reactions reported herein had a nominal 1 : 1 ratio of cuprate to CyI. Blanks showed that the BuLi solutions contained 1–2% BuBu per mmol, and control reactions without CyI showed that the yields of BuBu generated during cuprate preparation were 10% for **1a** and 1% for **1b**. The BuBu from these sources has been subtracted in Table 1. The mean butyl conversions \hat{C}_{Bu} (%), corrected for active cuprate, are $(35.3 \pm 2.8)/0.90 = 39 \pm 3$ for **1a** and $(45.4 \pm 1.8)/0.99 = 46 \pm 2$ for **1b**. BuCu and BuCu(CN)Li were unreactive under our conditions (<0.1% BuCy), so that $C_{\text{Bu}} = 50\%$ is the theoretical maximum. Renormalizing the butyl conversions, **1a** has reached $(39 \pm 3)/50 = 78 \pm 6\%$ of theoretical and **1b** has reached $(46 \pm 2)/50 = 92 \pm 4\%$.

These results explain why synthetic reactions often require a larger excess of iodo-Gilman reagent than cyano-Gilman reagent. They also explain why solutions of **1b** are yellow,

whereas those of **1a** are gray or black, owing to ‘colloidal copper’ from the redox reaction responsible for the BuBu. This side reaction may be caused by Cu^{II} impurities in the CuI,⁵ or it may be related to the electronic properties of BuCu and CuI.⁶

When the aged THF still was replaced by a ‘fresh’ one, the yield from **1a** in virgin glass tubes dropped from 58% the day before (*cf.* $59 \pm 1\%$ in polypropylene) to 46% the day after. Both reactions were run for 1 h at -78°C with the same lot of CuI, and they were protected from the atmosphere with argon supplied by the same tank and manifold.

To confirm the dependence of yield on still age, four 0.12 M reactions of **1a** with CyI in THF from the fresh Na/BP still were run in polypropylene tubes, and the average yield of BuCy after 1 h at -78°C was $46 \pm 1\%$, in agreement with the yield in virgin glass. Three analogous 0.12 M reactions of **1b** gave a $65 \pm 4\%$ average yield of BuCy. Upon changing stills, the yields from both reagents were depressed by essentially the same amount ($59 - 46 = 13\%$ and $81 - 65 = 16\%$, respectively).

The reactions of **1a** and **1b** with CyI were repeated in THF, distilled from K, so that there would be no issues arising from the presence of benzophenone, its reduction products, or its adducts with THF.⁷ The average yields of BuCy in polypropylene tubes were $43 \pm 9\%$ from **1a** and $60 \pm 6\%$ from **1b** (average of 3 runs each). They are statistically the same as those in THF from the fresh Na/BP still ($46 \pm 1\%$ and $65 \pm 4\%$, respectively) and significantly different from those in THF from the aged Na/BP still ($59 \pm 1\%$ and 81 ± 4 , respectively). Addition of small amounts (0.1 mol%) of benzophenone, benzhydrol or benzopinacol to **1a** in K-distilled THF did not significantly affect the outcome.

Etched glass, which has been characterized mechanically and chemically,⁸ had a dramatic effect on the reactions of **1a** with CyI. The yields of BuCy after 1 h at -78°C for a pair of duplicate reactions using THF from the aged Na/BP still were 15 and 42% in etched glassware. Previously, we had observed 15 and 31% yields of BuCy in etched glass with ultrapure CuI from a different lot and THF from a different aged Na/BP still.⁹

Etched glass affects the results from **1b** and CyI to, at most, a small degree. Duplicate runs gave 75 and 77% of BuCy after 1 h at -78°C with THF from the same aged Na/BP still used to measure the yields in polypropylene (*vide supra*, $81 \pm 4\%$).

Treatment of etched glass with concentrated nitric acid, water, concentrated ammonium hydroxide and finally deionized water gave ‘passivated’ glass, which was dried as usual. Duplicate runs with **1a** in passivated glassware gave 60 and 61% yields of BuCy after 1 h at -78°C with THF from the aged Na/BP still. These yields are essentially the same as the corresponding ones in polypropylene ($59 \pm 1\%$).

