## Some Observations on the Solution Composition of Gilman Reagents ("R<sub>2</sub>CuLi")

Bruce H. Lipshutz,\* Frank Kayser, and Konstantin Siegmann

Department of Chemistry University of California, Santa Barbara, CA 93106 [Fax: 805/893-4120]

Abstract. Low temperature oxidations of mixed diaryl cuprates prepared from both Cul and CuBr (with and without additives) offer insight regarding the manner in which halide ion influences coupling reactions of these reagents.

Organocuprates "R<sub>2</sub>CuLi" (1), formed according to the original Gilman recipe (Equation 1),<sup>1</sup> are among the most extensively utilized reagents in organic synthesis.<sup>2</sup> Reviews over the years,<sup>3</sup> including our recent comprehensive 'chapter' on this field,<sup>4</sup> restate the case for such species 1 based not only on their chemistry (*i.e.*, their coupling reactions with various substrates), but also from numerous spectroscopic studies. Moreover, solid state X-ray determinations<sup>5</sup> all seem to support the notion that this balanced equation is likely to be an accurate reflection of the *solution* composition of these lower order (L.O.) cuprates. Nonetheless, there is a considerable body of information at odds with this assessment. The discrepancy arises from the fact that the Cu(I) precursor affects the properties of "R<sub>2</sub>CuLi", as revealed by several observations (*e.g.*, reagent stability and/or color, reaction yields, etc.). Equation 1 implies, irrespective of CuX (with X = I, Br, CI, CN, SCN, or OTf), that a by-product lithium salt (LiX) is produced from cuprate formation as an *independent* species; thus, it should be of no consequence which CuX is selected *en route* to 1.



6694

For decades, there have been scattered reports throughout the literature suggesting that the situation may well be more complex than that represented by Equation 1, in particular concerning the role of LiX.<sup>6,7</sup> A detailed, direct comparison of 1,4-additions of R<sub>2</sub>CuLi prepared from several Cu(I) salts in THF has been described,<sup>8</sup> again supporting the impression that results from reactions of Gilman reagents may actually be *expected* to vary as the copper source is changed. We now describe our study on this topic which provides experimental evidence leading to one plausible explanation for these curious phenomena.

While developing the unsymmetrical biaryl coupling chemistry associated with our newly introduced 'kinetic' cuprates derived from CuCN,<sup>9</sup> the corresponding oxidation of a L.O. analog ArAr'CuLi derived from Cul-2Lil,<sup>10</sup> PhLi, and *o*-anisyllithium was run under identical conditions [*i.e.*, mode of reagent preparation and temperature (-125°) in 2-methyl THF] for comparison. Although the quality of the coupling (*i.e.*, the extent of Ar-Ar' product formed) was very low (*ca.* 10-15%; Scheme 1, case 1) compared to those of the corresponding cyanocuprates,<sup>9</sup> most intriguing was the presence of both starting aryl iodides among the product mix. Control experiments involving treatment of each iodide with 2 equiv of *t*-BuLi at -78° followed by proton quenching, not surprisingly showed *complete* consumption of the educts as determined by capillary GC analysis. Likewise, proton quenching of the mixed diaryl cuprate derived from these lithiated aromatics at low temperature afforded the identical result. Importantly, from the *o*-anisyl ligand-containing cuprate came *only o*-iodoanisole. Similar observations were realized using PhLi and *o*-tolyllithium (Scheme 1, case 2).

As an alternative to Cul+2Lil, the Whitesides complex,<sup>11</sup> Cul+PBu<sub>3</sub> was substituted in case 1 (Scheme 1). Remarkably, <1% of either aryl iodide ( $R = OCH_3$ ) was detected. Such was also the observation when CuBr+SMe<sub>2</sub> was used in place of Cul+2Lil.



Even more startling were the results from a crossover experiment, where lithiation of *bromo*benzene and *o-bromo*anisole followed by cuprate generation with Cul-2Lil and oxidation gave the aryl *iodides* as parts of the product mixture (Scheme 2). When these aryl bromides were lithiated,

but now exposed to CuBr•2LiBr (as in Scheme 2, but using CuBr•2LiBr in place of Cul•2Lil), none of either starting bromide was returned upon cuprate oxidation.



To rationalize the (reproducible) generation of any iodides from a solution composed of a L.O. diaryl cuprate and *iodide* ions, it would seem that some quantity of halide ion need be on copper, and therefore at least a percentage of the medium contain a "higher order" halocuprate, ArArCu(I)Li2. Oxidation of I- to Io followed by any product iodination is readily ruled out, given (a) the low temperature of the oxidation: (b) that both aromatics are iodinated, including the unactivated phenyl ring, yet none of the biaryl products are halogenated; and (c) the exclusive isolation of o-iodoanisole, rather than the predominantly para isomer expected from attack by I+ on anisole. The likelihood of any in situ generated lo guenching of a diaryl cuprate can also be negated, since (1) the presence of increased amounts (e.g., 6 equiv) of 1<sup>-</sup> does not change the percentage of anyl iodides formed.<sup>12</sup> (2) reactions of the corrresponding H.O. cyanocuprates (from ArLi + Ar'Li + CuCN).<sup>9</sup> in which iodide ions are present (from metal/halogen exchanges) afford none of the iodo aromatics; and (3) O2 is too weak an oxidizing agent (at least in H2O) to convert 21 to I2 (0.535V vs 0.401V for O2/HO-).13 In the presence of a phosphine or sulfide, I- is not as competitive a ligand for copper, thereby all but eliminating the opportunity for iodinated products to arise via reductive elimination from a presumed Cu(II) Intermediate bearing three ligands. Only cuprates originating (in this study) from CuBr and aryl bromides under phosphine/sulfide-free conditions appear to correspond to "ArAr'CuLi".14

