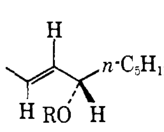
Mixed Cuprate Reagents of Type R_1R_2CuLi Which Allow Selective Group Transfer

Sir:

The type of reagent which results from the combination of a cuprous halide with 2 equiv of an organolithium or organomagnesium compound,[1,2] formally a cuprate species R_2Cu^-, has proved to be very useful for the conjugate addition of carbon groups to C=C-C=O[3,4] and C≡CC=O[5] systems, cross coupling reactions with carbon halides[6,7] and related electrophiles,[2,8,9] and homoconjugate addition to certain carbonyl-substituted cyclopropanes.[10,11] In most applications of the cuprate reagents the preformed reagent is used noncatalytically and only one of the organic groups attached to copper participates in the reaction. As a result the other organic group is not utilized, creating a serious problem whenever the group is valuable or obtainable only by a several-step synthetic process. Such an obstacle has been encountered during studies of synthetic routes to prostaglandins based on attachment of the (*S*)-*trans*-3-hydroxy-1-octenyl side chain **1** to a five-membered ring, both in this laboratory[10,12] and elsewhere.[13] Specifically, the cuprate **2** suffers from the severe disadvantage that one of the valuable (*S*)-*trans*-3-alkoxy-1-octenyl groups is essentially wasted.[14] We report herein a highly effective method for circumventing such difficulties based on the use of a mixed cuprate complex, R_rR_tCuLi, in which R_t represents the group to be transferred and R_r designates the residual group.



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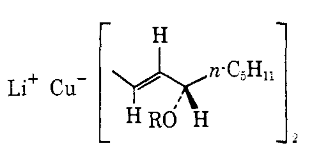

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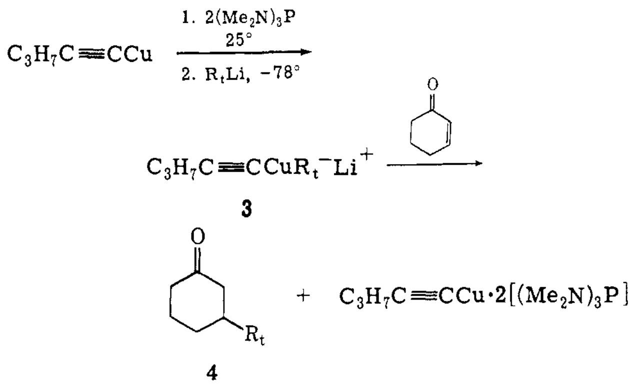
Initially two types of groups were selected as attractive candidates for the residual group, R_r = c-C_5H_5 and R_r = RC≡C, for the reason that both cyclopentadienyl[15] and ethynyl[16] ligands are tightly bound to copper. It soon became apparent, however, that the ethynyl complexes were preferable mainly because of ease of preparation and subsequent removal of the R_r-derived products during isolation. The 1-pentynyl group was found to be most satisfactory among the acetylenic ligands studied (*e.g.*, phenylethynyl and 1-heptynyl) because of its availability and the simplicity of separating the volatile 1-pentyne from reaction products. In the following discussion R_r refers to the ligand $CH_3(CH_2)_2C{\equiv}C$.

For the preparation of the mixed cuprate reagents, it appeared advantageous to utilize the approach $R_rCu + R_tLi \rightarrow R_rR_tCuLi$ for a number of reasons including the fact that the preparation of cuprous acetylides in pure condition is straightforward. One complication arose in this connection from the insolubility of the cuprous acetylide in suitable solvents. This can be overcome by the addition of 2 equiv of a trialkyl- or triarylphosphine to R_rCu which yields monomeric, very soluble complexes, $R_rCu(PR_3)_3$.[17] Unlike the uncomplexed cuprous acetylide, these complexes react reproducibly, rapidly, and cleanly with organolithium reagents in ether or tetrahydrofuran at −78° to form the desired mixed cuprates. Because of the difficulty of separating the tertiary phosphine from the reaction products, still another modification was necessary to achieve operational effectiveness and simplicity, *viz.* the use of a water-soluble phosphine. The commercially available hexamethylphosphorus triamide was found to possess all the required properties and to be ideal for this application. Thus the scheme adopted for the preparation of the mixed cuprate reagents **3** and their reaction with α,β-enones may be summarized as follows.



