to the C_{6v} form is sufficiently low, the molecular spectrum will show all the characteristics of a symmetric top. The only direct evidence from experimental data bearing on this question is the observed decrease in θ^* upon deuteration of the HCl. Similar decreases have been observed in the intensively studied linear inert gas–hydrogen halide systems.[1,7] As in those more carefully studied systems, the observed decrease in θ^* determined from the chlorine quadrupole coupling constants above tends to suggest a C_{6v} equilibrium structure with $\theta = 0$ in which all of the delocalized π electrons contribute equally to the bonding interaction.

We are presently undertaking further investigations of the benzene–HCl complex.

Acknowledgment. We would like to thank Dr. Paul Soper for his participation in the early phases of this project. The support of the National Science Foundation is gratefully acknowledged.

(7) M. R. Keenan, E. J. Campbell, T. J. Balle, L. W. Buxton, T. K. Minton, P. D. Soper, and W. H. Flygare, *J. Chem. Phys.*, **72**, 3070 (1980).

Chemistry of Higher Order, Mixed Organocuprates. 1. Substitution Reactions at Unactivated Secondary Centers†

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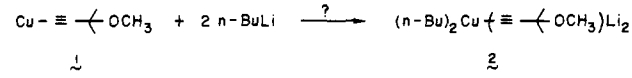
Received July 30, 1981

The variety of reactions which organocopper reagents are known to undergo has proven to be an invaluable tool for the construction of carbon–carbon bonds.[2] In general, relatively mild conditions prevail and efficient coupling processes are observed. One of the key transformations associated with Gilman-type reagents, R_2CuLi, is the facility with which they undergo substitution reactions at primary positions.[2a] While primary halides are excellent substrates in this regard, the literature consistently alludes to the inability of these reagents to transfer ligands to an *unactivated secondary* center in an efficacious manner. As examples, 2-bromopentane reacts with *n*-Bu_2CuLi to afford 4-methyloctane in 12% yield,[3] cyclohexyl bromide gives *n*-butylcyclohexane in 25% yield,[3] and iodocyclohexane upon treatment with Me_2CuLi leads to methylcyclohexane in 21% yield.[4] The main reaction pathways appear to follow a reduction and/or elimination mode. Surprisingly, this fundamental problem has received very little attention,[4] and yet a solution would be a valuable addition to the arsenal of synthetic methodology. We now report our preliminary studies in this area which have led to the development of a new procedure for effecting the desired coupling with minimal side reactions.

Initially we investigated the reaction between the cuprous acetylide **1**[5] and 2 equiv of *n*-BuLi. Literature precedent had shown that higher order organocopper species could be formed, although these were always derived from CuI and 3 equiv of RLi.[6] Adding *n*-BuLi (2 equiv) to **1** at −78 °C, which presumably formed the mixed cuprate **2**, followed by 0.5 equiv of iodocyclohexane



and warming the mixture to −20 °C overnight gave *n*-butylcyclohexane in ca. 60% yield. This result, which is considerably better than that which had been achieved earlier on secondary halides with Gilman reagents,[3,7] suggested that further experimentation was warranted.

In order to minimize manipulation of the copper-containing precursor prior to addition of RLi, we sought a readily available source of Cu(I) which already possessed a nontransferable "dummy" ligand attached to copper. Cuprous cyanide (CuCN) seemed to be ideal for the following reasons: (1) it is far less expensive than CuI;[8] (2) it is not hygroscopic; (3) it is quite stable as, and in fact prefers, the Cu(I) oxidation state;[9] (4) it is not light sensitive. Hence, treatment of CuCN in THF with 2 equiv of *n*-BuLi gave, by analogy with the formation of **2**, complex **3**, as a clear, tan solution.[10] Introducing cyclohexyl iodide (0.5 equiv)

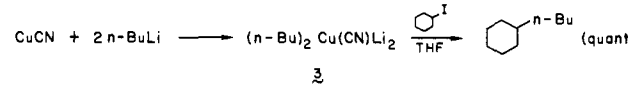


Table I. Reactions of Secondary Halides/Sulfonates with $(n\text{-Bu})_2Cu(CN)Li_2$

