Direct Formation and Reaction of Thienyl-Based Organocopper Reagents

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The preparation of a highly reactive zerovalent copper complex by the direct reduction of lithium (2-thienylcyano)cuprate with preformed lithium naphthalenide is described. This active copper species oxidatively adds to carbon–halogen bonds to form organocopper reagents. The ability to directly form the organocopper reagent from organic halides and active copper allows for the incorporation of a wide variety of functionalities to be present in the organic halides and the organocopper reagents. Significantly, this formulation of active copper was able to oxidatively add to allyl chlorides and acetates at low temperatures to allow the direct formation of allylic organocopper reagents without Wurtz-type homocoupling. These functionalized organocopper compounds are able to undergo a variety of reactions, such as cross-coupling with acid chlorides, 1,4-conjugate addition with α,β-unsaturated carbonyl compounds, and intermolecular and intramolecular epoxide-opening reactions. Subsequently, this copper species avoids the use of phosphine ligands affording the product isolation much more convenient than with phosphine-based organocopper reagents.

Introduction

Organocopper and organocuprate reagents have been intensively used in synthetic chemistry in the past two decades.[1] The vast majority of organocopper reagents are prepared by a transmetalation reaction involving an organometallic reagent and a copper(I) salt. A variety of organometallic reagents, derived from metals more electropositive than copper, have been utilized in the preparation of organocopper reagents. The most common organometallic precursors have been organomagnesium and organolithium. This approach severely limits the functionality that may be incorporated into the organocopper reagent. In recent years, we have found that the use of the traditional lithium or Grignard precursors can be circumvented by using a highly reactive zerovalent copper which directly undergoes rapid oxidative addition to organic halides.[2,3] The highly reactive zerovalent copper solution is prepared by the reduction of a soluble copper(I) salt complex by a stoichiometric amount of preformed lithium naphthalenide. Significantly, the organocopper reagents prepared by our laboratories utilizing this active copper may incorporate a wide variety of functionalities such as ester, nitrile, chloride, fluoride, epoxide, and ketone moieties. These functonalized organocopper reagents undergo many of the reactions typical of other organocopper species.

The choice of ligand used in solubilizing the copper(I) salt was a critical factor affecting the reactivity of the active copper species. We have previously reported that highly reactive copper solutions prepared by the reduction of copper(I) salt/phosphine complexes with preformed lithium naphthalenide are very reactive toward functionalized organic halides. The resulting organocopper reagents readily undergo a number of transformations such as cross-coupling reactions with acid chlorides, 1,4-conjugate additions with α,β-unsaturated carbonyl compounds, and intermolecular and intramolecular epoxide-opening reactions.[2]

The choice of the phosphine ligands was found to be crucial for the formation and subsequent reactivity of the organocopper species. Although organocopper reagents made from CuI·PBu_3 were found to be very nucleophilic and underwent epoxide-opening and conjugate addition reactions, the initial addition to alkyl bromides resulted in notable amounts of homocoupling. The use of PPh_3 curtailed the amount of homocoupling, but the resulting nucleophilicity of the organocopper reagent was decreased. Accordingly, the presence of the phosphine ligands interfered with product isolation. In our search to attain an active copper species which did not require the use of phosphine ligands, we discovered that the lithium naphthalenide reduction of a commercially available lithium (2-thienylcyano)cuprate solution produced a highly reactive zerovalent copper complex.[4] Initially, lithium (2-thienylcyano)cuprate was used by Lipshutz et al. to form

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(2) (a) Rieke, R. D.; Dawson, B. T.; Stack, D. E.; Stinn, D. E. *Synth. Commun.* **1990**, *20*, 2711. (b) O'Brien, R. A.; Rieke, R. D. *J. Org. Chem.* **1990**, *20*, 2711. (c) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443. (d) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482. (e) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513. (f) Wu, T.-C.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 6753. (g) Wu, T.-C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, 52, 5057. (h) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056. (i) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280. (j) Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445. (k) Rieke, R. D.; Kavaliunas, A. V. Rhyne, L. D.; Frazier, D. J. *J. Am. Chem. Soc.* 1979, *101*, 246.

(3) Ebert, G. W.; Klein, W. R. *J. Org. Chem.* **1991**, *56*, 4744.

(4) (a) Klein, W. R.; Rieke, R. D. *Synth. Commun.* **1992**, *18*, 2635. (b) Rieke, R. D.; Wu, T.-C.; Stinn, D. E.; Wehmeyer, R. M. *Synth. Commun.* **1989**, *19*, 1833.

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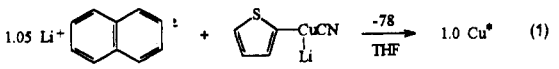
higher-order mixed cuprates.[5] The resulting organocopper species was found to be more reactive than the phosphine-based organocopper species and underwent the same transformations as previously described. Other investigations also led to promising results by the reduction of soluble CuCN·nLiX (X = Cl, Br; n = 1, 2) complexes.[6] The preceding paper compared and contrasted the chemistry between this formulation to that of Cu(I)salt/phosphine complexes. The reduction of other copper(I) salts was also investigated. 1-Hexynylcopper and other copper amine salts were used with limited success, whereas the active copper formed by the reduction of CuSPh oxidatively added to organic halides but the resulting cross-coupled products were accompanied by large amounts of the inseparable ligand-transfer byproduct.

The thienyl-based zerovalent copper will oxidatively add to organic halides under very mild conditions to form stable functionalized organocopper reagents in high yields at low temperatures. Subsequent product isolation was also much more convenient than with the phosphine-based organocopper reagents. The preparation of thienyl-based organocopper reagents and their reactions are discussed below.

Results and Discussion

Preparation of Highly Reactive Copper. The thienyl-based active copper (Cu*) was prepared by the reduction of lithium (2-thienylcyano)cuprate (THF, 0.25 M) with preformed lithium naphthalenide at −78 °C for 10 min, eq 1. A low reduction temperature was found to



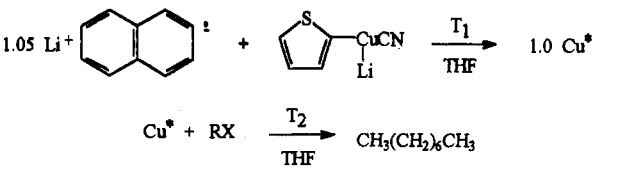
(1)

be crucial for the preparation of the active copper species. A series of reactions followed by saturated $NH_4Cl_{(aq)}$ quenches and analysis by gas chromatography at various reduction temperatures are summarized in Table I. The copper species prepared at −78 °C was superior to that prepared at 0 °C. The thienyl-based copper prepared at −78 °C reacted with 1-bromooctane at −78 °C, followed by protonation to give the reduced product, octane, in 90% yield. The active copper species totally consumed the starting material without accompaniment of either the homocoupled or elimination byproducts. However, there was not an appreciable difference in product yield when the reduction temperature was lowered to −108 °C followed by the addition of 1-bromooctane at −78 °C, whereas the copper species prepared at 0 °C and reacted at −45 °C only gave the reduced product in 50% yield. When the copper species was prepared at 0 °C and then cooled to −78 °C and subsequently reacted with 1-bromooctane at −78 °C, the amount of reduced product was reduced to 25%. This excludes any possible contributions by the reaction of active copper with the alkyl bromide at warmer temperatures.

(5) (a) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* 1987, *28*, 945. (b) Lipshutz, B. H.; Parker, D. A.; Ngugen, S. L.; McCarthy, K. E.; Barton, J. C.; Whitney, S. E.; Kotsuki, H. *Tetrahedron* 1986, *42*, 2873. (c) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Ngugen, S. L. *Tetrahedron Lett.* 1984, *25*, 5959.

(6) (a) Stack, D. E.; Rieke, R. D. *Tetrahedron Lett.*, in press. (b) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* 1992, *114*, 5110. (c) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* 1991, *113*, 4672.

