Preparation and Chemistry of the Active Copper Species Derived from CuI·PBu$_3$, CuI·PPh$_3$, and CuCN·nLiX Complexes

Reuben D. Rieke,* Douglas E. Stack, Bryan T. Dawson, and Tse-Chong Wu

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588-0304

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The preparation of highly reactive copper by the reduction of CuI·PBu$_3$, CuI·PPh$_3$, and CuCN·nLiX copper(I) complexes with the preformed lithium naphthalenide is described. It was found, for all three Cu(I) complexes, that the reduction temperature proved crucial to reactivity of the zerovalent copper species as measured by the ability of the active copper to undergo oxidative addition to carbon–halogen bonds. The lower the reduction temperature the more reactive the zerovalent copper species becomes. The low-temperature reduction allows for the formation of highly reactive copper from CuCN·nLiX complexes. This active copper species undergoes oxidative addition to alkyl and aryl bromides in high yield to form the corresponding organocopper reagent directly without the need for other organometallic precursors. Moreover, the alkyl and aryl bromides can contain a wide range of functional groups as they are not affected in the oxidative addition step. The functionalized organocopper reagents derived from CuCN·nLiX based active copper are the reagent of choice in the cross-coupling of acid chlorides to produce ketones as well as the 1,4-addition reaction with enones. The lack of phosphines associated with organocopper reagents stemming from CuCN-based active copper makes product isolation more facile. While the functionalized organocopper reagents derived from CuCN·nLiX complexes provide higher isolated yields in the formentioned reactions, they are not nucleophilic enough to undergo inter- or intramolecular epoxide openings. The use of both CuI·PBu$_3$ and CuI·PPh$_3$ Cu(I) complexes in the intramolecular epoxide openings of aryl bromoepoxides is presented. The regiochemistry, endo vs. exo, was shown to be affected by the Cu(I) complex used to generate the active copper species, the solvent, and the pattern of substitution around the epoxide moiety. The active copper species as well as the the resulting organocopper reagents derived from both CuI·PBu$_3$ and CuCN·nLiX were investigated using both ^{31}P and ^{13}C NMR. The data from ^{31}P NMR investigation held some evidence for a highly reduced copper(0)–phosphine complex while the ^{13}C studies of the CuCN·nLiX complexes indicated that these species have limited solubility in THF.

Introduction

Organocopper reagents are among the most widely accepted organometallic reagents used in the formation of C–C bonds.[1] Since organocopper reagents are softer nucleophiles than organolithium or Grignard reagents, they can contain a wide range of electrophilic functional groups. However, since traditional methods of preparing organocopper reagents involves the transmetalation of organolithium or Grignard reagents, the formation of functionalized organocopper reagents using this technique is not viable. Functionalized organocopper reagents have been produced by the transmetalation of functionalized organozinc compounds.[2] Over the past decade, research in these laboratories has developed new methods of preparing organocopper reagents which circumvent the need for other organometallic precursors.[3-6] The methodology involves the direct oxidative addition of zerovalent copper to organic halides to form the desired organocopper reagent directly.[4]

Since ordinary zerovalent copper is not sufficiently reactive to oxidatively add to organic halides, a new form of finely divided Cu(0) had to be developed. Initial attempts involved the reduction of various Cu(I) salts with K or Li along with a catalytic amount of naphthalene as an electron carrier.[3] While the heterogeneous gray-black powders formed by this process were found to be much

(1) (a) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980. (b) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253. (c) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1. (d) Lipshutz, B. H. *Synthesis* **1987**, 325. (e) Lipshutz, B. H. *Tetrahedron* **1984**, *40*, 5005. (f) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709. (g) Normant, J. F. *J. Organomet., Chem. Lib.* **1976**, *1*, 219. (h) Normant, J. F. *Synthesis* **1972**, 63. (i) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. (j) Marino, J. P. *Ann. Rep. Med. Chem.* **1975**, *10*, 327. (k) Jukes, A. E. *Adv. Organomet. Chem.* **1974**, *12*, 215. Black, D. C.; Jackson, W. R.; Swan, J. M. *Comperhensive Organic Chemistry*; Barton, D., Ollis, W. D., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, Chapter 15. (l) Van Koten, G.; Noltes, J. G. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Ed.; Pergamon Press: Oxford, 1982; Vol. 2, pp 709–763. (m) Carruther, W. *Comperhensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Ed.; Pergamon Press: Oxford, 1982; Vol. 7, pp 685–722.

(2) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *36*, 2865. (c) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (d) Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berck, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693. (e) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 3887. (f) Berck, S. C.; Yeh, M. C. P.; Jeong, N.; Knochel, P. *Organometallics* **1990**, *9*, 3053. (g) Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 6146. (h) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431. (i) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735.

(3) Early active copper work: (a) Rieke, R. D.; Rhyne, L. D. *J. Org. Chem.* **1979**, *44*, 3445. (b) Rieke, R. D.; Kavaliunas, A. V.; Rhyne, L. D.; Frazier, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 246.

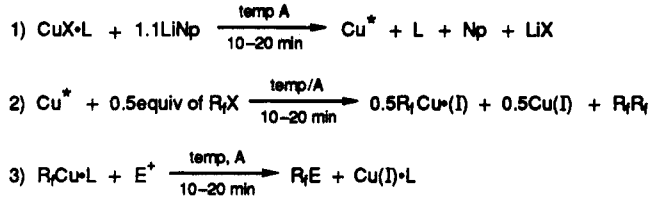
(4) For the preparation of other organometallic compounds using active metals see: Rieke, R. D. *Science* **1989**, *246*, 1260.

(5) Cu* derived from CuI·PR$_3$ complexes: (a) Ebert, G. M.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280. (b) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056. (c) Wu, T.-C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5057. (d) Wu, T.-C.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 2381. (e) Ebert, G. M.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482. (f) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513. (g) Wu, T.-C.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 6753. (h) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. M. *Tetrahedron* **1989**, *45*, 443. (i) O'Brien, R. A.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 788.

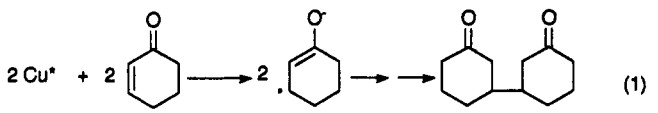
(6) Cu* derived from CuCN·nLiX: (a) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 4672. (b) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 5110. (c) Stack, D. E.; Rieke, R. D. *Tetrahedron Lett.*, in press.