Substrate	Conditions[a]	Product[b]	Yield[c] (%)
		 **6**	
R = I	−50°, 1 h	**6**	100
Br	rt, 2 h	**6**	22[d]
OMs	0°, 2 h	e	—
OTs	rt, 3 h	**6**	5[f]
		 **7**	
R = I	−78°, 2 h	**7**	82
Br	0°, 6 h	**7**	86
OTs	0°, 5 h	**7**	35[f]
		 **8**	
R = I	−50°, 2 h	**8**	99
Br	0°, 2 h → rt, 1 h	**8**	94
Cl	rt, 11 h	**8**	28
OMs	0°, 2 h → rt, 1 h	e	—
OTs	−25°, 24 h[g]	**8**	40
OTs	rt, 7 h	**8**	58
	rt, 3 h	e	—

[a] All reactions were conducted in THF unless specified otherwise. [b] Products were identified by comparison with authentic samples. [c] By quantitative GC using *tert*-butylcyclohexane as an internal standard. [d] 52% starting material remained. [e] None of the desired product was observed. [f] Starting material still observed. [g] Reaction was run in Et_2O; see ref 15.

† Dedicated to Professor H. H. Wasserman on the occasion of his sixtieth birthday.

(1) Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

(2) (a) Posner, G. H. *Org. React.* **1975**, *22*, 253. (b) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215. (c) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709. (d) Smith, R. A. J.; Hannah, D. J. *Tetrahedron* **1979**, *35*, 1183.

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

(4) (a) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1977**, *42*, 2805. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Ibid.* **1977**, *42*, 1099. (c) Corey, E. J.; Posner, G. *J. Am. Chem. Soc.* **1967**, *89*, 3911. Interestingly in this work, reaction of iodocyclohexane with Me_2CuLi (5 equiv., 0 °C, 10 h) gives methylcyclohexane in 75% yield.

(5) Corey, E. J.; Floyd, D. M.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

(6) Macdonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740. Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. Muller, P.; Phuong, N. T. M. *Tetrahedron Lett.* **1978**, 4727. House, H. O.; Koepsell, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003.

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

(8) For example, Ventron sells CuCN for $30/kg, and CuI, usually purchased "ultrapure" (unless it is to be recrystallized), is listed at $83/100 g.

(9) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry"; Wiley: New York, 1972.

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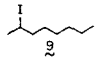
Table II. Reactions of Secondary Halides with $R_2Cu(CN)Li_2$

Substrate	RLi	Conditions	Product[a]	Yield(%)[b]
	MeLi	0°, 6h		89
	EtLi	-78°, 1.5h		100
	n-PrLi	-78°, 1 h		90[c]
		0°, 6 h		90[d]
	PhLi	0°, 6 h		7[e]

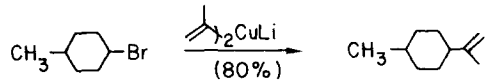
[a] All products were compared with authentic samples unless stated otherwise. [b] By quantitative VPC (6-ft × 1/8-in. 20% SE-30 column on Chromosorb W). [c] 10% starting material observed in addition to 90% product. [d] VPC indicated 6% starting material remained. [e] The major product resulted from reduction (i.e., octane). Peak on GC trace not compared with an authentic sample.

at −78 °C and then warming the resulting mixture to −50 °C for 30–60 min afforded the desired product in quantitative yield (VPC).[11] This remarkable coupling process contrasts quite favorably with previous studies[2-4] not only in terms of efficiency but with respect to reaction conditions as well. Traditionally, 5–10 equiv of reagent have been used at room temperature. In this case, 1.5–2 equiv of $R_2Cu(CN)Li_2$ (**4**) is sufficient at −50 °C (for iodides) in less than 1 h.

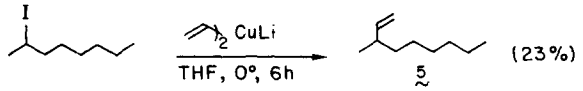
For an examination of the scope of the reaction, a number of cyclic and acylic secondary halides were allowed to react with **3**. The results are summarized in Table I. With cyclic systems, cyclohexyl halides coupled well only in the case of an iodide, the bromide giving ca. 50% at best even at higher temperatures.[12] Additives (e.g., HMPA, Me_2S, LiBr) designed to enhance the rate of reaction were found to have a negligible (HMPA) or deleterious (Me_2S, LiBr) effect on both rate and yield.[13] Cyclopentyl bromides and iodides gave good results, although, as was found to be general, bromides required higher temperatures and longer reaction times than iodides. Acyclic bromides and iodides gave excellent yields of branched-chain products. Secondary chlorides, in all systems, tended to be relatively unreactive.[14] Surprisingly, mesylates were inert and only tosylates reacted to any extent (ca. 5–60%) in both cyclic and acylic examples.