Table I. Reactions of Active Copper with Octyl Bromide at Various Temperatures



equiv of halide[a]	T_1	T_2	% yield[b]
0.33 $CH_3(CH_2)_7Br$	0	−45	50
0.33 $CH_3(CH_2)_7Br$	0	−78	25
0.33 $CH_3(CH_2)_7Br$	−35	−35	66
0.33 $CH_3(CH_2)_7Br$	−50	−50	82
0.33 $CH_3(CH_2)_7Br$	−78	−78	90
0.33 $CH_3(CH_2)_7Br$	−108	−78	88
0.33 $CH_3(CH_2)_7Cl$	−78	−78	81
0.33 $CH_3(CH_2)_7Cl$	−108	−78	81
0.50 $CH_3(CH_2)_7Cl$	−78	−78	56
0.50 $CH_3(CH_2)_7Cl$	−108	−78	57

[a] Equivalents based on active copper. [b] Quantitation by GC analysis with authentic samples using decane as the internal standard upon quenching with dilute acid.

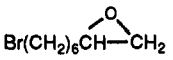
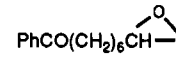
Similar observations occurred when alkyl chlorides were used. Significantly, the alkyl chloride was totally consumed by the active copper, formed at −78 °C, when 0.33 equiv of 1-chlorooctane was reacted at −78 °C to give the reduced product, octane, in an 81% yield. Up to 0.5 equiv of 1-chlorooctane may be used with the active copper at −78 °C to give octane in a 56% yield; however, 33% of the starting material then remains unreacted.

By comparison, the thienyl-based zerovalent copper is more reactive at lower temperatures than the phosphine-based copper and is also able to consume more equivalents of the alkyl chloride without accompaniment of homocoupled or eliminated byproducts.

Reaction of Cu* with Functionalized Halides and Cross-Coupling with Acid Chlorides. Thienyl-based active copper was observed to react with primary alkyl bromides at −78 °C and afforded stable alkylcopper reagents in high yields. The resulting alkylcopper reagents underwent cross-coupling reactions with benzoyl chloride at low temperature, −35 °C, to form ketones in good yields (Table II). Organocopper reagents prepared from 1-bromooctane or 4-bromobutyronitrile readily cross-coupled with benzoyl chloride to give the corresponding ketones in 73 and 61% isolated yields, respectively (entries 1 and 3). Similarly, 1-bromo-7,8-epoxybutane gave the corresponding epoxy ketone in 65% yield (entry 5).

All of the alkyl halides formed stable arylcopper compounds at 0 °C or lower. These arylcopper species underwent cross-coupling reactions with acid chlorides in good to excellent yields. For example, *p*-bromotoluene and *p*-bromoanisole gave the corresponding ketones in 86 and 87% yields, respectively (entries 6 and 7). Similarly, *p*-bromobenzonitrile and *p*-bromo-*N*,*N*-dimethylaniline gave *p*-cyanobenzophenone and *p*-(dimethylamino)benzophenone in 75 and 81% yield, respectively (entries 9 and 11). Cross-coupling with alkyl acid chlorides gave slightly lower yields. (*p*-Methoxyphenyl)copper reacted with valeryl chloride to produce *p*-methoxybenzobutanone in 63% yield (entry 8). Aryl iodides gave slightly higher yields of the cross-coupled products as compared to those derived from aryl bromides. For example, 1-chloro-4-iodobenzene gave *p*-chlorobenzophenone in a 90% yield (entry 12). However, *p*-bromobenzophenone afforded the corresponding ketone in 44% yield along with 50% of bis(*p*-benzoylphenyl)phenylmethyl benzoate (entry 14).

Table II. Cross-Coupling Reactions of Organocopper Reagents with Acid Chlorides

entry	halide[a]	acid chloride[b]	product	% yield[c]
1	$Br(CH_2)_7CH_3$	PhCOCl	$PhCO(CH_2)_7CH_3$	73
2	$Br(CH_3)_3CO_2Et$	PhCOCl	$PhCO(CH_2)_3CO_2Et$	47
3	$Br(CH_2)_3CN$	PhCOCl	$PhCO(CH_2)_3CN$	61
4	$Br(CH_2)_6Cl$	PhCOCl	$PhCO(CH_2)_6Cl$	42
5		PhCOCl		65
6	$BrC_6H_4(p\text{-}CH_3)$	PhCOCl	$PhCOC_6H_4(p\text{-}CH_3)$	86
7	$BrC_6H_4(p\text{-}OCH_3)$	PhCOCl	$PhCOC_6H_4(p\text{-}OCH_3)$	87
8	$IC_6H_4(p\text{-}OCH_3)$	*n*-BuCOCl	$n\text{-}BuCOC_6H_4(p\text{-}OCH_3)$	63
9	$BrC_6H_4(p\text{-}CN)$	PhCOCl	$PhCOC_6H_4(p\text{-}CN)$	75
10	$BrC_6H_4(m\text{-}CN)$	PhCOCl	$PhCOC_6H_4(m\text{-}CN)$	62
11	$BrC_6H_4(p\text{-}NMe2)$	PhCOCl	$PhCOC_6H_4(p\text{-}NMe_2)$	81
12	$IC_6H_4(p\text{-}Cl)$	PhCOCl	$PhCOC_6H_4(p\text{-}Cl)$	90
13	$BrC_6H_4(p\text{-}F)$	PhCOCl	$PhCOC_6H_4(p\text{-}F)$	93
14	$BrC_6H_4(p\text{-}COPh)$	PhCOCl	$PhCOC_6H_4(p\text{-}COPh)$	44[d]

[a] 0.3–0.4 equiv was used based on Cu*. [b] 1.0 equiv was used based on Cu*. [c] Isolated yields. All products have consistent ^1H and ^{13}C NMR and IR. [d] The reaction also gave 50% of bis(*p*-benzoylphenyl)phenylmethyl.

Reaction of Cu* with Allylic Chlorides and Acetates and Subsequent Cross-Coupling with Acid Chlorides. Allylic organocopper reagents are of current interest in the literature, especially since Lipshutz's development of higher-order allylic cyanocuprates.[7] Common methods employed to form allylic organocopper reagents involve the transmetalation of allylic stannanes with an organocopper reagent. However, the organocopper reagent is initially formed from a transmetalation reaction of an organolithium or Grignard reagent, thus preventing the insertion of functional moieties. Other work from our laboratories has shown that functionalized allylic organocopper reagents can be formed from the low-temperature reduction of a CuCN·2LiBr complex with preformed lithium naphthalenide.[6b,c]

The thienyl-based active copper reacted with allyl chlorides and acetates to produce the corresponding allylic organocopper reagents with less than 5% of the homocoupled diene byproduct, as observed by GC. Occasionally, the reactions were accompanied with less than 2% of the thienyl ligand transfer byproduct.

Low reaction temperatures dominate the reactivity of the allylic organocopper reagents (Table III). Optimal conditions were observed when the lithium (2-thienylcyano)cuprate was reduced at −78 °C, followed by the addition of the allylic substrate at −108 °C and finally cross-coupled with the electrophile at −95 °C. The addition of the allylic substrate at −108 °C was required to minimize the amount of Wurtz-type byproduct formation.

The allylic organocopper reagents reacted with benzoyl chloride and benzaldehyde to give the corresponding ketones and alcohols in moderate to good yields (Table IV). Prenylcopper reacted with the electrophile via γ attack (entries 1 and 2). It is postulated that the reaction of 3-chloro-1-butene (entries 3 and 4) also reacted via γ attack. Hence, it is assumed that 3-chloro-1-butene

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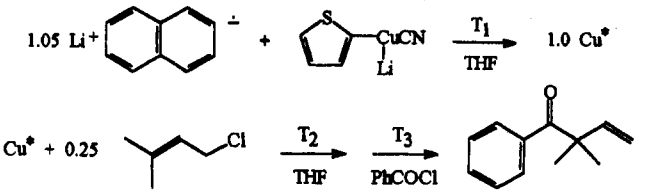
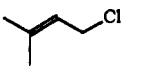
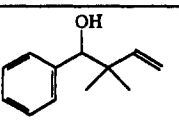
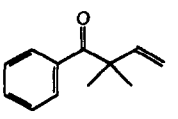
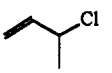
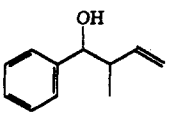
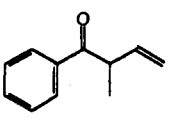
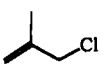
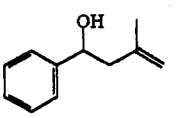
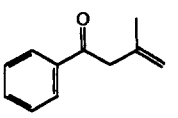
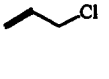
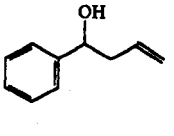
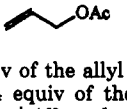
Table III. Formation and Reaction of Prenylcopper with Benzoyl Chloride at Various Temperatures



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

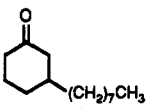
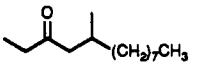
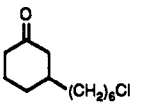
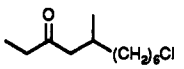
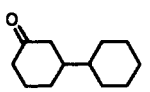
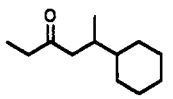
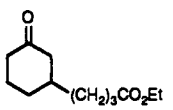
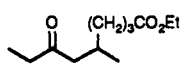
[a] Quantitation by GC analysis with authentic samples using decane as the internal standard.