0022-3263/93/1958-2483$04.00/0

Scheme I



more reactive than copper bronze, they could not undergo oxidative addition at temperatures low enough to form preformed organocopper reagents. It was discovered that the reduction of the Cu(I) salt had to be carried out quickly in order to prevent the newly formed active copper, Cu*, from sintering and forming copper beads. Thus, by using preformed lithium naphthalenide radical anion, along with a Cu(I) complex that was soluble in THF, the reduction was essentially diffusion controlled and new forms of Cu* were formed. These new forms of active copper appeared homogeneous and could be stirred for prolonged periods of time without sintering. Moreover, these new Cu* species could undergo oxidative addition with functionalized alkyl and aryl organic halides to form the corresponding functionalized organocopper reagent at temperatures conducive to organocopper compounds.[5]



(1)

Although many Cu(I), THF-soluble, complexes have been reduced by lithium naphthalenide, CuI·PR_3[5] (R = PPh_3, Bu_3) and CuCN·nLiX (X = Cl or Br, n = 1 or 2)[6] complexes have been shown to be the most versatile with regards to both formation of the organocopper species and reactions with various electrophiles. The chemistry of both the active copper and organocopper reagents derived from the reduction of CuI·PR_3 and CuCN·nLiX complexes, along with the advantages and disadvantages of each is presented below.

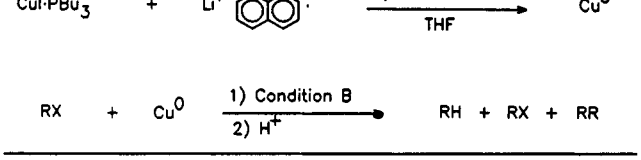
Results and Discussion

Generation of Cu* and Oxidative Addition to RX. Scheme I shows the three essential steps in active copper chemistry. All steps are conducted in THF under an argon atmosphere free from oxygen and water. Step 1 involves reduction of the Cu(I) complex by lithium naphthalenide. *The reduction temperature plays a major role in the resulting reactivity of the zerovalent copper* and will be discussed in detail below. The newly formed copper species is then reacted with an appropriate organic halide which may or may not contain a functional group. The oxidative addition, step 2, is usually carried out at −78 to −35 °C for alkyl bromides or −35 to 0 °C for aryl bromides and can be accompanied with varying amounts of undesired homocoupling of the organic halide. The resulting organocopper reagent is then reacted with a suitable electrophile to form the desired product, step 3.

Prior work involving the formation of a formal copper anion[7] demonstrated the marked effect the reduction temperature had on formation of Cu* (temp A, step 1, Scheme I). Tables I–III illustrate how the reactivity of

(7) Rieke, R. D.; Dawson, B. T.; Stack, D. E.; Stinn, D. E. *Synth. Commun.* **1990**, *20*, 2711.

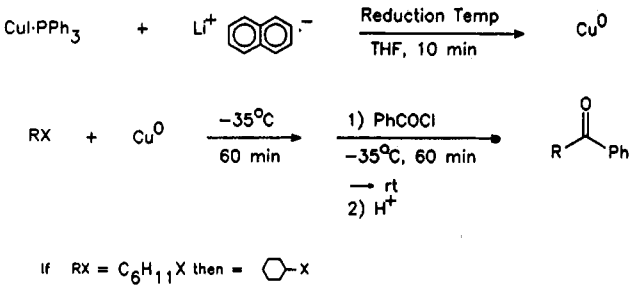
Table I. Reactions of PBu_3-Based Active Copper, Prepared at Various Reduction Temperatures, with RX[a]



entry	RX = $CH_3(CH_2)_7X$	ondn A (°C, min)	condn B (°C, min)	% yield[b] RH	RX	RR
1	**RBr**	0, 20	−78, 20	65	5	25
2	**RBr**	−78, 10	−78, 60	76	6	16
3	**RBr**	−107, 10	−35, 60	76	0	17
4	**RCl**	0, 20	−50, 80	23	71	0
5	**RCl**	−78, 10	−50, 60	63	32	0
6	**RCl**	−107, 10	−35, 60	64	31	0

[a] In general, 1.1 equiv of LiNp and 0.4 equiv of halide were used based on the equivalents of CuI·PBu_3 complex. [b] Yield of the alkane, unreacted halide, and homocoupled product were determined by GC analysis after a 1-mL quench of reaction mixture in $NH_4Cl_{(sat)}$.

Table II. Influence of Reduction Temperature on Yields of Reactions with PPh_3-Based Active Copper[a]



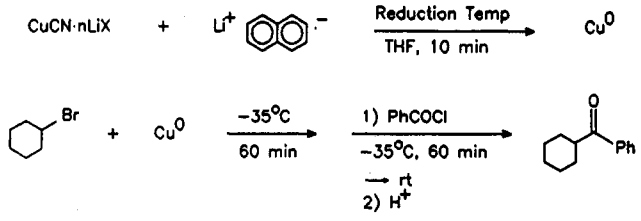
entry	red. temp (°C)	RX	% yield[b,c] RCOPh
1	0	C_6H_{11}**Br**	25
2	−78	C_6H_{11}**Br**	62
3	−100	C_6H_{11}**Br**	82
4	0	C_6H_{11}**Cl**	<10
5	−78	C_6H_{11}**Cl**	46
6	−100	C_6H_{11}**Cl**	69
7	0	**PhCl**	2
8	−60	**PhCl**	44
9	−100	**PhCl**	61

[a] In general, 1.1 equiv of lithium naphthalenide and 0.5 equiv of RX were used based on 1 equiv of CuI·PPh_3. [b] Yield based on RX. [c] GC yield based on a response factor calculated from a standard containing authentic product.

Cu* is increased with a decrease in the reduction temperature. Since Cu* produced from CuI·PBu_3 is of high reactivity, its oxidative addition to alkyl bromides showed little correlation between reduction temperature and Cu* reactivity (entries 1–3, Table I). Oxidative addition to alkyl chlorides displayed a marked increase when the reduction temperature was lowered from 0 to 78 °C (entries 4 and 5, Table I). Decreasing the temperature below −78 °C showed little effect on Cu* derived from CuI·PBu_3.