Other lithium reagents were also found to participate in this procedure. Methyl, ethyl, *n*-propyl, and vinyl groups could be introduced, as illustrated in Table II. Only the reagent prepared from PhLi (i.e., **4**, R = Ph) gave unsatisfactory results. Both methyl- and vinyllithium-derived cuprates were considerably more sluggish than the other alkyl-based intermediates, an observation in line with previous reports on homocuprates.[15] Both ethyl and *n*-propyl ligands transferred at even lower temperatures relative to *n*-Bu (−78 vs. −50 °C), which may be a reflection on relative size as opposed to electronic factors.

It is worthy of note that olefin **5** could be formed via vinyl ligand delivery to a secondary iodide (see Table II). To our knowledge, there is only a single report in 1968 on the substitution of a secondary halide by a vinylcopper species,[16] as shown below.



In the light of somewhat later reports[3,4] attesting to the poor yields realized with cyclohexyl bromide (vide supra) and our experiences with cyclic bromides, we attempted to effect displacement with lithium divinylcuprate on a far more reactive iodide. The reaction, run otherwise under similar conditions, afforded 3-methylnonene in only 23% yield, compared with the 90% realized using **4** (R = vinyl).



The observations delineated herein raise many questions concerning these hybrid, higher order mixed cuprates. Their greater reactivity may be attributed to a change in the nature of the copper cluster. While Gilman reagents are dimeric,[17] evidence has accrued from Ashby's laboratory suggesting that "Me_3CuLi_2" is monomeric.[18] The experimental finding that ≤2 equiv of **4** suffices for good reactions in cases necessitating temperatures around 0 °C (e.g., **4**, R = Me, vinyl) attests to the increased stability of these intermediates relative to those derived from CuI and *two* RLi.[2a] These points (i.e., **4** showing *both* increased reactivity *and* stability relative to R_2CuLi) may, indeed, seem incongruous. Waack et al.[19] have shown that relative reactivities are a consequence of reaction order varying with reagent structure. Kinetic data have led to the suggestion that while RLi is predominantly aggregated, reaction occurs to a great extent through a "less aggregated" form, believed to be the monomer. The stability question is complex but may be ascribed to the presence of a cyanide ligand, which is strongly bound to copper by way of $d\pi^*$ backbonding.[9]

Another interesting aspect concerns the difference in reactivity between secondary halides and sulfonates. Our results are anomalous when compared with literature reports on the ease with which primary tosylates can be displaced (more readily than iodides!)[4c] with R_2CuLi.[15] This may shed some light on the mechanism of the reaction *at copper*.[20]

In summary, this methodology adds a new dimension to organic synthesis, heretofore not available, by providing an alternative for elaboration of a carbon framework via a displacement event at a secondary center. These highly reactive organocopper compounds permit low-temperature coupling of alkyl and vinyl ligands to a carbon backbone in good yields. The experimental procedure[21]

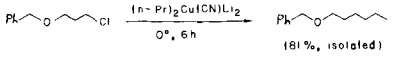
(10) CuCN comes in three forms (see Merck Index). The tan, powdery material (purchased from MCB) gave tan solutions of **4**, while the green, crystalline form (from Fluka) affords much lighter, slightly yellowish solutions.

(11) This result was reproducible regardless of the form or source of CuCN. Control reactions clearly indicated that the ratio of 2 RLi to 1 CuCN is the key to the success of the coupling process. As expected, *n*-BuLi alone (on cyclohexyl iodide) resulted in 19% product and 46% starting material (−78 °C, 1 h), *n*-BuLi/CuCN (1:1) gave ca. 10% product, the remainder being starting material (same substrate, −50°, 1 h), and *n*-BuLi/CuCN (3:1) on 2-bromopentane (0 °C, 2 h) gave 40% product (no starting material).

(12) Cyclohexyl bromides (and sulfonates) are well-known to be reluctant to undergo substitution reactions; see examples in ref 3, 4, and 14.

(13) (a) The effect of HMPA on reactions of cuprates has been reported: House, H. O.; Lee, T. V. *J. Org. Chem.* **1978**, *43*, 4369. (b) Me_2S has oftentimes been found beneficial in promoting cuprate reactions. For example, see: Kojima, Y.; Wakita, S.; Kato, N. *Tetrahedron Lett.* **1979**, 4577. (c) LiBr has been observed to enhance reactivity in certain cases. For example, see: Vermeer, P.; Westmijze, H.; Kleijn, H.; van Dijck, L. A. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 56.