Table IV. Reaction of Allylic Organocopper Reagents with Electrophiles

entry	allyl chloride[a]	electrophile	product[b]	% yield[c]
1		PhCHO		80
2	"	PhCOCl		56
3		PhCHO		70[d]
4	"	PhCOCl		40
5		PhCHO		78
6	"	PhCOCl		55
7		PhCHO		61
8		PhCHO	"	26

[a] 0.25 equiv of the allyl chloride used with 1.0 equiv of benzoyl chloride. 0.4 equiv of the allyl chloride used with 0.2 equiv of benzaldehyde. [b] All products have consistent ^1H and ^{13}C NMR and IR. [c] Isolated yields based on the limiting allyl chloride or electrophile. [d] A 70:30 syn to anti mixture as determined by NMR.

Table V. 1,4-Conjugate Addition Reactions with Organocopper Reagents

entry	equiv of halide[a]	equiv of additive	equiv of enone[b]	product[c]	% yield[d]
1	0.5 $Br(CH_2)_7CH_3$	2.0 TMSCl	0.25 A		91 (100)
2	0.5 $Br(CH_2)_7CH_3$	2.0 $BF_3{\cdot}Et_2O$	0.25 A		59
3	0.5 $Br(CH_2)_7CH_3$	1.0 TMSCl	0.25 A		71 (84)
4	0.5 $Br(CH_2)_7CH_3$	1.0 $BF_3{\cdot}Et_2$	0.25 A		64 (70)
5	0.5 $Br(CH_2)_7CH_3$	1.0 TMSCl	0.167 A		81 (88)
6	0.5 $Br(CH_2)_7CH_3$	1.0 TMSCl	0.125 A		97 (100)
7	0.5 $Br(CH_2)_7CH_3$	none	0.125 A		20 (16)
8	0.33 $Br(CH_2)_7CH_3$	0.65 TMSCl	0.163 A		30 (29)
9	0.5 $Cl(CH_2)_7CH_3$	2.0 TMSCl	0.25 A		71 (77)
10	0.5 $Cl(CH_2)_7CH_3$	1.0 TMSCl	0.25 A		65
11	0.5 $Cl(CH_2)_7CH_3$	none	0.25 A		16
12	0.5 $Cl(CH_2)_7CH_3$	2.0 TMSCl	0.167 A		85
13	0.5 $Cl(CH_2)_7CH_3$	1.0 TMSCl	0.167 A		87
14	0.5 $Cl(CH_2)_7CH_3$	1.0 TMSCl	0.125 A		85
15	0.5 $Br(CH_2)_7CH_3$	1.0 TMSCl	0.125 B		88
16	0.5 $Cl(CH_2)_7CH_3$	1.0 TMSCl	0.125 B		87
17	0.5 $Br(CH_2)_6Cl$	2.0 TMSCl	0.25 A		77
18	0.5 $Br(CH_2)_6Cl$	1.0 TMSCl	0.25 A		80 (84)
19	0.5 $Br(CH_2)_6Cl$	1.0 TMSCl	0.167 A		81
20	0.5 $Br(CH_2)_6Cl$	1.0 TMSCl	0.125 A		84 (88)
21	0.33 $Br(CH_2)_6Cl$	0.65 TMSCl	0.163 A		65
22	0.33 $Br(CH_2)_6Cl$	none	0.163 A		28 (30)
23	0.5 $Br(CH_2)_6Cl$	1.0 TMSCl	0.125 B		83
24		1.0 TMSCl	0.125 A		72
25		1.0 TMSCl	0.125 B		80
26	0.5 $Br(CH_2)_3CO_2Et$	1.0 TMSCl	0.125 A		79
27	0.5 $Br(CH_2)_3CO_2Et$	1.0 TMSCl	0.125 B		81

[a] All equivalents based on Cu*. [b] Enones, A = 2-cyclohexen-1-one, B = 4-hexen-2-one. [c] All products have consistent ^1H and ^{13}C NMR and IR. [d] Isolated yields based on the enone (GC yields with authentic samples using decane as the internal standard).

initially formed the secondary allylcopper species with subsequent rearrangement to the more favorable primary allylic structure. Other zerovalent metals have been shown to initially react with secondary allyl chlorides and then rearrange to the primary structure.[8] The reaction of allyl chloride with active copper did not afford the desired product when cross-coupled with benzoyl chloride. Similarly, allyl acetate only gave the electron-transfer product, allyl benzoate, in 46% isolated yield. 3-Chloro-1-butene reacted with benzaldehyde to yield a 70:30 syn to anti diastereiomeric mixture of the homoallylic alcohol product (entry 3). Methyl allyl chloride reacted with benzoyl chloride to give 3-methyl-1-phenyl-3-buten-1-one (entry 6) in 55% yield along with 2% of the separable thienyl ligand transfer byproduct.

1,4-Conjugate Addition Reactions with Thienyl-Based Organocopper Reagents. Conjugate addition of the organocopper reagents to α,β-unsaturated ketones has been investigated and found to proceed in excellent yields. The addition of TMSCl to the organocopper reagent prior to the addition of the enone allowed for the facile formation of the 1,4-conjugate product at low temperatures. Table V shows several conjugate addition reactions with varying ratios of the halide/additive/enone. The addition of TMSCl significantly increased product formation[9] as much as 5-fold and was essential for product formation. When 2 equiv of TMSCl was added to *n*-octylcopper (entry 6), the conjugate product was obtained in a 97% yield, whereas the conjugate product was obtained in only a 20% yield when the additive was omitted (entry 7). Similarly, ethyl

(8) (a) Whitesides, G. M.; Nordlander, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 2010. (b) Nordlander, J. E.; Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 494.

(9) (a) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

Table VI. Reactions of Organocopper Reagents with 1,2-Epoxybutane

entry	halide[a]	product[b]	% yield[c]
1	$Br(CH_2)_7CH_3$	$CH_3CH_2CH(OH)(CH_2)_8CH_3$	71[d]
2	$Br(CH_2)_5OPH$	$CH_3CH_2CH(OH)(CH_2)_6OPh$	60
3	$Br(CH_2)_6Cl$	$CH_3CH_2CH(OH)(CH_2)_7Cl$	68
4	$IC_6H_4(p\text{-}CH_3)$	$CH_3CH_2CH(OH)CH_2C_6H_4(p\text{-}CH_3)$	64
5	$IC_6H_4(p\text{-}OCH_3)$	$CH_3CH_2CH(OH)CH_2C_6H_4(p\text{-}OCH_3)$	78
6	$IC_6H_4(p\text{-}Cl)$	$CH_3CH_2CH(OH)CH_2C_6H_4(p\text{-}Cl)$	62

[a] 0.33 equiv based on Cu*. [b] All products have consistent ^1H and ^{13}C NMR and IR. [c] Isolated yields. [d] GC yield with authentic sample using decane as the internal standard.

4-bromobutyrate reacted with active copper and 2 equiv of TMSCl to give the conjugate product, 3-(3-carbethoxypropyl)cyclohexanone (entry 26) in a 79% yield. Without the additive, the product was not formed. The ideal TMSCl to organocopper ratio varied, depending on the substrate, from 2:1 up to 4:1. Likewise, the organocopper to enone ratio also varied[10] from 2:1 up to 4:1. By comparison, the Lewis acid addition of $BF_3{\cdot}Et_2O$[11] did not have as a dramatic effect on product formation when compared to TMSCl (entries 1–4). Competitive 1,2-additions were not seen for these reactions as determined by GC. Both cyclic and acyclic enones worked well with this formulation of active copper. However, the use of more sterically hindered enones, such as isophorone, carvone, and 2,4,4-trimethyl-2-cyclohexen-1-one, did not afford the desired 1,4-conjugate product.