Although CuI·PPh_3 is not soluble in THF, the reduction of this Cu(I) complex provides active copper comparable in reactivity to that of CuI·PBu_3-based Cu*. CuI·PPh_3-based Cu* also shows an increase in reactivity with decreasing reduction temperature. Alkyl bromides, alkyl chlorides, and aryl chlorides all displayed the same trend. The formation of ketone products by the cross-coupling of the organocopper reagent with benzoyl chloride provides a good measure of how much organocopper reagent is formed in the oxidative addition step. Unlike the CuI·PBu_3 complexes, active copper from CuI·PPh_3 produces little homocoupling (<2%) with alkyl bromides. Also, lowering

Table III. Cold Temperature Reduction Effects on CuCN·nLiX-Based Active Copper[a]



	CuCN·nLiX			
entry	n	LiX	red. temp (°C)	% yield[b,c] $C_6H_{11}COPh$
1	2	LiBr	−100	57
2	1	LiBr	−100	38
3	2	LiBr	−78	40
4	2	LiBr	−20	9
5	2	LiCl	−100	55
6	1	LiCl	−100	42
7	2	LiCl	−78	43

[a] Reactions involve 1.1 equiv of lithium naphthalenide and 0.5 equiv of RX per 1 equiv of CuCN·nLiX complex. [b] Yield based on cyclohexyl bromide. [c] GC yield based on a response factor calculated from a standard containing authentic product.

the reduction temperature below −78 °C proved significant with CuI·PPh_3-based active copper (entries 2 and 3, 5 and 6, 8 and 9, Table II).

Initial attempts to make Cu* from CuCN·nLiX complexes was met with limited success. However, the cold-temperature reduction effects seen with other Cu(I) complexes led to a successful approach for Cu* formation from CuCN·nLiX. Table III illustrates that lowering the reduction temperature from −20 to −100 °C greatly facilitates the oxidative addition step, again measured by ketone formation (entries 1, 3, and 4, Table III). The yields in Table III are based on reacting 0.5 equiv of cyclohexyl bromide (0.5 equiv is the maximum equivalents for the one-electron Cu* reagent) with Cu*. Typical reactions using CuCN·nLiX-based active copper involve 0.3–0.2 equiv (relative to Cu*) of RBr with Cu*. Like CuI·PPh_3-based Cu*, active copper derived from CuCN·nLiX produces very little homocoupling, ca. 1%, of the alkyl bromide. Better yields were obtained when 2 equiv of lithium salt were used to solublize CuCN (entries 1 and 2, Table III). LiBr and LiCl[8] produced comparable results. The manner in which the CuCN·nLiX complex and lithium naphthalenide are added together also effects the reactivity of the resulting Cu* solution. Better results were obtained when the CuCN·nLiX complex was added to lithium naphthalenide than vice versa.

The data displayed in Tables I–III indicate that active copper made from CuI·PBu_3 and CuI·PPh_3 is more reactive than Cu* derived from CuCN·nLiX. However, Cu* made from CuCN·nLiX complexes offers several advantages. First, CuCN is a very inexpensive and stable source of Cu(I) which can be used as received without the need for purification. Both Cu* chemistry and organocopper chemistry involving CuI have been shown to be greatly affected by the purity of the CuI used.[9] Second, product isolation using CuCN·nLiX-based Cu* is much easier and product purity is greatly improved using this phosphine-free source of Cu(I). Since the LiX ligands are removed during aqueous workup, the products can be obtained smoothly by flash silica gel chromatography. The use of phosphine in CuI·PR_3 complexes can make product isolation difficult,[10] and acceptable elemental analysis using phosphine based Cu* is difficult to achieve. Also, since reactions involving CuI·PR_3 based Cu* often require the use of an additional 1–2 equiv of PR_3, the removal of large amounts of malodorous phosphines can be laborious. Third, as will be discussed below, organocopper reagents derived from CuCN·xLiX undergo 1,4-conjugate addition to enones as well as cross-coupling with acid chlorides. When using organocopper reagents derived from CuI·PR_3, one must vary the nature of the phosphine to suit the electrophile being used. Thus, organocopper reagents derived from CuCN·nLiX are more adaptable to various electrophiles. However, the use of CuI·PR_3-based active copper is, to date, the best copper(I) complex for both inter- and intramolecular epoxide openings.

Table IV. Cross-Coupling of Benzoyl Chloride with Organocopper Reagents Derived from CuCN·2LiBr-Based Active Copper

entry	halide (equiv)[a]	product	% yield[b]
1	$Br(CH_2)_7CH_3$ (0.25)	$PhCO(CH_2)_7CH_3$	82
2	$Br(CH_2)_6Cl$ (0.25)	$PhCO(CH_2)_6Cl$	80
3	$Br(CH_2)_3CO_2Et$ (0.25)	$PhCO(CH_2)_3CO_2Et$	81
4	$Br(CH_2)_2CO_2Et$ (0.25)	$PhCO(CH_2)_2CO_2Et$	43
5	$Br(CH_2)_3CN$ (0.25)	$PhCO(CH_2)_3CN$	86
6	bromobenzene (0.20)	PhCOPh	87
7	p-BrC_6H_4CN (0.20)	p-NCC_6H_4COPh	60
8	o-BrC_6H_4CN (0.20)	o-NCC_6H_4COPh	74
9	o-$BrC_6H_4CO_2Et$ (0.20)	o-$EtO_2CC_6H_4COPh$	51
10	p-BrC_6H_4Cl (0.20)	p-ClC_6H_4COPh	83

[a] Based on 1 equiv of CuCN. [b] Isolated yields.

Reactions with Acid Chlorides. The reaction of functionalized organocopper reagents with acid chlorides proceeds smoothly at −35 to 0 °C to produce the corresponding ketone in good to excellent yield. While organocopper reagents derived from CuI·PBu_3, CuI·PPh_3,[5f,h] or CuCN·nLiX-based Cu* all react with acid chlorides, the best isolated yields are obtain using Cu* derived from CuCN·nLiX.[6a] Since excess Cu* will react with acid chlorides,[5d] an excess of acid chloride must be employed, necessitating the yield be based on the starting organic halide. Since CuI·PBu_3-based Cu* yields ca. 30% homocoupling in the oxidative addition of alkyl bromides, its use in acid chloride reactions is not competitive with CuCN·nLiX-based Cu*. Also, while CuI·PPh_3-based active copper yields comparable or even slightly higher GC yields of ketones upon reaction with acid chlorides, the phosphine-free CuCN·nLiX complex provides higher isolated yields of greater purity.

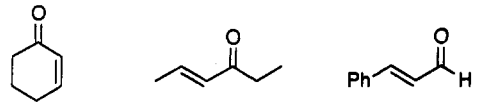
Table IV displays the results of various functionalized organocopper reagents, produced from the corresponding alkyl and aryl bromides, reacting with PhCOCl to form functionalized, unsymmetrical ketones. Chloride, nitrile, and ester functionalities can be incorporated into the organocopper reagent. If the functional group is in close proximity to the carbon–bromine bond, yields are lower (compare entries 3 and 4, Table IV). While reaction with bromobenzene proceeds in high yield, electron-withdrawing groups on the aryl bromide cause varying amounts of reductive cleavage in the oxidative addition step (compare entries 6 and 7, Table IV). The reductive cleavage is more

(8) Recent work with CuCN based Cu* has found it more suitable to use LiCl. The lower molecular weight makes the handling of less salt more convenient.