Yields of BuCy from **1a**, prepared in polypropylene tubes from another lot of ‘ultrapure’ CuI, were 48 and 52% after 1 h at -78°C with THF from the aged Na/BP still, significantly lower than the yields from the first lot ($59 \pm 1\%$). The second lot was darker in color than the first, and Cu^{II} impurities are a possible explanation for both the color and the chemistry.⁵

† Electronic supplementary information (ESI) available: experimental section, including Table 2, yields of products from 4 s reactions. See <http://www.rsc.org/suppdata/ob/b4/b416612d/>

Table 1 Yields and conversions (%) of products from butyl cuprates and cyclohexyl iodide in polypropylene (aged Na/BP still)^a

Entry	Reagent	c/M	Time/h	BuCy	CyH	Cy(-H)	CyCy	BuBu ^b	C _{Bu}	C _{Cy}
1	Bu ₂ CuLi·LiI	0.12	1.00	59.4	8.5	3.8	8.2	8.6	38.3	79.9
2		0.12	1.00	57.0	8.9	4.4	11.0	6.9	35.4	81.3
3		0.12	2.00	57.7	11.4	3.7	7.5	2.5	31.3	80.3
4		0.12	2.00	59.6	10.9	3.8	7.9	6.1	35.9	82.2
5		0.25	1.00	58.0	7.0	2.6	7.2	2.1	31.1	74.8
6		0.25	1.00	58.5	7.8	2.9	7.6	3.1	32.3	76.8
7		0.50	1.00	62.0	10.3	4.9	12.6	8.9	39.9	89.8
8		0.50	1.00	58.2	10.8	4.1	10.5	8.9	38.0	83.6
9	Bu ₂ CuLi·LiCN	0.12	1.00	79.2	7.4	1.1	3.7	3.8	43.4	91.4
10		0.12	1.00	77.1	7.3	1.1	4.0	4.0	42.5	89.5
11		0.12	1.00	77.5	8.3	1.5	4.9	4.9	43.6	92.2
12		0.12	1.00	84.3	5.1	1.6	5.5	5.0	47.1	96.5
13		0.25	1.00	86.5	4.5	1.0	4.2	4.0	47.2	96.2
14		0.25	1.00	89.3	4.5	1.0	5.2	3.9	48.5	100.0
15		0.50	1.00	79.1	5.5	0.74	5.7	5.0	44.5	91.0
16		0.50	1.00	77.6	9.1	1.2	7.7	7.3	46.1	95.6

^a Determined by GLC calibrated with authentic products and internal standard. ^b Corrected for BuBu from cuprate preparation (see text).

Reactions were also run for 4 s, the shortest practical time, at $-78\text{ }^{\circ}\text{C}$ with THF from the K still. The yields of BuCy were $18 \pm 4\%$ from **1a** and $1.9 \pm 0.9\%$ from **1b** (average of 5 runs each). The corrected values of \hat{C}_{Cy} (%) are $(24.6 \pm 5.1)/0.90 = 27 \pm 6$ and $(2.5 \pm 1.7)/0.99 = 2.5 \pm 1.7$, respectively. While the relative errors tend to be high for 4 s reactions, the differences in the means are significant at the 99% confidence level (*t* test for means).⁴

