

Preparation of Higher Order Cyano and "Non-Ate" Allyl Copper Reagents from the Reaction of Allyl Chlorides with a Formal Copper Anion

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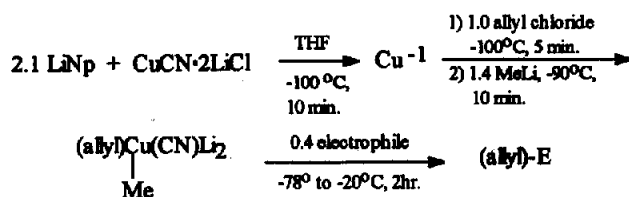
Abstract: The generation of higher order and "non-ate" allyl organocopper reagents have been achieved through the low temperature reaction of allyl chlorides with a formal copper anion. The copper anion is generated via the low temperature reduction of Cu(I) complexes by two equivalents of lithium naphthalenide and then oxidatively adds to allyl chlorides with minimal homocoupling. These allyl organocopper reagents undergo substitution reactions with alkyl chlorides and epoxides as well as 1,4-conjugate addition reactions in good to excellent yields.

The preparation of allyl organometallics has seen substantial improvement recently through the use of active metals.^{1,2} The manipulation of active metals in preparing these reagents has proven successful due in large part to the reduction of homocoupled side products. We have recently developed a facile method for the preparation of allyl organocopper reagents from allyl chlorides employing a highly reactive, zero-valent copper solution. Active copper, derived from THF soluble cuprous cyanide/lithium halide complexes, undergoes oxidative addition to allyl chlorides at low temperatures with little homocoupling. Moreover, a diverse range of electrophilic functional groups can be present in the allyl chloride precursor.¹

While zero-valent, active copper allows for the straightforward production of allyl organocopper compounds, the type of cuprate generated possess reactivities comparable to that of lower order cyanocuprates. Lipshutz *et al.* have shown that higher-order allyl cyanocuprates possess remarkable reactivities which undergo substitution with alkyl chlorides and epoxides at -78 °C.³ Furthermore, in order to add an allyl moiety in a 1,4 manner across an α,β -unsaturated enone, Lipshutz developed a less reactive "non-ate" allyl copper reagent.⁴ We now report the production of both higher order and "non-ate" allyl copper reagents directly from allyl chlorides utilizing a formal copper anion solution.

Although Lagowski's Au anion remains the only fully characterized transition metal anion in solution,⁵ the low temperature, two equivalent reduction of Cu(I) complexes with lithium naphthalenide leads to a reagent that behaves chemically as a formal copper anion. These copper anion solutions exhibit extraordinary reactivity as measured by their ability to undergo oxidative addition to alkyl and aryl chlorides and to some extent even to aryl fluorides.⁶

Table I shows both the general scheme and results of producing higher order allyl cyanocuprates with the copper anion. The reaction between the allyl chloride and the copper anion is similar to that previously reported,¹ but in order to form a higher order cuprate, methyllithium is added to act as a non-transferable "dummy" ligand. The resulting copper solution shows reactivity comparable to that of higher order


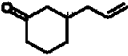

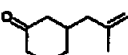

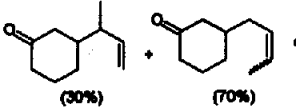

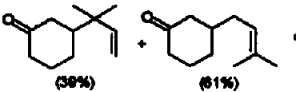
Table I. Production of Higher Order Allyl Cyanocuprates

entry	allyl chloride	electrophile	product ^a	% yield ^b
1				98
2				98
3			 	97
4				82
5		$\text{PhO}(\text{CH}_2)_4\text{Cl}$	 	81
6			 	86

a) All products gave consistent ^1H and ^{13}C NMR, FT-IR and HRMS spectral data. b) Isolated yields. c) Ratio determined by ^1H NMR

allylcyanocuprates as previously described. The regioselectivity of the unsymmetrical allyl chlorides proved a disappointment as substantial yields of α and γ attack were observed. Since higher order allyl cyanocuprates produced via transmetalation of allyl stannanes have shown regioselective addition to various electrophiles,³ the nature of these higher order allyl cyanocuprates must be associated with their method of preparation.