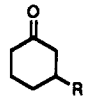
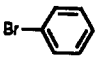
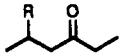
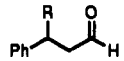
(9) (a) Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashe, C. M.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. (b) Lipshutz, B. H.; Whitney, S.; Kozolowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273.

(10) Preparative TLC is often needed to remove excess phosphines.

Table V. Conjugate Addition Reactions with Organocopper Reagents Derived from CuCN·2LiBr



A B C

product	entry	XR[a]	enone (equiv)	% yield[b]
 1	a	$Br(CH_2)_7CH_3$	A (0.17)	92
	b	$Cl(CH_2)_7CH_3$	A (0.16)	42
	c	$Br(CH_2)_3CO_2Et$	A (0.17)	70
	d	$Br(CH_2)_3CO_2Et$	A (0.12)	90
	e	$Br(CH_2)_3CN$	A (0.12)	87
	f	$Br(CH_2)_6Cl$	A (0.12)	82
	g		A (0.12)	80
	h		A (0.11)	45
 2	a	$Br(CH_2)_3CO_2Et$	B (0.11)	94
	b	$Br(CH_2)_3CN$	B (0.11)	92
 3	a	$Br(CH_2)_7CH_3$	C (0.20)	68
	b	$Br(CH_2)_3CO_2Et$	C (0.11)	87

[a] The CuCN to halide ratio was 1:0.25–0.30. A 2–3-fold excess of TMSCl, with respect to the equiv of enone was injected neat into the flask (a 6-fold excess of TMSCl was used for the preparation of product 3a. [b] All isolated products gave consistent IR, HRMS, ^1H, and ^{13}C spectral data.

pronounced when the electron-withdrawing functional group is placed in the para position (compare entries 7 and 8, Table IV).

Reaction with α,β-Unsaturated Ketones and Aldehydes. Functionalized organocopper reagents derived from CuCN·*n*LiX complexes were also the reagent of choice in 1,4-conjugate addition reaction to enones in the presence of TMSCl.[6a] While organocopper reagents derived from CuI·PBu_3 also undergo conjugate addition reactions,[5b] the necessity of an additional 1–2 equiv of a PBu_3 makes product isolation very difficult. Organocopper reagents derived from CuI·PPh_3 undergo conjugate addition in only modest yield, ca. 30%, in the presence of TMSCl; without TMSCl yields were less than 5%. Thus, due to ease of product isolation, 1,4-conjugate additions are best carried out using CuCN·*n*LiX active copper in the presence of TSMCl.

Table V shows the reaction of cyclic and acyclic α,β-unsaturated ketones and aldehydes with functionalized organocopper reagents derived from CuCN·2LiBr in the presence of TMSCl. The use of TMSCl was essential for success. Entry 1, product **1a**, in Table V shows a 92% yield in the conjugate addition of *n*-octylcopper to 2-cyclohexenone. When the same reaction was conducted without TMSCl, less than 10% of product **1a** was obtained. Other additives such as $BF_3·Et_2O$ did provide **1a** in 50% yield, and mixtures of both $BF_3·Et_2O$ and TMSCl resulted in a 69% isolated yield of **1a**. HMPA provided no product. Thus, TMSCl was the additive of choice, and its use in promoting conjugate addition reactions with organocopper reagents is well known.[11]

The method of addition of the α,β-unsaturated adduct, e.g., 2-cyclohexenone, to the organocopper reagent proved critical. Neat injection of the enone via disposable syringe resulted in a 10% cut in yield due to formation of 3-substituted cyclohexanone dimer, eq 1. Electron transfer of the excess Cu* to the enone and subsequent dimerization of the enone was reduced to zero by the dilute (0.1 M), dropwise addition of the enone in THF.

Use of TMSCl by Corey in other organocopper reactions has shown that 1,4-conjugate addition to α,β-unsaturated aldehydes can occur without competitive 1,2 addition.[12] The functionalized organocopper reagents derived from CuCN·2LiBr also show exclusive 1,4-conjugate to α,β-unsaturated aldehyde[6a] in the presence of TMSCl (entries 11 and 12, Table V). The products of 1,2 addition were not detected by G.C. or NMR.

Reactions with Epoxides. Of the three copper complexes, CuI·PBu_3, CuI·PPh_3, and CuCN·*n*LiX, only CuI·PBu_3-based Cu* provided an organocopper reagent nucleophilic enough to undergo *inter*molecular epoxide openings.[5c] An active copper method employing lithium (2-thienylcyano)cuprate solution, free of phosphines, has been developed which will undergo intermolecular epoxide reactions. This will be discussed in the following publication. Although Cu* derived from CuI·PPh_3 does not produce an organocopper species reactive enough to undergo *inter*molecular epoxide-opening reactions, CuI·PPh_3-based Cu* can be used to facilitate *intra*molecular epoxide openings; CuCN·*n*LiX-based active copper underwent intramolecular epoxide openings in low yield, ca. 20–40%. Indeed, CuI·PPh_3 offers advantages over CuI·PBu_3-based active copper in intramolecular *alkyl* epoxide-opening reactions. First, little of the starting alkyl bromide is lost to homocoupling, and second, separation of PPh_3 from the product is much easier than PBu_3. The intramolecular reactions of a variety of alkyl bromoepoxides with active copper derived from CuI·PPh_3 have been presented.[5g] The bromoepoxides can contain other functional groups, and the role of solvent on both the regiochemical and chemical outcome of these carbocyclizations has been discussed.[5f,g]

Parham cyclialkylations[13] and cyclicacylations[14] involve an anionic cyclization of ortho-functionalized aryllithium compounds and have been found to be synthetically useful.[15] As a part of our continuing interest in the intramolecular expoxide-opening reactions, we have explored this type of reaction utilizing Cu*. Since homocoupling does not occur to any appreciable extent with aryl bromides, both CuI·PBu_3- and CuI·PPh_3-based Cu* can be employed. A summary of intramolecular epoxide-opening reactions of epoxyaryl bromides using Cu* is presented in Table VI.

As shown in Table VI, the intramolecular cyclizations of epoxyarylcopper compounds could have exo ring closure to form 2,3-dihydrobenzofuran or endo closure to yield

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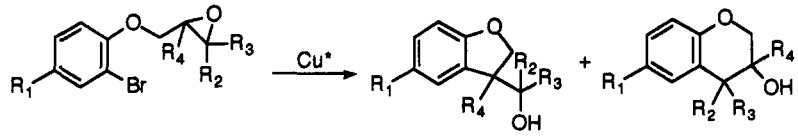
(15) (a) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2935. (b) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. (c) Brewer, P. D.; Tagat, J.; Hergruetor, C. A.; Helquist, P. *Tetrahedron Lett.* **1977**, *18*, 4573.