Intermolecular Epoxide-Opening Reactions. The thienyl-based organocopper reagents were also found to be nucleophilic enough to undergo epoxide-opening reactions with 1,2-epoxybutane to form single regioisomers in good isolated yields (Table VI). *n*-Octylcopper and (5-phenoxypentyl)copper underwent epoxide-opening reactions with 1,2-epoxybutane to give 3-dodecanol and 1-phenoxy-7-nonanol in 71 and 60% yields, respectively (entries 1 and 2). The reaction of (6-chlorohexyl)copper with 7,8-epoxyoct-1-ene gave 14-chloro-7-hydroxy-1-tetradecene in 34% yield. We have attempted to activate the epoxide using Lewis acids to accelerate the organometallic epoxide-opening reaction. However, the reaction gave the undesired product 1-bromooct-7-en-2-ol in 91% yield.

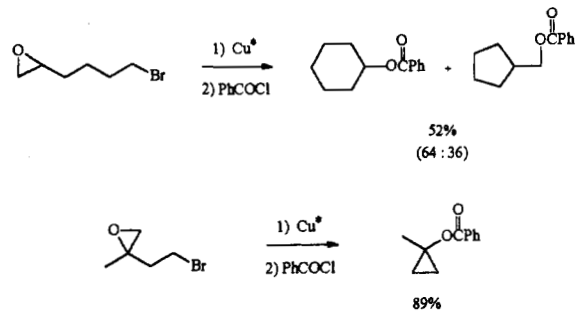
In the arylcopper series, the oxirane cleavage reaction required moderate heating to 45 °C. The arylcopper reagents appear to be very stable under these reaction conditions. Similarly, the reactions were also highly regioselective with arylation taking place only at the less hindered position of the epoxides. *p*-Tolylcopper, *p*-anisylcopper, and (*p*-chlorophenyl)copper reacted with 1,2-epoxybutane to give *p*-(2-hydroxybutyl)toluene, *p*-(2-hydroxybutyl)anisole, and *p*-(2-hydroxybutyl)-chlorobenzene in 64, 78, and 62% isolated yields, respectively (entries 4–6).

Minor amounts of the thienyl ligand transfer byproducts have been observed in some of the epoxide-opening reactions. These thienyl ligand transfer byproducts only affected product isolation occasionally. For example, 1-bromo-6-chlorohexane gave the major product along with less than 4% of the inseparable thienyl ligand transfer byproduct, 1-(2-thienyl)-2-butanol (entry 3).

(10) Larger excesses of the organometallic reagent (10 equiv) have been reported: (a) Oppolzer, W.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. (b) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta* **1981**, *64*, 2808.

(11) Lipshutz, B. H.; Ellsworth, E. L.; Shiahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351.

Scheme I



Intramolecular Epoxide-Opening Reactions. Intramolecular cyclizations via an epoxide cleavage process can also be effected by this thienyl-based active copper, Scheme I. Treatment of 6-bromo-1,2-epoxyhexane with active copper in THF at −78 °C formed (epoxyhexyl)-copper which underwent intramolecular cyclization upon warming. Trapping of the intermediate with benzoyl chloride at −35 °C gave a 64:36 mixture of cyclohexyl benzoate and cyclopentylmethyl benzoate in 52% isolated yield. The reaction of 4-bromo-2-methyl-1,2-epoxybutane with active copper gave only the 3-membered ring product in an 89% yield upon trapping with benzoyl chloride.

In general, the thienyl-based copper species seems to be more reactive toward the intramolecular epoxide-opening reactions when compared to the phosphine-based copper species. However, product isolation is much more convenient when utilizing the thienyl-based active copper.

Substitution Reactions. Unfortunately, cross-coupling reactions with alkyl iodides, bromides, or tosylates with the thienyl-based organocopper reagents did not prove amenable. *n*-Octylcopper reacted with methyl iodide to give nonane in only a 32% yield. Upon reaction with benzyl bromide only the homocoupled product, bibenzyl, and the reduced product, toluene, were found in 48 and 20% yields, respectively. Reactions with butyl tosylate also proved fruitless. It is worth noting that in certain circumstances this lack of reactivity may prove to be valuable in the elaboration of complex molecules.

NMR Investigations. The characterization of the thienyl-based active copper species has been attempted with the aid of low-temperature ^{13}C NMR spectroscopy. The ^{13}C spectrum of lithium (2-thienylcyano)cuprate at −78 °C was complex and remained unchanged upon warming to room temperature. The region from 10 to 40 ppm was obscured due to the hexanes contained in solution. Therefore, the studies were focused on the downfield region of 110–170 ppm. In this region lithium (2-thienylcyano)-cuprate gave 9 signals (156.6, 148.2, 133.9, 132.7, 126.9, 126.4, 125.9, 125.8, 125.3 ppm). Upon reduction with 1 equiv of lithium naphthalenide at −78 °C, giving active copper, the spectrum resolved into six distinct signals (163.4, 158.4, 131.2, 126.9, 125.5, 124.1 ppm). The original signals at 156.6 and 148.2 ppm disappeared upon reduction, and two new signals appeared downfield at 163.4 and 158.4 ppm and are tentatively attributed to CN.[12] The remaining four signals may indicate that only one thienyl structure is involved at the active copper stage. These four peaks do not correspond to the thienyl peaks associated in free lithium thiophene (177.2, 133.9, 127.4, 125.9 ppm) or 2-thienyl carbonitrile (138.5, 134.2, 128.1, 114.2, 109.3

(12) Peaks associated with LiCN (166.9 ppm) were not seen. This region is commonly attributed to CN peaks, see ref 15.

ppm). This indicates that the thiophene moiety remains involved in the active copper structure. Interestingly, the signals from naphthalene (133.6, 127.8, 125.8 ppm) were not observed.[13] Upon oxidative addition of the active copper solution with ethyl bromide, nine signals were observed (163.6, 133.4, 131.2, 127.7, 126.8, 125.6, 125.2, 124.1 ppm). Three new signals appeared (133.4, 127.7, 125.8 ppm) and were attributed to naphthalene (133.6, 127.8, 125.8 ppm). The signal intensity at 163.4 ppm decreased and shifted downfield slightly (163.6 ppm) while the peak at 158.4 ppm disappeared. Variable-temperature studies of this active copper species were also conducted. The active copper was formed at −78 °C, probed by ^{13}C NMR at −78 °C, and sequentially warmed in the NMR probe to −60, −40, and −20 °C. The spectra remained unchanged to −40 °C, although the signals did broaden. At −20 °C the signals at 163.4 and 158.4 ppm disappeared and the upfield signals broadened further and shifted slightly downfield (131.8, 128.3, 126.3, 124.5 ppm). The sample was immediately cooled back to −78 °C where the signals at 163.4 and 158.4 ppm reappeared along with three new signals and the broadened rearrangement of the upfield signals (133.4, 131.3, 127.8, 126.8, 125.8, 125.6, 125.3, 124.1 ppm). It is presumed that the new signals at 133.4, 127.8, and 125.8 ppm are attributed to naphthalene.[14] In contrast, the organocopper solution derived from ethyl bromide and active copper showed no appreciable change upon warming from −78 to 0 °C.

A new series of experiments were conducted using preformed lithium biphenylide to reduce the lithium (2-thienylcyano)cuprate. Upon reduction with 1 equiv of lithium biphenylide at −78 °C, giving active copper, nine signals were observed (163.4, 140.8, 131.3, 128.8, 127.2, 126.8, 125.6, 125.2, 124.1 ppm). Unlike the previous experiment, the signals attributed to biphenyl (141.2, 128.7, 127.1 ppm) were observed in the active copper spectrum. Upon oxidative addition of the active copper solution with ethyl bromide, the spectrum remained relatively unchanged, although the peak intensity at 163.4 decreased as seen in the naphthalene-based active copper.