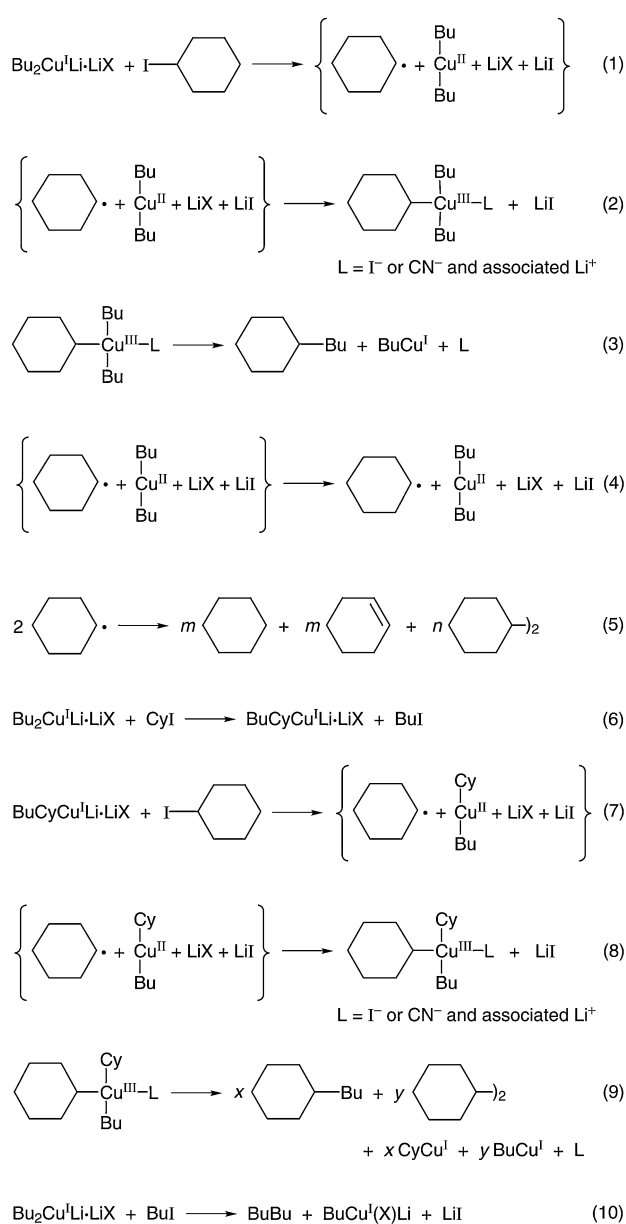
Our proposed mechanism for the reaction of butyl cuprates with CyI is summarized in Scheme 1. Rate limiting electron transfer from Bu₂CuLi·LiX (X = I, CN) to CyI affords Cy* and Bu₂Cu^{II} (step 1). They can combine in the initial solvent cage to give Bu(Cy)Cu^{III}(L)Bu (step 2), which undergoes *cis* reductive elimination to BuCy and BuCu^I (step 3) – or Cy* can escape from the solvent cage (step 4). Free Cy* gives CyH and Cy(-H) *via* disproportionation and CyCy *via* combination (step 5).

The reaction of **1a** with CyI is strongly inhibited by radical traps such as Ph₂P(O)H and styrene.¹ The observation of racemic product from a scalemic iodoalkane and a cyano-Gilman reagent suggests that radicals also mediate the reaction of **1b** with CyI.¹⁰ The lower yields of side products from the reaction **1b** + CyI and its insensitivity to the nature of surfaces can be explained by a greater efficiency of capture of Bu(Cy)Cu^{III}Bu or Bu₂Cu^{II} by cyanide than by iodide.

The selectivity of cuprate reactions with alkyl halides has been rationalized by a 'T-shaped' geometry,¹¹ since only *cis* groups can couple *via* reductive elimination. Coordination of a donor ligand L (*e.g.*, I⁻ or CN⁻ and the associated Li⁺) gives a square planar complex, which is stabilized towards isomerization.¹² The R-group in parentheses in formulas for the Cu^{III} intermediates is the one from the alkyl halide, and it is understood to be perpendicular to the two *trans* groups from the original cuprate, not in parentheses. Thus, in step 3 Bu(Cy)Cu^{III}(L)Bu can give BuCy *via* coupling of Cy with either Bu group, but it cannot give BuBu, since the two Bu groups are *trans*.

Transmetalation has been observed in reactions of cuprates with alkyl halides,³ and metathesis of Bu₂CuLi·LiX and CyI gives BuCyCuLi·LiX and BuI (step 6). The mixed cuprate can react with (excess) CyI *via* electron transfer in the same manner as the homocuprate to give Cy* and BuCyCu^{II} (step 7), which afford Bu(Cy)Cu^{III}(L)Cy (step 8), or Cy* can escape from the solvent cage and feed back into step 5. Reductive elimination from Bu(Cy)Cu^{III}(L)Cy (step 9) can give both BuCy and CyCy, and the CyCu^I co-product affords CyH upon aqueous work-up.

