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Direct Formation and Reactions of Allylic Thienyl-Based Organocopper Reagents

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DIRECT FORMATION AND REACTIONS OF ALLYLIC THIENYL-BASED ORGANOCOPPER REAGENTS

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Abstract: The lithium naphthalenide reduction of lithium 2-thienylcyanocuprate produces a highly reactive zero-valent copper complex. This allows for the direct formation of allylic organocopper reagents and ensuing cross-couplings with electrophiles.

We have previously reported that highly reactive copper solutions can be directly prepared by the reduction of copper(I)iodine/phosphine complexes with preformed lithium naphthalenide[1,2]. However, the presence of the phosphine ligands interfered with product isolation. In our efforts to attain an active copper species that did not require the use of phosphine ligands, we previously discovered that the lithium naphthalenide reduction of a commercially available lithium 2-thienylcyanocuprate solution produced a highly reactive zero-valent copper

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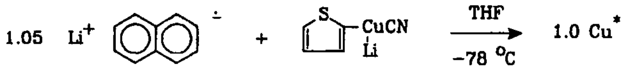
complex[3]. The resulting homogeneous copper solution undergoes the same transformations as previously reported[1], with subsequent product isolation being much more convenient than with the phosphine-based organocopper reagents. Lithium 2-thienylcyanocuprate was initially used by Lipshutz *et al.*[4] to form higher-order mixed organocuprates.

We would now wish to report that the active copper made from the reduction of a lithium 2-thienylcyanocuprate solution oxidatively adds to allyl chlorides and acetates at low temperatures to allow the direct formation of allylic organocopper reagents without Wurtz-like homocoupling products.

The thienyl-based active copper is prepared by the reduction of a lithium 2-thienylcyanocuprate solution (0.25 M, THF) with preformed lithium naphthalenide under an argon atmosphere at -78 °C for 10 minutes, equation 1. The reduction temperature is critical in determining the reactivity of the active copper. At lower reduction temperatures a more reactive copper solution is generated[3].



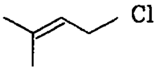
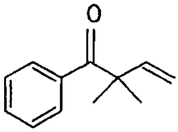
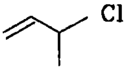
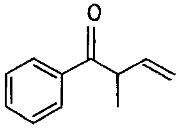
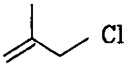
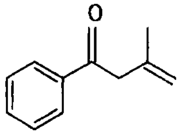
(Eq. 1)

Allyl organocopper reagents are currently of interest in the literature, especially with Lipshutz's development of higher-order allylic cyanocuprates[5]. Common methodologies used to form allylic organocopper reagents include the transmetalation of allylic stannanes with an appropriate organocopper reagent. However, this organocopper reagent is formed from a transmetalation of an organolithium or Grignard reagent, which precludes the incorporation of functionalities. Our laboratories have also shown that functionallized allylic organocopper reagents can also be formed from the low temperature reduction of a soluble CuCN·2LiBr complex with preformed lithium naphthalenide[6]. Significantly, our thienyl-based active copper species is formed at -78 °C, without necessitating the need for a liquid nitrogen bath. Once formed, the thienyl-based copper reacts with allyl chlorides and acetates to produce the corresponding allylic organocopper species with less than 5% of the homocoupled diene by-product and occasionally, ca. 2%, with the thienyl-ligand transfer side product.

The resulting allylic organocopper reagents reacted with benzoyl chloride to produce the corresponding ketones, Table I, in moderate yields. However, the reaction of allyl chloride and allyl acetate with active copper did not afford the desired product when trapped with benzoyl chloride. Prenyl copper reacts with benzoyl chloride via gamma attack (Table I, entry 1), therefore, the reaction of 3-chloro-1-butene must behave in a similar manner. Since it is known that prenyl copper reacts with cyclohexenone via alpha attack[5a], it is presumed that 3-chloro-1-butene (Table I, entry 2), initially forms the secondary allylcopper species, but then rearranges to the more favorable primary allylic structure. It is known that other zero-valent metals react with secondary allyl chlorides, and then equilibrate to the primary structure[7].

As mentioned previously, the reduction temperature is critical in determining the reactivity of the active copper. As seen from Table II, the optimum conditions for product formation occurs when the lithium

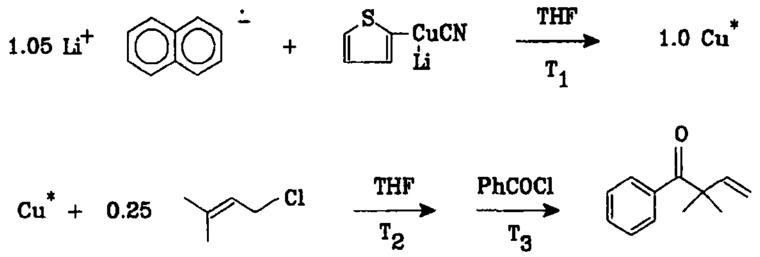
Table I. Reactions of Allylic Thienyl-Based Organocopper Reagents with Benzoyl Chloride.

Entry	Allyl Chloride[a]	Product[b]	%Yield[c]
1			56
2			40
3			55

[a]0.25 Equiv. allyl chloride added to the active copper at -108 °C [b]All products had consistent ^1H NMR, ^{13}C NMR, IR and were compared with authentic samples. [c]Isolated yields.