The reaction of the yellow, soluble reagents **3** derived from vinyllithium, *n*-butyllithium, and *tert*-butyllithium with 2-cyclohexenone proceeded with excellent selectivity in each case to afford cleanly the desired products, **4** (R_t = CH=CH$_2$), **4** (R_t = *n*-C_4H_9), and **4** (R_t = *t*-C_4H_9), *all in >95% yield.* The reaction of **3** (R_t = *n*-C_4H_9) with methyl propiolate[5a] at −100° gave methyl *trans*-2-octenoate in 97% yield. These results impressively illustrate the potential of the mixed

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(1) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952); H. Gilman and J. M. Straley, *Recl. Trav. Chim. Pays-Bas*, **55**, 821 (1936).

(2) For a review see J. F. Normant, *Synthesis*, **2**, 63 (1972).

(3) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(4) M. S. Kharasch and P. O. Tawney, *J. Amer. Chem. Soc.*, **63**, 2308 (1941).

(5) (a) E. J. Corey and J. A. Katzenellenbogen, *ibid.*, **91**, 1851 (1969); (b) E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *ibid.*, **94**, 4395 (1972).

(6) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967); **90**, 5615 (1968).

(7) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).

(8) P. Rona, I. Tokes, J. Tremble, and P. Crabbé, *Chem. Commun.*, 43 (1969).

(9) (a) R. J. Anderson, *J. Amer. Chem. Soc.*, **92**, 4978 (1970); (b) R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970).

(10) E. J. Corey and P. L. Fuchs, *ibid.*, **94**, 4014 (1972).

(11) G. Daviaud and Ph. Miginiac, *Tetrahedron Lett.*, 997 (1972).

(12) Various schemes involving displacement of oxygen by organo cuprates, which have been under investigation at Harvard since 1968 by Drs. R. Noyori, J. Mann, and D. J. Beames, will be reported in due course.

(13) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972).

(14) In fact, the use of **2** in greater than stoichiometric amounts results in even poorer efficiency (*cf.* ref 13).

(15) The complexes $C_5H_5CuPR_3$ are known to be fairly stable and to involve pentahapto C_5H_5; see F. A. Cotton and T. J. Marks, *J. Amer. Chem. Soc.*, **91**, 7281 (1969); and G. Wilkinson and T. S. Piper, *J. Inorg. Nucl. Chem.*, **2**, 32 (1956).

(16) R. Nast, *Chem. Soc., Spec. Publ.*, No. **13**, 103 (1959).

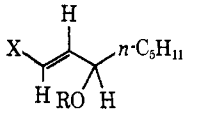
(17) G. E. Coates and C. Parkin, *J. Inorg. Nucl. Chem.*, **22**, 59 (1961).

cuprate reagents **3**. A typical experimental procedure follows.

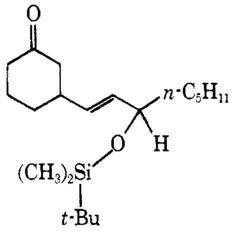
3-*n*-Butylcyclohexanone. A slurry of 0.64 g of dry *n*-propylethynylcopper[18] (4.90 mmol) in 10 ml of anhydrous ether was treated with 1.80 ml of dry hexamethylphosphorus triamide (9.80 mmol), and the mixture was stirred at room temperature under an argon atmosphere until a clear solution was obtained (5–10 min). To the cooled (−78°) solution was then added 3.10 ml of a 1.49 *M* solution of *n*-butyllithium (4.62 mmol) in hexane, and the resulting yellow solution was stirred for 15 min at −78°. The solution of mixed cuprate so formed was then treated with 2.50 ml of a 1.80 *M* solution of 2-cyclohexenone (4.50 mmol) in anhydrous ether, stirred for 15 min at −78°, quenched by pouring into ice-cold aqueous ammonium sulfate solution, and extracted with ether. The ethereal layers were extracted with ice-cold 2% (v/v) sulfuric acid, then filtered through Celite, and washed with aqueous sodium bicarbonate (5%). The dried (Na_2SO_4) extracts afforded almost pure 3-*n*-butylcyclohexanone (0.675 g, 97%), homogeneous by tlc analysis (R_f 0.40; ether–benzene, 1:10), and >99% pure by glpc analysis (glpc retention time, SE-30, 10-ft, 10% column, 170°, 5.2 min). The infrared and nuclear magnetic resonance spectra were also satisfactory for **4** (R_t = *n*-C_4H_9).