Reaction of the BuI from step 6 with (excess) Bu₂CuLi·LiX affords BuBu (step 10). Under our conditions ($-78\text{ }^{\circ}\text{C}$, 1 h, THF from the fresh Na/BP still), BuI gave a 55% yield of BuBu from **1a** and 67% from **1b**.¹³ In support of this mechanism, trace amounts (<1%) of BuI were detected by GC-MS in reaction mixtures quenched after short times (4 s, *vide supra*). Both **1a**

**Scheme 1**

and **1b** give BuBu upon oxidation,¹⁴ so that dioxygen must be rigorously excluded at all stages, including the aqueous quench.

Another possible source of BuBu is reductive elimination from the 'free' $\text{Bu}_2\text{Cu}^{\text{II}}$ that results when Cy[•] escapes from the initial solvent cage (step 4);¹ however, theoretical calculations suggest that this pathway is not energetically favorable,¹² which also means that BuCy does not come from $\text{BuCyCu}^{\text{II}}$ (step 7).

In light of Scheme 1, we can calculate the yields of products that arise *via* transmetallation with the aid of eqns. 11–14, where $y(\text{P})$ is the yield of product P, $Y_{\text{R}}(\text{P})$ is the yield of P from radical routes that do not involve transmetallation, and $Y_{\text{T}}(\text{P})$ is the yield of P from routes that involve transmetallation. In the latter case transmetallation may be followed by radical reactions.

$$Y_{\text{R}}(\text{Cy}(-\text{H})) = y(\text{Cy}(-\text{H})) \quad (11)$$

$$Y_{\text{R}}(\text{CyH}) = y(\text{Cy}(-\text{H})) \quad (12)$$

$$Y_{\text{R}}(\text{CyCy}) = 1.5 y(\text{Cy}(-\text{H})) \quad (13)$$

$$Y_{\text{T}}(\text{P}) = y(\text{P}) - Y_{\text{R}}(\text{P}) \quad (14)$$

Eqn. 11 originates with the observation that $\text{Cy}(-\text{H})$ only appears in step 5 and the assumption that there is no other source of this product. Based on the classic study of the thermal decomposition of BuCu^{I} by Whitesides *et al.*,¹⁵ thermal decomposition of CyCu^{I} would be expected to produce $\text{Cy}(-\text{H})$ *via* β -hydride elimination and CyH *via* reaction of the HCu^{I} co-product with CyCu^{I} . β -Hydride elimination in cuprates is negligible at -78°C ,¹⁶ so that this assumption is a good one. It is important to note that BuBu does not result from the thermal decomposition of BuCu or Bu_2CuLi .^{15,16}

Eqn. 12 follows from the stoichiometry of step 5, in which equimolar amounts of CyH and $\text{Cy}(-\text{H})$ are formed. Eqn. 13 is derived from eqns. 11 and 12 and the experimentally determined ratio of disproportionation to combination for cyclohexyl radicals, $k_{\text{d}}/k_{\text{c}} = [Y_{\text{R}}(\text{CyH}) + Y_{\text{R}}(\text{Cy}(-\text{H}))]/Y_{\text{R}}(\text{CyCy}) = 1.3$.² Eqn. 14 results from the fact that the two routes represented by $Y_{\text{R}}(\text{P})$ and $Y_{\text{T}}(\text{P})$ are mutually exclusive as defined, and thus $y(\text{P}) = Y_{\text{R}}(\text{P}) + Y_{\text{T}}(\text{P})$.