(14) Primary chlorides, however, give good reactions. Whitesides, et al.[3] have reported that these substrates react at room temperature with 5 equiv of R_2CuLi to give 80% (by VPC) substitution product. We have found that 2 equiv of $R_2Cu(CN)Li_2$ at 0 °C will give similar results, as in the example below.



(15) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777, 7783.

(16) Vig, O. P.; Kapur, J. C.; Sharma, S. D. *J. Ind. Chem. Soc.* **1968**, *45*, 1026.

(17) (a) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. (b) Pearson, R. G.; Gregory, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 4098 and references within.

(18) Ashby, E. C.; Watkins, J. J. *J Am. Chem. Soc.* **1977**, *99*, 5312.

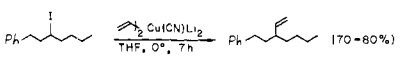
(19) West, P.; Waack, R.; Purmort, J. I. *J. Am. Chem. Soc.* **1970**, *92*, 840 and references therein.

(20) A complete discussion on the mechanism of the coupling process at both the carbon and the copper sites will be presented in a full account of this work.

is less complicated than that followed for the preparation of "standard" Gilman-type reagents.[2] The implications of this work, we feel, are far reaching, not only with respect to further studies with these and related intermediates in synthesis[22] but also for potential replacement of CuI by CuCN in many situations where cost, reagent and/or product sensitivity, and time are crucial factors. Finally, we are striving to develop a modified protocol which utilizes even more highly mixed systems, $R_TR'Cu(CN)Li_2$, where only a single (potentially valuable) transferable group (R_T) is needed,[23] along with two nontransferable, "dummy" ligands (i.e., R' and CN).

Acknowledgment. We are pleased to acknowledge financial support from the National Institutes of Health (GM 28128), the American Cancer Society (JFRA No. 37 to B.H.L.) and, in part, the Committee of Research at UCSB. We also thank Professor R. G. Pearson for helpful discussions.

(21) In a typical procedure, CuCN (1 mmol) was placed in a dry two-necked flask and azeotroped with toluene (2 × 1 mL) at room temperature under vacuum. The tan powder was placed under argon and THF (1 mL) was introduced. The slurry was cooled to −78 °C and RLi (2 mmol) was added dropwise. The heterogeneous mixture was allowed to warm to 0 °C (becomes homogeneous) at which temperature it was stirred for a further 1–2 min and then recooled to −78 °C (may get cloudy). The iodide (bromide) was introduced (neat or in THF) and stirred at the appropriate temperature until TLC (or VPC) indicated that the reaction was complete. The mixture was quenched with 10% concentrated NH_4OH/saturated NH_4Cl solution followed by a standard extractive workup (Et_2O). In the case below, chromatography on silica gel with hexanes gave 3-(β-phenethyl)hept-1-ene in 70–80% isolated yield [TLC: R_f = 0.56 (hexanes); IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ 7.15 (5 H, s, br), 5.55 (1 H, m), 5.0 (1 H, d, J = 1 Hz), 4.85 (1 H, dd, J = 2.7 Hz), 2.52 (2 H, m), 1.25 (12 H, m). MS, m/e (relative intensity, %) 202 (M^+, 4.7), 160 (4.0), 145 (4.7), 131 (4.7), 118 (3.4), 117 (8.1), 105 (34.9), 104 (100). High-resolution MS, calcd for $C_{15}H_{22}$ 202.1720; found 202.1728].



(22) For example, we have found that these reagents react very efficiently with mono-, di-, and trisubstituted epoxides, as well as α,β-unsaturated ketones: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J., manuscripts in preparation.

(23) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400. Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *Chem. Commun.* **1973**, 88.

Racemization-Free Photochemical Coupling of Peptide Segments

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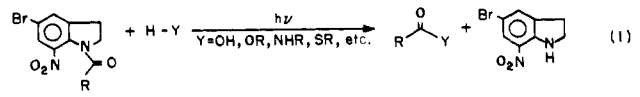
Received June 5, 1981

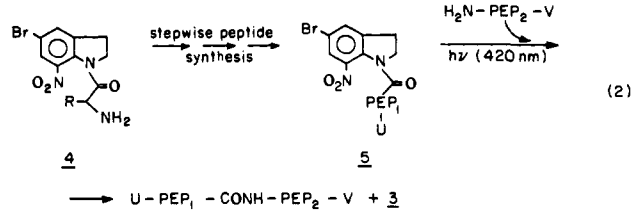
Today, segment condensation is the strategy of choice for the preparation of long peptides. However, in order to form a peptide bond between two segments, the C-terminal amino acid of one of them must be activated; present-day methods for this lead to considerable racemization of the activated amino acid and to optically impure products. Some techniques, though, are better than others, and condensation by the azide method or by use of dicyclohexylcarbodiimide with various additives produce minimal racemization. Yet, even with these methods, optical impurity at bothersome levels occurs sometimes.[1,2]