In summary, by oxidative treatment of mixed L.O. diaryl cuprates prepared from various combinations of anyl and Cu(I) halides, differences in reagent composition in solution have been manifested. However, since these electron transfer reactions lead to halogenated products in relatively small amounts, caution need be exercised in drawing conclusions as to the major species in solution, or the cuprate form from which substrate-L.O. reagent couplings take place, in general. Nonetheless, these data do implicate several distinct species in solution, including (1) ArAr'Cu(I)Li<sub>2</sub>; (2) ArAr'Cu(PBu<sub>3</sub>)Li; 3) ArAr'Cu(SMe<sub>2</sub>)Li; and (4) ArAr'CuLi, and by extrapolation, perhaps other

homo- and mixed L.O. cuprates (Scheme 3). Clearly, there is no reason to assume that the synthetic chemistry of each reagent combination toward the same substrate should necessarily be the same.



Acknowledgements. Financial support provided by the NIH (GM 40287) and the NSF (CHE 93-03883) is most appreciated. We also warmly thank the DFG for a postdoctoral fellowship to F.K. and the SNF for fellowship support provided to K.S.

## **References** and Notes

- 1.
- Gilman, H., Jones, R. G., Woods, L.A., J. Org. Chem., 1952, 17, 1630. Collman, J.P., Hegedus, L.S., Norton, J.R., Finke, R.G., Principles and Applications of 2. Organotransition Metal Chemistry, University Science Books, Mill Valley, CA, 1987.
- Posner, G.H., Org. React., 1975, 22, 253; ibid., 1972, 19, 1; Chapdelaine, M. J., Hulce, M., ibid., 1990, 38, 225; Yamamoto, Y., Angew. Chem. Intl. Ed. Engl., 1986, 25, 947; Taylor, 3. R.J.K., Synthesis, 1985, 364; Erdik, E., Tetrahedron, 1984, 40, 641; Normant, J.F., Alexakis, A., Synthesis, 1981, 841; Normant, J.F., Pure Appl. Chem., 1978, 50, 709.
- 4. Lipshutz, B.H., Sengupta, S., Org React., 1992, 41, 135.
- As examples, see Van Koten, G., Jastrzebski, J.T.B.H., Muller, F., Stam, C.H., J. Am. Chem. 5. Soc., 1985, 107, 697; Hope, H., Oram, D., Power, P.P., ibid., 1984, 106, 1149; Khan, S.I., Edwards, P.G., Yuan, H.S.H., Bau, R., ibid., 1985, 107, 1682; Eaborn, C., Hitcock, P.B., Smith, J.O., Sullivan, A.C., J. Organomet. Chem., 1984, 263, C23; Martin, S.F., Fishpaugh, J.R., Power, J.M., Giolando, D.M., Jones, R.A., Nunn, C.M., and Cowley, A.H., J. Am. Chem. Soc., 1988, <u>110</u>, 7226.
- 6. (a) Such is the case with the 1:1 reaction between RLi and Cul, as investigated with respect to Yamamoto's reagent, "RCu-BF3",6b which clearly has Lil as part of the cuprate cluster; cf. Lipshutz, B.H., Ellsworth, E.L., and Dimock, S.H., J. Am. Chem. Soc., 1990, 112, 5869; (b) Yamamoto, Y., Yamamoto, S., Yatagai, H., Ishihara, Y., Maruyama, K., J. Org. Chem., 1982, 47, 119; Yamamoto, Y., Maruyama, K., J. Am. Chem. Soc., 1978, 100, 3240.
- 7. For examples, see Alexakis, A., Mutti, S., Normant, J.F., J. Am. Chem. Soc., 1991, 113, 6332; Bertz, S.H., Dabbagh, G., J. Am. Chem. Soc., 1988, 110, 3668.
- Bertz. S.H., Gibson, C.P., Dabbagh, G., Tetrahedron Lett., 1987, 28, 4251. For a detailed 8. study on the effects of lithium salts on coupling reactions of Bu2CuLi+Lil, see Bertz, S.H., Dabbagh, G., Mujsce, A.M., J. Am. Chem. Soc., 1991, 113, 631.
- 9. Lipshutz, B.H., Siegmann, K., Garcia. E., Tetrahedron, 1992, 48, 2579; J. Am. Chem. Soc., 1991, 113, 8161.
- 10. That Lil can be used to solubilize Cul at low temperatures is itself suggestive of formation of a dihalo (LiCul2) or trihalo (Li2Cul3) cuprate.
- 11. Whitesides, G.M., Casey, C.P., Drieger, J.K., J. Am. Chem. Soc., 1971, 93, 1379.
- 12. Furthermore, cuprate oxidations at -78°, rather than at -125°, conditions under which any conversion of 21- to 12 should be more facile, afford less of the aryl iodides (ca. 1-2% vs 6-7%).
- 13. These are standard reduction potentials, from the CRC Handbook of Chemistry and Physics, Weast, V.R.C., Ed., CRC Press, Boca Raton, 59th Ed., 1978-79, pp D-193-198; see also. Krause, N., Arndt, S., Chem. Ber., 1993, 126, 261.
- 14. Since the original Gilman protocol<sup>1</sup> was conducted in Et<sub>2</sub>O rather than in THF, it is not certain that any of these species (cf. Scheme 3) are actually "Gilman reagents". Just what the role of LiX is in Et<sub>2</sub>O solutions of "R<sub>2</sub>CuLi" awaits further study.