Table VI. Intramolecular Epoxide-Opening Reactions of Epoxy Aryl Halides Using Phosphine-Based Active Copper



entry	no.	R1	R2	R3	R4	PR_3	solvent	temp (°C)	exo:endo[a]	% yield[b]
1	3	H	H	H	H	PBu_3	THF	0 → rt	82:18	61
2	3	H	H	H	H	PPh_3	THF	0 → rt	88:12	63
3	3	H	H	H	H	PPh_3	Toluene	0 → rt	58:42	29
4	3	H	H	H	H	PBu_3	THF/DMF[c]	0 → rt	92:8	25
5	3	H	H	H	H	PPh_3	THF/DMF[c]	0 → rt	100:0	5
6	4	CO_2Et	H	H	H	PBu_3	THF	0	87:13	80
7	5	Cl	H	H	H	PBu_3	THF	0 → rt	83:17	53
8	5	Cl	H	H	H	PPh_3	THF	0 → rt	89:11	63
9	6	Me	H	H	H	PBu_3	THF	0 → rt	82:18	59
10	6	Me	H	H	H	PPh_3	THF	0 → rt	87:13	56
11	7	H	Me	H	H	PBu_3	THF	0	100:0	86
12	7	H	Me	H	H	PPh_3	THF	0	100:0	85
13	8	CO_2Et	Me	H	H	PBu_3	THF	0	100:0	74
14	8	CO_2Et	Me	H	H	PPh_3	THF	0	100:0	68
15	9	Cl	Me	H	H	PBu_3	THF	0	100:0	96
16	10	Cl	Ph	H	H	PBu_3	THF	0	84:16	86
17	11	Cl	H	H	Me	PBu_3	THF	0	0:100	53
18	12	CO_2Et	Me	Me	H	PBu_3	THF	0	100:0	79

[a] Products shown were isolated by column chromatography or preparative thin-layer chromatography. Product ratios were determined by ^1H NMR. [b] Isolated yields. [c] THF to DMF ratio was 1:1.5 (v/v), respectively.

3-chromanol. The regioselectivity of these cyclizations is affected by the substitution pattern, reaction solvent, and the CuI·PR_3 complex used to generate the active copper. In general, the exo mode of ring closure is usually preferred for these reactions.[16]

Reaction of 2-(2,3-epoxypropoxy)phenyl bromide with CuI·PBu_3-derived copper gave a 4.5:1 mixture of 2,3-dihydrobenzofuran and 3-chromanol (entry 1, Table VI). The regioselectivity increased to 7.5:1 when the CuI·PPh_3 complex was used (entry 2, Table VI). Solvent effects were also quite important for the cyclizations. A 1.4:1 mixture of 5-membered and 6-membered ring products was obtained when the reaction was carried out in toluene (entry 3, Table VI). In a polar solvent system, endo attack was strongly preferred (entries 4 and 5, Table VI).

Significantly, the bromo epoxides can contain some functionalities such as esters and chlorides. With a strong withdrawing group, e.g., $-CO_2Et$, at the para position, the regioselectivity slightly increased to 6.8:1 (entry 6, Table VI). Also of note is that the epoxy arylcopper species, with a strong withdrawing group in the benzene ring, readily undergoes an intramolecular epoxide reaction at 0 °C in high yields while the intermolecular counterpart gave a very low yield of adduct, even in refluxing THF.

For the equally substituted epoxides, reactions strongly preferred the exo attack and gave exclusively 5-membered products in high yield. For example, bromo epoxides **7**, **8**, and **9** gave only 5-membered ring alcohols in 86%, 96%, and 74% yield, respectively (entries 11, 13, and 15, Table VI). As expected, bromo epoxide **10** gave a mixture of exo and endo products in a 5.2:1 ratio due the substituent effect of the phenyl group at the epoxide (entry 16, Table VI).

Methyl substitution in epoxide **11** gave only a 6-membered ring alcohol in 53% yield (entry 17, Table VI) since substitution at the inside position of the epoxide increases nonbonded interactions for the exo-mode of ring closure.[16]

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

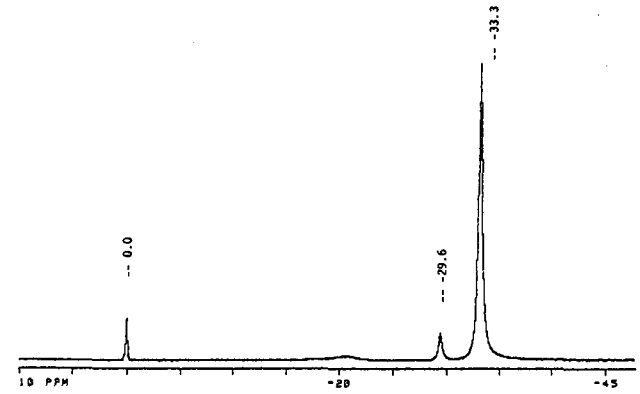


Figure 1. ^{31}P NMR spectrum of CuI·PBu_3 in THF at −80 °C. The external reference of PPh_3 was set at 0.00 ppm.

In a highly substituted case, bromo epoxide **12** readily underwent an intramolecular epoxide-opening reaction at 0 °C to furnish the 5-membered ring product in 79% yield (entry 18, Table VI).

NMR Investigations. We have attempted to characterize the active copper species using NMR spectroscopy. Phosphines, such as PBu_3 and PPh_3, have a profound effect in the reduction and subsequent reactivity of the copper(I) complex; therefore, it was believed ^{31}P NMR would help characterize the role of the phosphine in the active copper solution. Soluble in THF, CuI·PBu_3 provided a favorable system for ^{31}P NMR study. Figure 1 shows that the ^{31}P NMR spectrum of CuI·PBu_3 at −80 °C in THF contained a sharp singlet at 33.3 ppm upfield from PPh_3 reference and a small peak at 29.6 ppm. Using inert atmosphere techniques, a CuI·PBu_3-derived active copper solution was transferred via cannula to an NMR tube containing an external reference of acetone-d_6/PPh_3. Figure 2 shows the ^{31}P NMR spectrum taken at −80 °C contained a large singlet at 26.2 ppm upfield from PBu_3, with the same PPh_3 reference, gave a similar peak at 26.5 ppm upfield from the PPh_3 reference. The resonance at 26.2 ppm for the Cu* solution is believed to be free PBu_3,

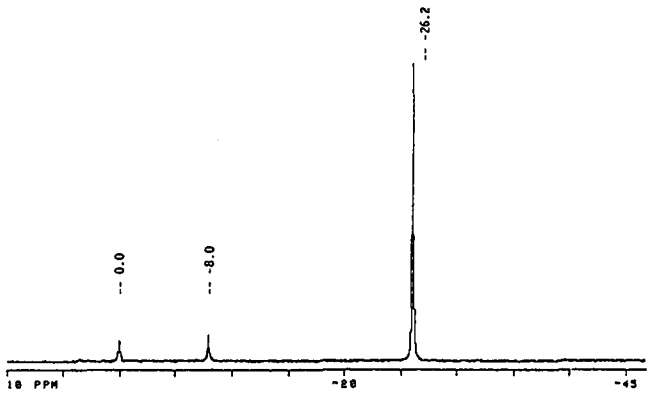


Figure 2. ^{31}P NMR of CuI·PBu_3-based active copper in THF at −80 °C.