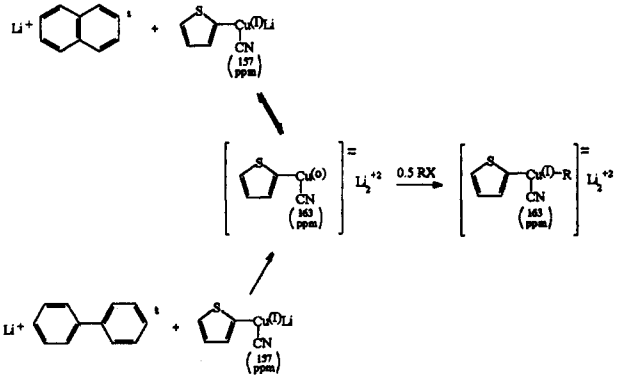
Noticeably, signals associated with LiCN, lithium thiophene, or 2-thienylcarbonitrile were not observed in any of the above spectra. Therefore, the thienyl moiety must be directly involved with the zerovalent active copper complex. The disappearance of naphthalene signals may be a result of the partial reduction of naphthalene back to the radical anion, resulting in an equilibrium with the zerovalent active copper species, Scheme II. This would explain the two signals seen in the cyano region of the spectrum (163.4 and 158.4 ppm). In contrast, the difference between the reduction potential of the zerovalent active copper species and biphenyl (which is higher than naphthalene) is too great for an equilibrium to exist. This explains the observance of the biphenyl peaks in the copper spectrum and the existence of only one cyano signal. Complete characterization of organocopper species have proven difficult, as evidenced by recent NMR investigations of higher-order cuprates which led to polemic discussions.[15] Further investigations into the characterization of the active copper species are underway.

(13) The disappearance of the naphthalene signals has also been observed in other active copper species. See the preceding paper this issue.

(14) These signals were very broad and not as well resolved as those seen in the original −78 °C organocopper spectrum.

(15) (a) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. (b) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032.

Scheme II



Conclusion. The difficulty of product isolation using phosphine-based organocopper reagents led us to explore nonphosphine-based organocopper species. Although a minor amount of the thienyl ligand transfer byproduct occurred and occasionally interfered with product purification, product isolation is much more convenient using the thienyl-based organocopper reagents as opposed to the phosphine-based organocopper reagents. The zerovalent active copper species derived from lithium (2-thienylcyano)cuprate undergoes oxidative addition reactions more readily than those generated from CuI/phosphine complexes. The ability to directly form organocopper compounds utilizing a thienyl-based active copper solution readily allows the preparation of functionalized organocopper containing ester, nitrile, chloride, fluoride, epoxide, amine, and ketone moieties. These functionalized thienyl-based organocopper reagents readily undergo many transformations such as cross-coupling reactions with acid chlorides, intermolecular and intramolecular epoxide-opening reactions, and 1,4-conjugate addition reactions.

Experimental Section

Melting points were obtained on a Thomas Hoover melting point apparatus or an Electrothermal melting point apparatus and are corrected. Infrared spectra were taken on an Analect RFX-65 FT-IR spectrophotometer or on a Perkin-Elmer 283 spectrophotometer, neat between NaCl or KBr plates, KBr pellets, or KBr powder. Proton NMR spectra were obtained on a General Electric Ω-300 or a Varian VXR-200 spectrometer. All chemical shifts are reported in parts per million downfield from an internal tetramethylsilane standard. Fully decoupled ^{13}C NMR spectra were obtained on a General Electric Ω-300 or a Varian VXR-200 spectrometer. The center peak of $CDCl_3$, 77.0 ppm, was used as an internal reference. High-resolution mass spectra were acquired by the Midwest Center for Mass Spectrometry at the University of Nebraska–Lincoln using a Kratos MS-80 mass spectrometer. Elemental analyses were performed by Oneida Research Services, Inc. (Whitesboro, NY) and Galbraith Laboratories (Knoxville, TN).

Analytical gas chromatography analyses were performed on a Hewlett-Packard 5890A gas chromatograph or a Varian 3700 gas chromatograph using stainless steel columns (12 ft × $^1/_8$ in.) packed with 3% OV-17 on Chromosorb G-AW (100/200 mesh), 5% SE-30 on Chromosorb GM-NAW (100/200 mesh), 10% SP-2100 or 10% SP-2250 on Supelcoport, and a megabore glass capillary column (15-m × 0.53-mm bonded FSOT RSL-160 polydimethylsiloxane, 2.65-μm film thickness). All GC yields were calibrated by determining response factors for pure isolated samples or from authentic commercially available compounds. The percent yields were then calculated relative to the internal standard, typically *n*-alkanes, which were introduced into the reaction after the formation of the active copper. Preparative GC analysis was done on a Varian 920 gas chromatograph using

a stainless steel column (10 ft × 1/4 in.) packed with 10% GS SP-2100 on Supelcoport.

All inert atmosphere manipulations were carried out on a dual manifold vacuum/argon system. Linde prepurified grade argon was further purified by passing it through several columns containing a 150 °C BASF R3-11 catalyst, phosphorous pentoxide, and granular potassium hydroxide. Tetrahydrofuran, 1,2-dimethoxyethane, and toluene were freshly distilled prior to use from a sodium/potassium alloy under an argon atmosphere. Commercially available reagents were used as received unless noted otherwise.

General Procedure for the Preparation of Thienyl-Based Active Copper. Lithium (8.40 mmol) and naphthalene (9.20 mmol) were placed into a 100-mL two-neck round-bottom flask equipped with a Teflon stir bar in an argon drybox and then sealed with a rubber septum and stopcock outlet. Freshly distilled THF (10 mL) was then added, and the solution was allowed to stir at room temperature under argon for 2 h, yielding a dark green solution which was then cooled to −78 °C. Lithium (2-thienylcyano)cuprate (0.25 M, 8.00 mmol) was syringed into a 50-mL two-neck round-bottom flask under argon, cooled to −60 °C, and then cannulated to the preformed lithium naphthalenide solution with stirring. The dark black-brown active copper solution was used after it stirred for an additional 10–30 min at −78 °C. In the epoxide-opening reactions, the lithium (2-thienylcyano)cuprate was concentrated in vacuo to approximately one-third of the original volume prior to use.

Typical Procedure for Cross-Coupling Reactions of Thienyl-Based Organocopper Reagents with Acid Chlorides. To the thienyl-based active copper solution (4.13 mmol) was added *p*-bromoanisole (1.59 mmol) via syringe at −78 °C. After being stirred for 10 min at −78 °C, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 30 min. The reaction was then cooled to −35 °C, and benzoyl chloride (3.91 mmol) was added neat via syringe. After being stirred for an additional 30 min the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ solution. The reaction mixture was then extracted with diethyl ether (3 × 70 mL), and the combined organic layers were sequentially washed with an aqueous NaOH solution (1 N, 15 mL) and distilled water (30 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash silica gel chromatography using gradient mixtures of hexanes/EtOAc gave (4-methoxyphenyl)phenylmethanone[16] in 87% yield (1.48 mmol): mp = 60–61 °C (lit.[17] mp 60–61 °C; IR (KBr) 1651, 1599, 1281, 1257, 845, 741, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.71–7.86 (m, 4 H), 7.39–7.60 (m, 3 H), 6.90–6.99 (m, 2 H), 3.85 (s, 3 H); ^{13}C NMR (50 MHz, $CDCL_3$) 195.3, 163.1, 138.2, 132.4, 131.7, 130.0, 129.6, 128.1, 113.4, 55.3.

1-Phenyl-1-nonanone:[18] IR (neat) 3060, 2930, 2860, 1690, 1600, 1585, 1450, 1260, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.90–8.02 (m, 2 H), 7.38–7.62 (m, 3 H), 2.96 (t, J = 7.4 Hz, 2 H), 1.14–1.74 (m, 12 H), 0.88 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 200.6, 137.2, 132.8, 128.5, 128.0, 38.6, 31.8, 29.4, 29.4, 24.4, 22.6, 14.0; MS (EI) m/e (relative intensity) 281 (M^+, 3.0), 133 (12.1), 120 (92.5), 105 (100.0), 77 (30.7); HRMS (EI) calcd for $C_{15}H_{22}O$ m/e 218.1671, found m/e 218.1676. Anal. Calcd: C, 82.51; H, 10.16. Found: C, 82.11; H, 10.32.