We wish to describe a novel method for peptide segment condensation which is virtually free of racemization. This condensation is based on the unusual photochemical properties of the 5-bromo-7-nitroindolinyl (Bni) group.[3]

The Bni group has been used in the past to block the carboxylic function[3] through formation of an amide derivative, 1-acyl-5-bromo-7-nitroindoline (**1**). Irradiation of **1** at 420 nm or below activates the acyl function toward nucleophilic attack. In the presence of water, this results in photohydrolysis of the amide bond with quantitative formation of a free carboxylic acid **2** (Y = OH, reaction 1) and 5-bromo-7-nitroindoline (**3**).[3,4] When **1** is irradiated in the presence of other nucleophiles (reaction 1), carboxylic acid derivatives **2** are formed by a unique photoacylation reaction.[5]



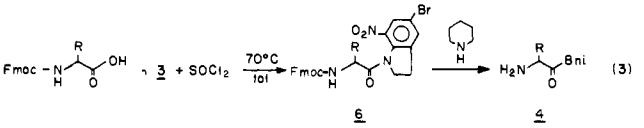
Clearly, the Bni group can be used to protect the carboxylic function, as well as to activate it, upon irradiation, toward the attack of nucleophiles. Because of this dual function, the Bni group is promising for use in peptide synthesis. It may be initially used to block the C terminus during the stepwise synthesis of peptide segment **5** and finally to couple this segment photochemically to a second segment (reaction 2).



PEP - a peptide segment

U;V - protecting groups

The attachment of the Bni group to a Boc- or Z-protected amino acid to form **4** fails with standard acylation methods due to the poor nucleophilicity of 5-bromo-7-nitroindoline. Other workers were therefore forced to use an indirect and rather lengthy route for the preparation of Bni derivatives.[4] We have, however, developed a simple, one-step attachment method, which involves heating a mixture of **3** and 9-[(fluorenylmethyl)oxy]carbonyl (Fmoc)-protected amino acids with thionyl chloride in toluene at 40–70 °C for several hours. This yielded the desired derivatives **6** in high optical purity (99.5 ± 0.5%).[6] The Fmoc group is easily and selectively removed from **6** by brief treatment with piperidine[7] to afford **4** in 70–85% overall yield.



Following the scheme presented in reaction 2, we have prepared two opiate peptides: [Leu^5]-enkephalin (**7**) and [D-Ala^2]-[Leu^5]-enkephalinamide (**8**) via [4 + 1] and [2 + 3] photocoupling reactions, respectively[8] (reactions 4 and 5). In the initial attempts

(1) (a) Finn, F. M.; Hofmann, K. *Proteins (3rd Ed.)* **1976**, *2*, 192–193. (b) Erikson, B. W.; Merrifield, R. B. *Ibid.* **1976**, *2*, 412–415.

(2) (a) Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A. "Peptide Synthesis", 2nd ed.; Wiley: New York, 1976; pp 181–182. (b) Kemp, D. S. In "The Peptides: Analysis, Synthesis, Biology"; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. I, pp 315–383.

(3) Amit, B.; Ben-Efraim, D. A.; Patchornik, A. *J. Am. Chem. Soc.* **1976**, *98*, 843–844. In Hebrew, Bni means *my son.*

(4) Goissis, G.; Erikson, B. W.; Merrifield, R. B. *Pept., Proc. Am. Pept. Symp., 5th*, **1977**, 559–561.

(5) For a recently reported example of some similarity, see: Burton, L. P. J.; White, J. D. *Tetrahedron Lett.* **1980**, 3147–3150.

(6) The optical purity of amino acids and peptides was determined according to: Charles, R.; Butler, U.; Feibush, B.; Gil-Av, E. *J. Chromatogr.* **1975**, *112*, 121–133. Amino acid derivatives or peptides were hydrolyzed in 6 N HCl and the resulting set of amino acids transformed to the corresponding set of trifluoroacetyl aminoacyl isopropyl esters. The set was analyzed gas chromatographically on an optically active, stationary phase—docosanoyl-L-valine-*tert*-butyl amide which is able to separate each derivativatized L-amino acid from its D enantiomer.

(7) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409.

0002-7863/81/1503-7674$01.25/0