Table II. 1,4 Conjugate Additions with "Non-Ate" Allyl Organocopper Reagents

$2.1 \text{ LiNp} + \text{CuI}\cdot\text{LiCl} \xrightarrow[\text{-100}^\circ\text{C, 10 min.}]{\text{THF}} \text{Cu}^-1 \xrightarrow[\text{-78}^\circ\text{C, 1 hr.}]{\substack{1) 1.0 \text{ allylchloride} \\ \text{-100}^\circ\text{C, 5 min.} \\ 2) 1.0 \text{ TMSCl} \\ 3) 0.25 \text{ cyclohexene-2-one}}} \text{cyclohexenone (allyl)}$			
entry	allylchloride	product ^a	% yield ^b
1			72
2			91
3			24
4			98

a) All products gave consistent ^1H and ^{13}C NMR, FT-IR and HRMS spectral data. b) Isolated yields. c) Ratio determined by ^1H NMR

In order to facilitate 1,4-conjugate addition to α,β -unsaturated enones, the production of a less reactive "non-ate" organocopper reagent was sought. Since the cyano ligand is known to remain fixed in organocuprates produced from cuprous cyanide salts,⁷ the THF soluble $\text{CuI}\cdot\text{LiCl}$ copper(I) complex was chosen as the copper anion precursor. The reaction scheme and the results of various allyl moieties in their transfer to α,β -unsaturated enones are shown in Table II. As seen with many less reactive organocopper reagents, the use of TMSCl is essential in these reactions.⁸ The use of Lewis acids such as $\text{BF}_3\cdot\text{Et}_2\text{O}$ did not enhance the conjugate product yields in comparison to TMSCl.

Representative Procedures

Copper Anion: All reactions were conducted under an argon atmosphere using inert atmosphere techniques. THF was freshly distilled under argon over a Na/K alloy. Lithium (8.20 mmol) and naphthalene (9.02 mmol) were dissolved in 15 ml THF until all of the lithium was consumed (2 hr) and then cooled to -100°C . In a separate flask CuCN (4.00 mmol) and LiCl (8.00 mmol) were dissolved in 10 ml THF, cooled to -78°C and then cannulated into the preformed lithium naphthalenide solution at -100°C . After stirring for 5 min. at -100°C , the copper anion solution was ready to use. Similarly, the $\text{CuI}\cdot\text{LiCl}$ (4.00:4.00 mmol) anion was generated.

H.O. Allylcuprates: The allyl chloride (4.00 mmol) was cooled to $-78\text{ }^{\circ}\text{C}$ in a septum covered vial admixed with 2 ml of THF. The allyl chloride was then cannulated into the $\text{CuCN}\cdot 2\text{LiCl}$ derived copper anion solution at $-100\text{ }^{\circ}\text{C}$ and stirred for 10 min. Methylolithium (5.60 mmol) was then added to the reaction mixture at $-90\text{ }^{\circ}\text{C}$ and stirred for 10 min. at which time the reaction temperature was allowed to warm to $-78\text{ }^{\circ}\text{C}$. The final electrophile (1.6 mmol) was then added to the cuprate at $-78\text{ }^{\circ}\text{C}$ and stirred for 1 hr. The temperature was then slowly raised to $-20\text{ }^{\circ}\text{C}$ over a one hour period. The reaction was quenched with 5 ml of sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$, washed with brine and then back extracted with Et_2O . The solvent was removed and the product was isolated via flash silica gel chromatography using mixtures of hexanes and EtOAc.

1,4-Additions: The allyl chloride (4.00 mmol) was admixed with 4 ml THF in a septum sealed vial, cooled to $-78\text{ }^{\circ}\text{C}$, and then cannulated into the $\text{CuI}\cdot\text{LiCl}$ generated copper anion solution at $-100\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 5 min. and then warmed to $-78\text{ }^{\circ}\text{C}$. TMSCL (4.00 mmol) was then syringed neat into the reaction mixture. The enone (1.00 mmol) was dissolved in a septum sealed vial with 15 ml of THF, cooled to $-78\text{ }^{\circ}\text{C}$ and then slowly cannulated into the reaction over a 30 min. period. After stirring for an additional hour the reaction was quenched with 5 ml of 5% HCl, washed with brine and then back extracted with Et_2O . The solvent was removed and the product was isolated via flash silica gel chromatography using mixtures of hexanes and EtOAc.

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