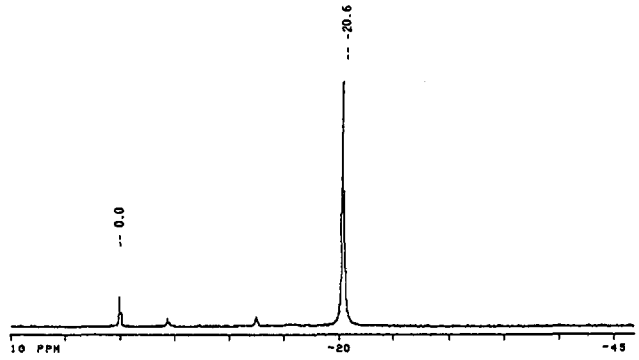


Figure 3. ^{31}P NMR spectrum of $CH_3(CH_2)_7Cu{\cdot}PBu_3$ in THF. The spectrum was recorded after the addition of 1-bromooctane to active copper at −80 °C.

and the standards accounted for 97% free phosphine in the active copper solution. The second noteworthy peak in Figure 2 at 8.0 ppm upfield from the PPh_3 reference was presumed to be from the remaining 3% PBu_3. This peak was well resolved regardless of the temperature at which the spectrum was taken. This resonance did not represent an unreactive byproduct, since it disappeared after the addition of the alkyl bromide. Addition of 1-bromooctane to the active copper solution provided a ^{31}P NMR spectrum with a lone singlet at 20.6 ppm for the $CH_3(CH_2)_7Cu{\cdot}PBu_3$ species, Figure 3. The peak at 8.0 ppm may provide evidence for an active, highly reduced, solvated copper–phosphine complex.

NMR studies of active copper derived from CuCN·*n*LiX complexes did not lend themselves to easy investigations. The first two steps of an active copper reaction involve the reduction of the CuCN·*n*LiX complex with 1 equiv of lithium naphthalenide and the formation of the organocopper species. The relative simplicity of the first steps encouraged further investigation of the reaction mixtures with ^{13}C NMR. Indeed, the ^{13}C NMR spectrum of CuCN solubilized with LiBr resulted in an observable signal at 145.0 ppm for the copper(I) nitrile. Reduction of CuCN·2LiBr at −100 °C with lithium naphthalenide provided a sample of Cu* which in turn was probed by ^{13}C NMR at temperatures ranging from −90 to −20 °C. Notably, a peak associated with LiCN (166.9 ppm) was not observed. Furthermore, the peaks associated with naphthalene were absent.

Organocopper reagents oftentimes are soluble in THF, and the NMR studies of higher order lithium cyanocuprates have proved controversial.[17] Oxidative addition involving MeI or EtBr with Cu* presumably resulted in an insoluble organocopper complex which disallowed characterization. Nitrile signals were not observed, either complexed to copper or in the form of free LiCN. As the zerovalent active copper is a one-electron reagent, the maximum ratio for oxidative addition is 1:2, respectively. Therefore, since LiCN was not observed, all nitrile ligands must be incorporated in some insoluble RCu structure. Also, addition of RX to active copper resulted in the reappearance of the naphthalene signals not observed in the Cu* spectrum. While the disappearance of the naphthalene peaks may be due to the paramagnetic Cu* species, other ^{13}C NMR signals of small amounts of additives (*n*-butyl ether) were observed at low concentrations, ca 0.02 M. The possibility of a zerovalent copper–naphthalene complex, insoluble in THF, could account for the disappearance of the naphthalene signals. Further investigations into the nature of the Cu* species are underway.

Conclusions

Both the highly reactive form of zerovalent copper and the subsequent organocopper reagents derived from CuI·PBu_3, CuI·PPh_3, and CuCN·*n*LiX copper(I) complexes have been compared, and the advantages of each reagent have been discussed. The temperature at which all three complexes are reduced plays an important role in the resulting reactivity of the zerovalent copper species. With all three Cu(I) complexes, the lowering of the reduction temperature results in a more reactive Cu* reagent. The low-temperature methodology allows for the production of Cu* from CuCN solubilized copper(I) precursors. The functionalized organocopper reagents derived from CuCN·*n*LiX undergo cross-couplings with acid chlorides as well as 1,4 conjugate addition reactions with α,β-unsatured ketones and aldehydes. Functionalized organocopper reagents produced from CuI·PBu_3 and CuI·PPh_3 are able to react with epoxides in both an inter- and intramolecular mode. The carbocyclizations of a variety of functionalized aryl bromoepoxides with Cu* allow for the facile synthesis of 2,3-dihydrobenzofuran and 3-chromanol ring systems. NMR studies of both the zerovalent copper species and the resulting organocopper complex derived from CuI·PBu_3 show that the Cu* species may exist as a mixture of free Cu(0) and a highly reduced copper–phosphine complex. In summary, several novel forms of highly reactive copper have been generated which undergo oxidative addition to a wide range of carbon–halogen bonds. Of special interest is the fact that these organocopper reagents can be generated with a wide range of functional groups.

Experimental Section

All manipulations were carried out in a Schlenk apparatus connected to a dual manifold providing vacuum and argon. The Linde prepurified-grade argon was further purified with a BASF R3-11 catalyst column at 150 °C, a phosporus pentoxide column, and a granular potassium hydroxide column. Lithium, naphthalene, CuCN, LiCl, and LiBr were weighed as needed in an argon Vaccum Atmosphere Co. drybox. All chemicals were purchased from Aldrich Chemical Co. and used without further purification unless otherwise specified. LiCl and LiBr were dried overnight at 120 °C (0.5 Torr) before being transferred to the

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drybox. CuI was purified by the method of Kauffman and Teter[18] and stored in a septum-covered round-bottom flask under argon. Tetrahydrofuran and toluene were distilled from a Na/K alloy under an argon atmosphere immediately before use. Low-temperature conditions were maintained by utilizing a Neslab Endocal ULT-80 refrigerated circulating or by utilizing dry ice/acetone baths. All temperatures reported are bath temperatures.