Ethyl 4-benzoylbutanoate:[19] ^1H NMR (200 MHz, $CDCl_3$) 7.90–8.04 (m, 2 H), 7.36–7.64 (m, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.05 (t, J = 7.2 Hz, 2 H), 2.43 (t, J = 7.2 Hz, 2 H), 2.07 (m, 2 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 199.2, 173.0, 136.9, 132.9, 128.5, 127.9, 60.2, 37.4, 33.4, 19.4, 14.1.

4-Benzoylbutanenitrile:[20] ^1H NMR (200 MHz, $CDCl_3$) 7.90–8.04 (m, 2 H), 7.36–7.66 (m, 3 H), 3.16 (t, J = 6.8 Hz, 2 H), 2.51 (t, J = 7.0 Hz, 2 H), 2.10 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) 198.0, 136.5, 133.3, 128.6, 127.9, 119.2, 36.3, 19.8, 16.5; MS (EI) m/e (relative intensity) 173 (M^+, 10.4), 147 (0.1), 133 (0.8), 120 (2.6), 105 (100.0), 77 (33.1); HRMS (EI) calcd for $C_{11}H_{11}NO$ m/e 173.0841, found m/e 173.0839.

8,9-Epoxy-1-phenyl-1-nonanone:[2b] IR (neat) 3060, 2940, 2860, 1690, 1600, 1580, 1450, 1255, 1210 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.90–8.04 (m, 2 H), 7.38–7.64 (m, 3 H), 2.97 (t, J = 7.3 Hz, 2 H), 2.83–2.98 (m, 1 H), 2.74 (dd, J = 5.0, 4.0 Hz, 1 H), 2.45 (dd, J = 5.0, 2.6 Hz, 1 H), 1.75 (m, 2 H), 1.31–1.63 (m, 8 H); ^{13}C NMR (50 MHz, $CDCl_3$) 200.3, 137.0, 132.8, 128.4, 127.9, 52.2, 47.0, 38.4, 32.3, 29.2, 29.1, 25.7, 24.1; MS (EI) m/e (relative intensity) 232 (M^+, 0.2), 231 (0.3), 133 (5.2), 120 (68.4), 105 (100.0), 77 (36.6); HRMS (EI) calcd for $C_{15}H_{20}O_2$ m/e 232.1463, found m/e 232.1456.

(4-Methylphenyl)phenylmethanone:[21] IR (neat) 1657, 1604, 1277, 1313, 835, 731, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.67–7.81 (m, 4 H), 7.36–7.61 (m, 3 H), 7.26 (dm, J = 7.9 Hz, 2 H), 2.42 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 196.3, 143.1, 137.9, 134.8, 132.0, 130.2, 129.8, 128.9, 128.1, 21.5.

1-(4-Methoxyphenyl)-1-pentanone:[22] IR (neat) 2958, 2935, 1678, 1603, 1259, 1171, 1032, 841 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.87 (dm, J = 9.0 Hz, 2 H), 6.96 (dm, J = 9.0 Hz, 2 H), 3.86 (s, 3 H), 2.9 (t, J = 7.4 Hz, 2 H), 1.62–1.86 (m, 2 H), 1.30–1.51 (m, 2 H), 0.95 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 193.4, 193.2, 130.2, 130.2, 113.6, 55.3, 37.9, 26.7, 22.5, 13.9.

4-Benzoylbenzonitrile:[23] mp = 113.0–113.5 °C (lit.[17] mp 113–113.5 °C); IR (KBr) 2227, 1649, 1311, 1281, 856, 737, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.4–7.95 (m, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) 194.9, 141.1, 136.3, 133.2, 132.1, 130.1, 130.0, 128.6, 117.9, 115.6.

3-Benzoylbenzonitrile:[24] mp 90.0–91.5 °C (lit.[17] mp 90.5–91.5 °C); IR (KBr) 2231, 1662, 1281, 721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.46–8.09 (m, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) 194.3, 138.5, 136.2, 135.3, 133.7, 133.3, 133.2, 129.9, 129.3, 128.6, 117.9, 112.8.

(4-(Dimethylamino)phenyl)phenylmethanone:[25] mp = 88.0–90.0 °C; IR (KBr) 1597, 1317, 1286, 831, 739, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.68–7.85 (m, 4 H), 7.38–7.58 (m, 3 H), 6.67 (dm, J = 9.0 Hz, 2 H), 3.06 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 195.1, 153.2, 139.3, 132.7, 131.0, 129.4, 127.9, 124.7, 110.5, 40.0. Anal. Calcd: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.57; H, 6.57; N, 5.91.

(4-Chlorophenyl)phenylmethanone:[26] mp = 74.5–76.5 °C (lit.[17] mp 77–78 °C); IR (KBr) 1649, 1583, 1284, 1090, 845, 729, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.71–7.84 (m, 4 H), 7.41–7.65 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) 195.4, 138.8, 137.2, 135.8, 132.6, 131.4, 129.9, 128.6, 128.4.

(4-Fluorophenyl)phenylmethanone:[27] IR (neat) 1660, 1599, 1504, 1277, 1228, 1157, 850, 737, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.73–7.90 (m, 4 H), 7.42–7.64 (m, 3 H), 7.08–7.22 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) 195.1, 165.3 (d, J = 252.6 Hz), 137.4, 133.7 (d, J = 3.0 Hz), 132.7, (d, J = 9.2 Hz), 132.4, 129.8, 128.3, 115.4 (d, J = 21.8 Hz).

(4-Benzoylphenyl)phenylmethanone:[28] mp = 160–161 °C; IR (KBr) 1657, 1595, 1271, 922, 858, 708, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.89 (s, 4 H), 7.81–7.88 (m, 4 H), 7.45–7.68 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) 195.8, 140.6, 136.9, 132.9, 130.0, 129.6, 128.4.

Ethyl 4-benzoylbenzoate:[2b] IR (neat) 1720, 1662, 1275, 1105, 714 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 8.11–8.19 (m, 2 H), 7.77–7.88 (m, 4 H), 7.44–7.72 (m, 3 H), 4.42 (m, 3 H), 4.42 (q, J = 7.1 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 196.0, 165.8, 141.2, 136.9, 133.5, 132.9, 130.0, 129.7, 129.4, 128.4, 61.4, 14.3; MS (EI) m/e (relative intensity) 254 (M^+, 0.2), 226 (4.9), 209 (35.2), 177 (51.0), 149 (10.6), 105 (100.0), 77 (32.8); HRMS (EI) calcd for $C_{16}H_{14}O_3$ m/e 254.0943, found m/e 254.0938.

Typical Procedure for the Cross-Coupling Reactions of Thienyl-Based Allylic Organocopper Reagents with Electrophiles. Prenyl chloride (2.00 mmol) was weighed into a vial and sealed with a septum. Using a freeze–pump–thaw technique,

(16) *Sadtler*: IR, 34510; ^1H, 20288; ^{13}C, 1197.
(17) Nishida, S. *J. Org. Chem.* **1967**, *32*, 2692.
(18) Freeksen, R. W.; Selikson, S. J.; Wroble, R. R. *J. Org. Chem.* **1983**, *48*, 4087.
(19) Woessner, W. D. *Synth. Commun.* **1978**, *8*, 279.
(20) Ito, M. M.; Nomura, Y.; Takeuchi, Y.; Tomoda, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 641.
(21) *Sadtler*: IR, 29055; ^1H, 11036; ^{13}C, 644.
(22) Friour, G.; Cahiez, G.; Mormant, J. F. *Synthesis* **1984**, 37.
(23) (a) Frimer, A. A.; Farkash-Soloman, R.; Aljadeff, G. *J. Org. Chem.* **1986**, *51*, 2093. (b) Exner, O.; Budesinsky, M. *Magn. Reson. Chem.* **1989**, *27*, 27.
(24) Wagner, P. J.; Siebert, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 7329.
(25) *Sadtler*: IR, 16731; ^1H, 8618; ^{13}C, 8585.
(26) *Sadtler*: IR, 8632; ^1H, 3260; ^{13}C, 1758.
(27) *Sadtler*: IR, 18376; ^1H, 6057; ^{13}C, 10089.
(28) *Sadtler*: IR, 36346; ^1H, 9826; ^{13}C, 2493.

air was removed from the vial 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 THF (4 mL) in a vial, cooled t −78 °C, and then cannulated to the prenyl copper solution at −95 °C. The reaction was allowed to warm to −78 °C and stirred for 30 min. The solution was then quenched with saturated $NH_4Cl_{(aq)}$, extracted with Et_2O (3 × 20 mL), and washed with brine (3 × 20 mL), and the organic layer was dried over $MgSO_4$. Flash silica gel chromatography using gradient mixtures of hexanes/EtOAc afforded 2,2-dimethyl-1-phenyl-3-buten-1-one[29] (1.12 mmol) for a 56% yield: IR (neat) 3085, 3059, 2975, 1679, 1635, 1466, 1412, 971, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.85–7.89 (m, 2 H), 7.32–7.46 (m, 3 H), 6.11–6.26 (dd, J_1 = 17.52 Hz, J_2 = 10.63 Hz, 1 H), 5.17–5.27 (m, 2 H), 1.39 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 204.5, 143.8, 137.1, 131.5, 129.1, 127.8, 113.9, 50.1, 25.9.