The demonstration that mixed cuprates of formula **3** are capable of highly efficient and selective transfer with R_t = primary alkyl, tertiary alkyl, and vinyl would seem to indicate utility through a large range of alkyl and substituted vinyl groups.[19] In connection with the question of selectivity of group transfer from mixed cuprates, it is relevant that G. Whitesides and coworkers have observed preferential transfer of the 2-norbornyl group (exo or endo) from a mixed cuprate having *tert*-butyl as the second group.[20]

The efficient generation and use of the mixed cuprate **3** in which R_t = **1** raised unexpected problems which were finally overcome by the following approach. *n*-Amyl *trans*-β-chlorovinyl ketone[21] was converted to the corresponding β-iodovinyl ketone, mp 36–37° (>95% yield), with dry sodium iodide in acetone at reflux for 7 hr and thence by treatment with sodium borohydride in ethanol (0°, 1 hr) to 3-hydroxy-*trans*-1-octenyl iodide (**5**) (95% yield).[22,23] This last intermediate was protected as the *tert*-butyl dimethylsilyl ether (**6**).[24] Reaction of **6** in ether at −78° with 2 equiv of *tert*-butyllithium (2.75 *M* reagent in pentane) for 2 hr led to formation of the desired lithium reagent **7** in *ca.* 90% yield as judged by tertiary alcohol formation with benzophenone. The use of 2 equiv of *tert*-butyllithium allowed the conversion of *tert*-butyl iodide, the initial product of lithium halogen exchange, to the innocuous products lithium iodide and isobutylene.[25,26] Treatment of an ethereal solution of the lithium reagent **7** so obtained with an ethereal solution of the 2:1 complex from hexamethylphosphorus triamide and 1-pentynylcopper at −78° afforded a yellow solution of the mixed cuprate **3**, R_t = **1**, which upon treatment with 1 equiv of 2-cyclohexenone gave the desired conjugate addition product **8** in 80% yield. This experiment shows the effectiveness of the mixed cuprate reagent **3** also holds for the O-protected 3-oxy-*trans*-1-octenyl group, an important result in connection with various synthetic approaches to prostaglandins.[27]



5, X = I; R = H
6, X = I; R = *t*-Bu(CH3)2Si
7, X = Li; R = *t*-Bu(CH3)2Si



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[18] C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966).

[19] It has previously been reported that nonmixed ethynyl cuprates do not transfer an ethynyl group to an enone under normal conditions; see H. O. House and W. F. Fischer, *J. Org. Chem.*, **34**, 3615 (1969).

[20] Personal communication from Professor G. Whitesides, Oct 1971.

[21] Prepared from hexanoyl chloride, acetylene, and aluminum chloride in carbon tetrachloride solution; see C. C. Price and J. A. Pappalardo, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 186.

[22] Satisfactory infrared, nuclear magnetic resonance, and mass spectral data were obtained for all intermediates using chromatographically homogeneous samples.

[23] This sequence was first carried out in these laboratories by Dr. R. Noyori in 1969.

[24] E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972). The *tert*-butyldimethylsilyl protecting group was found to be definitely superior to the tetrahydropyranyl group in this instance.

[25] The generation of the lithium reagent **7** from the iodide **6** using lithium metal or lithium metal containing 2% sodium could not be effected in high yield despite numerous attempts. The reaction of **6** with 1 equiv of isopropyllithium afforded **7** in *ca.* 80% yield (ether, −78°); however, it was found that the isopropyl iodide formed as coproduct interfered seriously with subsequent generation and use of the cuprate reagent.

[26] The synthesis of the lithium reagent **6** with R = α-ethoxyethyl, in a yield of *ca.* 25%, has recently been reported.[18]

[27] Initial indications of the utility of mixed ethynyl cuprate reagents were obtained in this laboratory by Dr. Robert L. Carney. We are grateful to him and to Drs. John Mann and Philip Fuchs for many discussions which were helpful in dealing with the numerous obstacles which had to be overcome. Financial assistance from the U. S. Agency for International Development and the National Institutes of Health is also acknowledged.

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An Intermediate Species in Aluminum(III)-Catalyzed Transamination in Methanol

Sir:

The well-known mechanism for transamination between α-amino acids and α-keto acids catalyzed by vitamin B_6 involves formation and isomerization of Schiff bases, *i.e.*, aldimine and ketimine.[1] Studies of

$$\text{pyridoxal} + RCH(NH_2)COOH \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \text{aldimine} \rightleftharpoons$$
$$\text{ketimine} \underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}} \text{pyridoxamine} + RCOCOOH$$

these steps in nonenzymatic systems have greatly helped

[1] (a) A. E. Braunstein and M. M. Shemyakin, *Biokhimiya*, **18**, 393 (1953); (b) D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem. Soc.*, **76**, 648 (1954).