NMR spectra were obtained from a Nicolet NT-360, Varian VXR-200, G.E. Omega-500, or G.E. Omega-300. All NMR samples were dissolved in $CDCl_3$. ^1H NMR signals are reported in parts per million (δ) downfield from TMSCl as an internal standard. ^{13}C NMR chemical shifts (δ) were reported in reference to the 77.00 ppm NMR peak for $CDCl_3$. Infrared spectra were recorded on an Analect RFX-65 FTIR spectrophotometer. Analytical GC was performed on a Hewlett-Packard 5890A or Varian 3700 gas chromatographs equipped with 12-ft lengths of $^1/_8$-in. stainless steel tubing packed with 5% SP2100 or SP2250 on a Supelco support and interfaced with a Perkin-Elmer LCI-100 integrator. GC yields were quantified by determining response factors for pure samples and calculating the yield relative to an internal standard.

Product purification was typically performed by column chromatography with the use of Merk flash silica gel 60 (230–400 mesh). Fractions were monitored with analytical thin-layer aluminum-backed Merck 5735 indicating plates precoated with silica gel 60 F_{254} (layer thickness 0.2 mm). If the product was not UV active, the thin-layer plates were typically developed with a vanillin solution.[19] Elemental analysis were performed by Galbraith Labs, Knoxville, TN. High-resolution mass spectra were obtained from the Midwest Regional Center of Mass Spectrometry, University of Nebraska—Lincoln.

Typical Procedure for the Formation of Cu* from CuI·PBu$_3$, Table I. Lithium (10.3 mmol) and naphthalene (12.42 mmol) were weighed into a 100-mL two-neck round-bottom flask equipped with an elliptical Teflon stir bar in an argon drybox, and the flask was sealed with a septum and stopcock. Freshly distilled THF, 10 mL, was added to the flask, and the solution was stirred until all the lithium was consumed (2–3 h). CuI·PBu_3[20] (9.33 mmol) was weighed into a two-neck 50-mL round-bottom flask, equipped with a stir bar, and sealed with a septum and stopcock. The CuI·PBu_3 complex was brought to a manifold, and the contents were evacuated and refilled three times with argon. The flask was then changed with 5 mL of THF, stirred until the CuI·PBu_3 complex dissolved, and transferred via a cannula to the dark green lithium naphthalenide solution at the temperatures stated in Table I (typically 0 °C for alkyl bromides). 1-Bromooctane (3.73 mmol) and GC internal standard decane (3.50 mmol) were weighed in a vial and covered with a septum, and air was removed via a freeze–pump–thaw cycle. THF, 2 mL, was added to the vial, and its contents were added to the reddish-black Cu* solution at −78 °C via a cannula. The resulting organocopper solution was then analyzed by GC by taking a 1-mL quench into a test tube containing saturated aqueous ammonium chloride, separation of the organic layer, and drying over magnesium sulfate.

Typical Procedure for the Formation of Cu* from CuI·PPh$_3$, Table II. A two-neck round-bottom flask, equipped with a stir bar, was charged with lithium (4.16 mmol) and naphthalene (4.62 mmol) in an argon drybox and capped with both a septum and a stopcock. A second flask was charged with CuI (1.99 mmol) and PPh_3 (2.10 mmol) was capped with a septum, and the contents were evacuated and refilled three times with argon. The lithium naphthalenide was formed in THF (7 mL) for 2.5 h, and the CuI·PPh_3 complex was formed in THF (15 mL). The CuI·PPh_3 flask was cooled to −100 °C for 10 min prior to the transfer of the precooled (−35 °C) lithium naphthalenide via a cannula.[21] The reduction was allowed to continue for 10 min before cyclohexyl bromide (1.94 mmol) and decane (0.915 mmol) were transferred from a septum-covered vial in 2 mL of THF. The reaction flask was was warmed to −35 °C for 30 min prior to the neat injection of PhCOCl (2.99 mmol). After 2 h, the flask was gradually warmed to room temperature and a 2 mL reaction quench was removed for GC analysis as described above.

Typical Procedure for the Formation of Cu* from CuCN·*n*LiX, Table III. Lithium (5.43 mmol) and naphthalene (6.45 mmol) were weighed into a 100-mL, two-neck round-bottom flask equipped with a Teflon stir bar in an argon drybox, and the flask was sealed with a septum and stopcock outlet. Similarly, CuCN (5.03 mmol) and LiCl (10.5 mmol) were weighed into a 50 mL, two-neck round-bottom flask, equipped with a stir bar, and the flask was sealed with a septum and stopcock. The lithium and naphthalene were dissolved in 15 mL of THF, and the solution was cooled to 0 °C. The CuCN·2LiCl solution was transferred via cannula to the lithium naphthalenide, which has been previously cooled to −100 °C.[21] The solution was stirred for 5–10 min at −100 °C and was then ready for immediate use. The reaction with cyclohexyl bromide and subsequent cross-coupling with PhCOCl was the same as the procedure described above.

Typical Procedure for the Cross-Coupling of Functionalized Organocopper Reagents Derived from CuCN·2LiBr with Acid Chlorides, Table IV. To a freshly prepared solution of Cu* (8.01 mmol) derived from CuCN·2LiBr, prepared by the method described above and held at −100 °C, was added ethyl 4-bromobutyrate (1.95 mmol) from a vial covered with a septum in 2 mL of THF (the air in the vial was removed prior to transfer and replaced with argon using a freeze–pump–thaw cycle). The reaction was allowed to stir for 30 min during which time the solution was warmed to −35 °C. PhCOCl (4.16 mmol) was added neat via disposable syringe to the organocopper solution at −35 °C and the resulting solution for 2 h. The solution was then warmed to room temperature, quenched with $NH_4Cl_{(sat.)}$ (10 mL), washed with brine (1 × 50 mL), washed with 0.5 M NaOH (1 × 50 mL), and back-extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and separated via flash silica gel chromatography using gradient mixtures of hexanes and ethyl acetate to yield **ethyl 5-oxo-5-phenylbutanoate**,[22] 81% (1.58 mmol). R_f = 0.35 in 4:1 (v/v) hexane and ethyl acetate, respectively. IR (neat): 3060, 2960, 1735, 1690, 1600, 1580, 1450, 1375, 1240, 1205 cm^{-1}. ^1H NMR (360 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), 3.06 (t, J = 7.2 Hz, 2 H), 2.43 (t, J = 7.2 Hz, 2 H), 2.08 (t t, J = 7.2, 7.2 Hz, 2 H), 1.26 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 199.4, 173.2, 136.8, 133.0, 128.5, 128.0, 60.3, 37.4, 33.4, 19.4, 14.2.