2,2-Dimethyl-1-phenyl-3-buten-1-ol:[30] IR (neat) 3029, 1637, 1452, 1024, 998 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.24–7.28 (m, 5 H), 5.84–5.93 (dd, J_1 − 17.41 Hz, J_2 = 10.73 Hz, 1 H), 5.00–5.12 (m, 2 H), 4.37 (s, 1 H), 2.23 (s, 1 H), 0.98 (s, 3 H), 0.93 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) 144.9, 140.6, 127.7, 127.3, 113.6, 80.4, 42.0, 24.2, 20.9.

2-Methyl-1-phenyl-3-buten-1-ol:[30] IR (neat) 3400, 3062, 1639, 1492, 1020, 914, 761, 701 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.22–7.35 (m, 5 H), 5.66–5.84 (m, 1 H), 5.12–5.19 ((m, 2 H) also multiplet for diasteriomer at 4.98–5.05), 4.53 ((d, J = 5.73 Hz, 1 H) also doublet for diasteriomer at 4.32 (J = 7.63 Hz)), 2.39–2.60 (m, 1 H), 2.35 (s, 1 H), 0.98 ((d, J = 6.91 Hz, 3 H) also doublet for diasteriomer at 0.85 (J = 6.68 Hz)); ^{13}C (75 MHz, $CDCl_3$) 142.7, 142.4, 140.5, 140.3, 128.1, 127.9, 127.5, 127.2, 126.7, 126.4, 116.5, 115.3, 77.7, 77.2, 46.0, 44.5, 16.4, 14.0.

2-Methyl-1-phenyl-3-buten-1-one:[29] IR (neat) 3081, 3060, 2975, 1687, 1633, 1448, 1216, 962, 919, 703 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.9–8.00 (m, 2 H), 7.41–7.56 (m, 3 H), 5.91–6.09 (m, 1 H), 5.10–5.22 (m, 2 H), 4.18 (quin, 1 H), 1.32–1.35 (d, 3 H); ^{13}C (75 MHz, $CDCl_3$) 201.3, 138.1, 136.3, 132.9, 128.6, 128.5, 116.5, 45.5, 17.0.

3-Methyl-1-phenyl-3-buten-1-ol:[31] IR (neat) 3396, 3073, 2967, 1646, 1452 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.2–7.24 (m, 5 H), 4.87 (d, 2 H), 4.78 (t, 1 H), 2.41 (d, 2 H), 2.23 (s, 1 H), 1.77 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) 144.0, 142.3, 128.3, 127.4, 125.7, 113.9, 71.4, 48.2, 22.2.

3-Methyl-1-phenyl-3-buten-1-one:[32] IR (neat) 3076, 2971, 2913, 1687, 1448, 1207, 690 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.96–7.99 (m, 2 H), 7.41–7.55 (m, 3 H), 4.98 (s, 1 H), 4.85 (s, 1 H), 3.68 (s, 2 H), 1.82 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) 197.9, 139.6, 136.7, 132.9, 128.4, 128.2, 114.8, 47.5, 22.7.

1-Phenyl-3-buten-1-ol:[33] IR (neat) 3380, 2929, 1641, 1454, 1047, 916, 757, 700 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) 7.23–7.36 (m, 5 H), 5.73–5.86 (m, 1 H), 5.10–5.18 (m, 2 H), 4.71 (m, 1 H), 2.47–2.53 (m, 2 H), 2.17 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) 143.8, 134.4, 128.3, 127.5, 125.8, 118.3, 73.3, 43.7.

Typical Procedure for the Conjugate Additions of Thienyl-Based Organocopper Reagents. 1-Bromooctane (4.00 mmol) and decane (4.00 mmol) were weighed in a vial and sealed with a septum. Using a freeze–pump–thaw technique air was removed from the vial and replaced with argon. THF (4 mL) was added to the vial, and the solution was then cooled to −78 °C. The solution was rapidly cannulated to the active copper solution (8.00 mmol) at −78 °C and stirred for 10 min. Then TMSCl (8.00 mmol) was syringed neat into the organocopper solution and the resulting solution was stirred for an additional 10 min. In a large vial, 2-cyclohexen-1-one (2.00 mmol) was weighed, sealed with a septum, dissolved in 15 mL of THF under argon as previously described, and then cooled to −78 °C. This solution was then slowly added dropwise via cannula to the organocopper/TMSCl solution over a period of 30 min at −78 °C. After being stirred for an additional 30 min, the reaction mixture was quenched with 20 mL of 5% HCl, extracted with Et_2O (3 × 20 mL), and washed with water (3 × 20 mL) and brine (3 × 20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash silica gel chromatography using gradient mixtures of hexanes/EtOAc afforded 3-*n*-octylcyclohexanone[2b] (1.42 mmol) in a 71% yield: IR (neat) 2954, 2844, 1710, 1465, 1457, 1421, 1224, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.50–2.50 (m, 8 H), 1.20–1.40 (br s, 15 H), 0.88 (t, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) 212.1, 48.2, 41.5, 39.0, 36.6, 31.8, 31.3, 29.6, 29.5, 29.2, 26.6, 25.3, 22.6, 14.0.

5-Methyl-3-tridecanone:[34] IR (neat) 2956, 2925, 2854, 1716, 1459, 1411, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 2.28–2.37 (m, 3 H), 2.09–2.17 (dd, J_1 = 15.74 Hz, J_2 = 8.10 Hz, 1 H), 1.87–2.02 (apparent octet, 1 H), 1.19 (br s, 14 H), 0.97 (t, 3 H), 0.79–0.83 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 211.5, 49.8, 36.9, 36.3, 31.8, 29.7, 29.5, 29.2, 26.9, 22.5, 19.8, 14.0, 7.6.

3-(6-Chlorohexyl)cyclohexanone:[2b] IR (neat) 2935, 2858, 1712, 1448, 1428, 1244 cm^{-1}; ^{1}H NMR (300 MHz), $CDCl_3$) 3.53 (t, 2 H), 1.22–2.45 (m, 19 H); ^{13}C NMR (300 MHz, $CDCl_3$) 211.8, 48.1, 45.0, 41.4, 38.9, 36.3, 32.4, 31.2, 28.8, 26.7, 26.4, 25.2; HRMS (EI) calcd for $C_{12}H_{21}ClO$ m/e 216.1281, found 216.1277.

11-Chloro-5-methyl-3-undecanone:[35] IR (neat) 2931, 2856, 1714, 1459, 1411, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 3.45 (t, 2 H), 2.28–2.38 (m, 3 H), 2.11–2.19 (dd, J_1 = 15.73 Hz, J_2 = 7.87 Hz, 1 H), 1.90–1.96 (apparent octet, 1 H) 1.65–1.74 (m, 2 H), 1.03–1.40 (m, 8 H), 0.97 (t, 3 H), 0.81 (d, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 211.4, 49.7, 44.9, 36.6, 36.3, 32.4, 29.0, 28.8, 26.7, 26.6, 19.7, 7.6.