2-thienylcyanocuprate solution is reduced at -78 °C, followed by the addition of the allylic substrate at -108 °C, and subsequent reaction with the electrophile at -95 °C. The allylic organocopper reagents also react with benzaldehyde to give the corresponding alcohols in good yields, Table III.

Table II. Formation and Reaction of Prenyl Copper with Benzoyl Chloride at Various Temperatures.



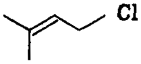
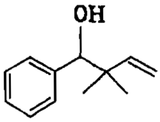
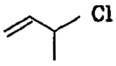
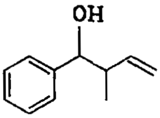
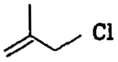
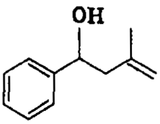
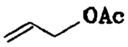
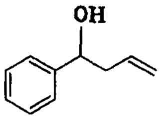
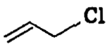
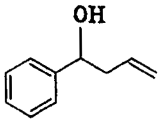
T_1	T_2	T_3	%Yield[a]
-78	-108	-95	65
-78	-78	-78	57
-50	-108	-95	51
-50	-50	-50	37
-28	-28	-28	0
-28	-108	-95	0

[a] Quantitation by GC analysis with authentic samples using decane as the internal standard.

The reaction of 3-chloro-1-butene with benzaldehyde gives a 70:30 syn to anti diasteriomeric mixture of the homoallylic alcohol product, Table III, entry 2.

In summary, a highly reactive zero-valent copper has been prepared which readily reacts with allylic chlorides and acetates at low temperatures to form the

Table III. Reactions of Allylic Thienyl-Based Organocopper Reagents with Benzaldehyde.

Entry	Allyl Chloride[a]	Product[b]	%Yield[c]
1			80
2			70[d]
3			78
4			26
5			61

[a] 0.4 Equiv. allyl chloride to active copper. [b] Ratio of the organocopper to the electrophile was 2:1. Products had consistent ^1H, ^{13}C NMR and IR. [c] Isolated yields based on electrophile. [d] A 70:30 syn:anti mixture determined by NMR.

corresponding allylic organocopper reagents. In turn, these organocopper reagents undergo cross-coupling reactions with benzoyl chloride and benzaldehyde to give the corresponding ketones and alcohols in moderate to good yields. Subsequently, product isolation has been immensely simplified due to the preclusion of phosphine ligands. The nature of these organocopper reagents as well as additional cross-coupling reactions are currently under investigation.

Experimental

^1H and ^{13}C NMR spectra were recorded on a G.E. Ω-300 spectrometer. NMR samples were prepared in $CDCl_3$ containing 1% TMS as an internal reference. Infrared spectra were recorded neat between NaCl plates on an Analect RFX-65 FT-IR spectrometer. Analytical GC was performed on a Hewlett-Packard 5890A gas chromatograph utilizing 12 ft x 1/8 inch columns containing 10% SP 2100 or SP 2250 on Supelcoport.

Preparation of Thienyl-Based Active Copper.

Lithium metal (8.40 mmol) and naphthalene (9.20 mmol) in freshly distilled THF (10 ml) were stirred at room temperature under an argon atmosphere for two hours, and then cooled to -78 °C. To this dark green preformed lithium naphthalenide solution was added a cold solution, -50 °C, of lithium 2-thienylcyanocuprate (0.25 M, 32 ml, 8.00 mmol) via cannula. The dark black-brown solution of active copper was used after stirring at -78 °C for 10-30 minutes.

Reaction of Allylic Organocopper Reagents with Benzoyl Chloride.

4-Chloro-2-methyl-2-butene (2.00 mmol) was weighed into a vial and sealed with a septum. Using a freeze-pump-thaw technique, air was removed and replaced with argon. THF (4 ml) was added to the vial and then cooled to -78 °C. The allyl chloride was then cannulated to the active copper solution (8.00 mmol) at -108 °C. The solution was stirred at -108 °C for 10 min and then warmed to -95 °C. Benzoyl chloride (8.80 mmol) and decane (2.00 mmol) were admixed with 4 ml of THF in a vial, cooled to -78 °C and then cannulated to the organocopper solution at -95 °C. The reaction mixture was allowed to warm to - 78 °C and stirred for 30 min. The solution was then quenched with saturated $NH_4Cl_{(aq)}$, extracted with ether (3 x 20 ml), washed with brine (3 x 50 ml), and the organic layer dried over $MgSO_4$. The solvent was removed under vacuum and the resulting mixture was isolated by flash-column chromatography on silica gel.

Reaction of Allylic Organocopper Reagents with Benzaldehyde.

4-Chloro-2-methyl-2-butene (3.20 mmol) was weighed into a vial and sealed with a septum. Using a freeze-pump-thaw technique, air was removed and replaced with argon. THF (4 ml) was added to the vial and then cooled to -78 °C. The allyl chloride was then cannulated to the active copper solution (8.00 mmol) at -108 °C. The solution was stirred at -108 °C for 10 min and then warmed to -78 °C. Benzaldehyde (1.60 mmol) and decane (3.20 mmol) were admixed with 4 ml of THF in a vial, cooled to -78 °C and then cannulated to the organocopper solution at -78 °C and stirred for 30 min. Product workup and isolation was performed as described above.

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