For the eight reactions of **1a** in Table 1, the average yields (%) are $y(\text{BuCy}) = 58.8 \pm 1.3$, $y(\text{CyH}) = 9.4 \pm 1.3$, $y(\text{Cy}(-\text{H})) = 3.8 \pm 0.5$, $y(\text{CyCy}) = 9.1 \pm 1.7$ and $y(\text{BuBu}) = 5.9 \pm 2.5$. Then, we have $Y_{\text{R}}(\text{CyH}) = 3.8$, $Y_{\text{R}}(\text{CyCy}) = 5.7$, $Y_{\text{T}}(\text{CyH}) = 5.6$ and $Y_{\text{T}}(\text{CyCy}) = 3.4$. Since $Y_{\text{T}}(\text{BuCy}) = Y_{\text{T}}(\text{CyCu}^{\text{I}}) = Y_{\text{T}}(\text{CyH})$, we can calculate the selectivity S of the reductive elimination in step 9 as $S = Y_{\text{T}}(\text{BuCy})/Y_{\text{T}}(\text{CyCy}) = 5.6/3.4 = 1.6$. This result is reasonable, given that the steric hindrance in the transition state is higher for CyCy than BuCy .

For the eight reactions of **1b** in Table 1, the average yields (%) are $y(\text{BuCy}) = 81.3 \pm 3.9$, $y(\text{CyH}) = 6.5 \pm 1.5$, $y(\text{Cy}(-\text{H})) = 1.2 \pm 0.2$, $y(\text{CyCy}) = 5.1 \pm 1.1$ and $y(\text{BuBu}) = 5.9 \pm 1.0$. Then, we have $Y_{\text{R}}(\text{CyH}) = 1.2$, $Y_{\text{R}}(\text{CyCy}) = 1.8$, $Y_{\text{T}}(\text{BuCy}) = Y_{\text{T}}(\text{CyH}) = 5.3$ and $Y_{\text{T}}(\text{CyCy}) = 3.3$. The selectivity of reductive elimination in step 9 is $S = Y_{\text{T}}(\text{BuCy})/Y_{\text{T}}(\text{CyCy}) = 5.3/3.3 = 1.6$. The agreement between the values of S for **1a** and **1b** gives us confidence that our mechanistic scheme is essentially correct, as L would not be expected to exert a significant steric influence.

The amount of CyH from transmetallation is approximately the same for **1a** and **1b**. In contrast, the amount of $\text{Cy}(-\text{H})$ from **1b** is one-third of that from **1a**. The main reason for the lower yields of BuCy from **1a** is the increased role of radical side reactions. The corrected mean cyclohexyl conversions \hat{C}_{Cy} (%) are $(81.1 \pm 3.8)/0.90 = 90 \pm 4$ for **1a** and $(94.0 \pm 3.0)/0.99 = 95 \pm 3$ for **1b**, whereas the renormalized butyl conversions (%) are 78 ± 6 and 92 ± 4 , respectively (*vide supra*).

After 1 h, the reactions of both **1a** and **1b** have reached plateaus, and from the corrected yields of BuCy , $(58.8 \pm 1.3)/0.90 = 65 \pm 1$ vs. $(81.3 \pm 3.9)/0.99 = 82 \pm 4$, respectively, the latter appears to be much more reactive. While one compound may be the 'desired product', all the products must be considered when discussing 'reactivity'. Then, the latter appears to be only slightly more reactive after 1 h, based on \hat{C}_{Cy} ($90 \pm 4\%$ vs. $95 \pm$

3% , *vide supra*). However, based on the corrected values of \hat{C}_{Cy} after 4 s ($27 \pm 6\%$ vs. $2.5 \pm 1.7\%$, *vide supra*), **1a** appears to be substantially more reactive.

True reactivity depends upon kinetic data, which our results only approximate; nevertheless, it can be stated unequivocally that **1b** is not remarkably more reactive than **1a**, as has been asserted.¹⁷ The reactivity patterns of **1a** and **1b** are now in harmony with the theoretical,¹⁸ spectroscopic,¹⁹ and X-ray investigations,²⁰ which concluded that both cuprates are in fact varieties of the Gilman reagent.²¹

These results make it clear that scrupulous attention to experimental detail is necessary for both mechanistic and synthetic organocopper chemistry and that statistical tests are essential. As a general precaution, all surfaces that come in contact with organocuprates should be either virgin or passivated glass or an inert material such as polypropylene, and the ages of solvent stills and lots of $\text{Cu}(\text{I})$ salts should be scrutinized.

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