3-Cyclohexylcyclohexanone:[34] IR (neat) 2923, 2852, 1714, 1448, 1423 cm^{-1}; H NMR (300 MHz, $CDCl_3$) 0.80–2.41 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) 212.6, 45.4, 44.5, 42.5, 41.5, 29.8, 29.7, 28.3, 26.5, 26.44, 26.40, 25.5.

5-Cyclohexyl-3-hexanone: IR (neat) 2923, 2850, 1714, 1457, 1448, 1413, 1376, 1272, 1112, 987, 889 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 2.25–2.41 (m, 3 H), 2.07–2.15 (dd, J_1 = 15.5 Hz, J_2 = 9.06 Hz, 1 H), 1.79–1.89 (m, 1 H), 1.51–1.68 (m, 5 H), 0.85–1.21 (m, 9 H, including t at 0.97, J = 7.39 Hz), 0.75 (d, J = 6.67 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 211.9, 47.0, 42.7, 36.3, 34.1, 30.2, 28.9, 26.59, 26.56, 26.51, 16.5, 7.7.

3-(3-Carbethoxypropyl)cyclohexanone:[34] IR (neat) 2937, 1731, 1712, 1448, 1421, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 4.13 (q, 2 H), 1.23–2.45 (m, 18 H, including t at 1.26); ^{13}C NMR (75 MHz, $CDCl_3$) 211.4, 173.2, 60.1, 47.8, 41.3, 38.6, 35.7, 34.1, 30.9, 25.0, 21.9, 14.1.

5-Methyl-7-oxononanoic acid, ethyl ester:[6c] IR (neat) 2975, 2958, 2938, 2875, 1737, 1714, 1460, 1413, 1375, 1349, 1301, 1247, 1178, 1114, 1099, 1033, 946 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 4.07 (q, 2 H), 2.31–2.39 (m, 3 H), 2.1.4–2.26 (m, 3 H), 1.86–1.97 (apparent octet, 1 H), 1.43–1.61 (m, 2 H), 1.04–1.26 (m, 5 H, including t at 1.20), 0.99 (t, 3 H), 0.85 (d, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 210.9, 173.3, 59.9, 49.3, 36.2, 36.0, 34.1, 28.7, 22.1, 19.5, 14.0, 7.5.

Typical Procedure for the Intermolecular Epoxide-Opening Reactions of Thienyl-Based Organocopper Reagents with 1,2-Epoxybutane. To the thienyl-based active copper solution (4.25 mmol) was added 1-bromo-6-chlorohexane (1.40 mmol) via syringe at −78 °C. After being stirred for 10 min, the reaction was allowed to warm to −35 °C. 1,2-Epoxybutane (5.96 mmol) was added via syringe, and the reaction mixture was gradually warmed to room temperature. In the arylcopper reactions, 1.0 equiv of the epoxide, relative to the active copper, was added and then heated to 40 °C for 1 h. The reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL) and then extracted with Et_2O (3 × 70 mL). The combined organic layers were washed with water (2 × 15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on flash silica gel using 20:1 hexanes/EtOAc. Further purification using preparative thin-layer chromatography gave 1-chloro-8-decanol[2b] in 70% yield (0.98 mmol): ^{1}H NMR (200 MHz, $CDCl_3$) 3.53 (t, J = 6.7 Hz, 2 H), 3.53 (m,

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1 H), 1.69–1.85 (m, 2 H), 1.23–1.62 (m, 13 H), 0.94 (t, J = 7.4 Hz, 3 H). The product contained less than 4% of the side product 1-(2-thienyl)-2-butanol.

1-Phenoxy-7-nonanol: IR (neat) 3130–3650, 2935, 1245, 754, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.21–7.33 (m, 2 H), 6.84–6.98 (m, 3 H), 3.95 (t, J = 6.5 Hz, 2 H), 3.52 (m, 1 H), 1.78 (m, 2 H), 1.25–1.60 (m, 11 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 159.1, 129.4, 120.4, 114.5, 73.2, 67.8, 36.8, 30.1, 29.4, 29.2, 26.0, 25.6, 9.8; MS (EI) m/e (relative intensity) 236 (M^+, 14.1), 141 (3.0), 94 (100.0), 83 (13.6); HRMS (EI) calcd for $C_{15}H_{24}O_2$ m/e 236.1776, found m/e 236.1769.

14-Chlorotetradec-1-en-7-ol: IR (neat) 3130–3650, 2927, 2854, 1641 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 5.82 (ddt, J = 17.0, 10.2, 6.6 Hz, 1 H), 4.90–5.08 (m, 2 H), 3.58 (m, 1 H), 3.53 (t, J = 6.7 Hz, 2 H), 2.07 (m, 2 H), 1.78 (m, 2 H), 1.20–1.56 (m, 17 H); ^{13}C NMR (50 MHz, $CDCl_3$) 138.9, 114.3, 71.8, 45.1, 37.4, 37.4, 37.3, 33.7, 32.6, 29.5, 28.9, 28.8, 26.8, 25.5, 25.1; MS (EI) m/e (relative intensity) 245 (M^+ – 1, 0.2), 228 (0.3), 200 (2.1), 163 (6.7), 109 (40.2), 95 (100.0); HRMS (EI) calcd for $C_{14}H_{17}O^{35}Cl$ m/e 245.1672, found m/e 245.1663.

1-(4-Methoxyphenyl)-2-butanol:[2b] IR (neat) 3130–3660, 3060, 3035, 2935, 2875, 1610, 1510, 1465, 1250, 1180, 1110, 1035, 970, 800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.13 (dm, J = 8.6 Hz, 2 H), 6.85 (dm, J = 8.6 Hz, 2 H), 3.78 (s, 3 H), 3.69 (m, 1 H), 2.77 (dd, J = 13.7, 4.4 Hz, 1 H), 2.57 (dd, J = 13.7, 8.2 Hz, 1 H), 1.60 (br s, 1 H), 1.40–1.64 (m, 2 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 158.2, 130.6, 130.3, 113.9, 74.0, 55.2, 42.6, 29.4, 10.0; MS (EI) m/e (relative intensity) 180 (M^+, 30.1), 163 (0.6), 151 (0.3), 122 (100.0), 121 (70.7), 107 (16.9), 91 (6.9), 77 (6.4); HRMS (EI) calcd for $C_{11}H_{16}O_2$ m/e 180.1150, found m/e 180.1150.

1-(4-Chlorophenyl)-2-butanol: mp = 51–52 °C; IR (KBr) 3100–3700, 2960, 2931, 1489, 1016, 808 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.28 (dm, J = 8.5 Hz, 2 H), 2 H), 7.15 (dm, J = 8.5 Hz, 2 H), 3.72 (m, 1 H), 2.80 (dd, J = 13.7, 4.4 Hz, 1 H), 2.62 (dd, J = 13.7, 8.2 Hz, 1 H), 1.38–1.66 (m, 3 H), 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) 137.2, 132.2, 130.7, 128.6, 73.9, 42.8, 29.6, 10.0; MS (EI) m/e (relative intensity) 186 (0.6), 184 (M^+, 1.9), 155 (5.3), 126 (83.7), 91 (65.7), 59 (100.0); HRMS (EI) calcd for $C_{10}H_{13}O^{35}Cl$ m/e 184.0655, found m/e 184.0655.

Typical Procedure for Intramolecular Epoxide-Opening Reactions of Thienyl-Based (Epoxyalkyl)copper Reagents. To the thienyl-based active copper (4.25 mmol) at –78 °C was added 1,2-epoxy-6-bromohexane (1.28 mmol), neat via syringe. The reaction mixture was warmed to 0 °C and stirred for 30 min. Benzoyl chloride (4.27 mmol) was added neat via syringe, and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (15 mL), extracted with Et_2O (3 × 20 mL), washed with water (3 × 20 mL) and brine (3 × 20 mL), and dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash silica gel chromatography using gradient mixtures of hexanes/EtOAc gave a crude yellow oil. Preparative TLC using hexanes/EtOAc (6:1) afforded a light yellow oil containing a 64:36 mixture, as determined by ^1H NMR, of cyclohexyl benzoate and cyclopentyl methyl benzoate in 52% yield (0.718 mmol). The relative areas of the doublet at 4.21 ppm and the multiplet at 4.95–5.10 ppm were used to assign the ratio of the product mixture.

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