1-Phenyl-1-nonanone.[23] ^1H NMR (200 MHz, $CDCl_3$): 7.90–8.02 (m, 2 H), 7.38–7.62 (m, 2 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, 29.2, 24.4, 22.6, 14.0.

7-Chloro-1-phenyl-1-heptanone.[5f] ^1H NMR (360 MHz, $CDCl_3$): 7.89–8.01 (m, 2 H), 7.35–7.62 (m, 3 H), 3.53 (t, J = 6.7 Hz, 2 H), 2.97 (t, J = 7.3 Hz, 2 H), 1.66–1.89 (m, 4 H), 1.30–1.60 (m, 4 H). ^{13}C (50 MHz, $CDCl_3$): 200.1, 137.1, 132.8, 128.5, 127.9, 44.8, 38.3, 32.4, 28.5, 26.7, 24.0.

Ethyl 4-Oxo-4-phenylbutanoate.[5f] ^1H NMR (200 MHz, $CDCl_3$): 7.95–8.05 (m, 2 H), 7.40–7.65 (m, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.32 (t, J = 6.5 Hz, 2 H) 2.76 (t, J = 6.6 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H). ^{13}C (50 MHz, $CDCl_3$): 198.1, 172.9, 136.6, 133.2, 128.6, 128.0, 60.6, 33.4, 28.3, 14.2.

4-Cyano-1-phenyl-1-butanone.[24] ^1H NMR (360 MHz, $CDCl_3$): 7.90–8.04 (m, 2 H), 7.36–7.65 (m, 3 H), 3.18 (t, J = 6.8 Hz, 2 H), 2.53 (t, J = 7.0 Hz, 2 H), 2.12 (tt, J = 6.9, 6.9 Hz, 2 H). ^{13}C (50 MHz, $CDCl_3$): 198.0, 136.3, 133.3, 128.6, 127.8, 119.3, 36.2, 19.6, 16.5.

4-Benzoylbenzonitrile.[25] ^1H NMR (360 MHz, $CDCl_3$): 7.40–7.95 (m, 9 H). ^{13}C (50 MHz, $CDCl_3$): 194.7, 141.2, 136.3, 133.2, 132.1, 130.1, 129.9, 128.5, 117.9, 115.6.

(18) Kauffman, G.; Teter, L. *Inorg. Synth.* **1963**, *7*, 9.
(19) *Dyeing Reagents for Thin Layer and Paper Chromatography*; E. Merck: Darmstadt, Germany, 1980.
(20) CuI·PBu_3 was prepared in a fashion analogous to that described by Kauffman and Teter: see ref 17.
(21) The −100 °C temperature is achieved in a bath of liquid N_2 and a 4:1 (v/v) mixture of hexane and Et_2O, respectively.
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3-Benzoylbenzonitrile.[5f] ^{1}H NMR (360 MHz, $CDCl_3$): 7.45–7.85 (m, 9 H). ^{13}C (50 MHz, $CDCl_3$): 193.6, 141.2, 135.8, 134.1, 133.7, 132.0, 131.3, 130.1, 129.9, 128.5, 116.9, 111.7.

(2-Carbethoxyphenyl)phenylmethanone.[26] ^{1}H NMR (360 MHz, $CDCl_3$): 8.05–8.07 (m, 1 H), 7.74–7.77 (m, 2 H), 7.51–7.63 (m, 3 H), 7.38–7.44 (m, 3 H), 4.07 (q, J = 7.1 Hz, 2 H), 1.05 (t, J = 7.1 Hz, 3 H). ^{13}C (50 MHz, $CDCl_3$): 196.9, 165.8, 141.5, 137.2, 133.0, 132.3, 130.1, 129.5, 129.3, 128.4, 127.6, 61.4, 13.6.

[4-(Chlorophenyl)phenyl]methanone.[27] ^{1}H NMR (360 MHz, $CDCl_3$): 7.74–7.78 (m, 4 H), 7.57–7.61 (m, 1 H), 7.44–7.51 (m, 4 H). ^{13}C (50 MHz, $CDCl_3$): 195.2, 138.7, 137.1, 135.7, 132.5, 131.3, 129.8, 128.5, 128.3.

Typical Procedure for the 1,4-Addition Reaction of CuCN Based Organocopper Reagents, Table V. Cu* (6.08 mmol), derived from CuCN·2LiBr, was prepared by the method described above at −100 °C, held at −100 °C for 10 min, and then warmed to −35 °C. Immediately after the Cu* solution was warmed to −35 °C, 1-chloro-6-bromohexane (1.70 mmol), in a septum covered vial mixed with 2 mL of THF, was transferred to Cu* at −35 °C and the solution stirred for 30 min. The solution was cooled to −78 °C, and after 10 min TMSCl (1.53 mmol) was injected neat prior to the dropwise addition of 2-cyclohexen-1-one (0.721 mmol) in 10 mL of THF. After 2 h at −78 °C, the flask was gradually warmed to room temperature and quenched with $NH_4Cl_{(sat.)}$. The organic layer was doubled in volume with Et_2O and extracted with H_2O (50 mL) and $NaCl_{(sat.)}$ (50 mL). The organic layer was dried over $MgSO_4$, filtered, and reduced in volume, and the remaining oil was subjected to flash silica gel chromatography (75 mL).

3-(3-Chlorohexyl)cyclohexanone (1f)[5f] was isolated in 82% yield (0.590 mmol). R_f = 0.15 in 9:1 (v/v) hexane and ethyl acetate, respectively. IR (neat): 2930, 2860, 1715, 1450, 1430, 1225 cm^{-1}. ^{1}H NMR (200 MHz): 3.53 (t, J = 6.65 Hz, 2 H), 2.47–1.31 (m, 19 H). ^{13}C NMR (125 MHz): 212.0, 48.1, 44.9, 41.4, 38.9, 36.3, 32.5, 31.2, 28.8, 26.7, 26.4, 25.2. Anal. Calcd for $C_{12}H_{21}ClO$: C, 66.50; H, 9.76; Cl, 16.36. Found: C, 66.26; H, 10.02; Cl, 16.12.

3-*n*-Octylcyclohexanone (1a).[5f] ^{1}H NMR (200 MHz): 1.50–2.50 (m, 9 H), 1.15–1.45 (m, 14 H), 0.88 (t, J = 6.5 Hz, 3 H). ^{13}C NMR (125 MHz): 212.2, 48.2, 39.0, 36.6, 31.8, 31.3, 29.6, 29.5, 29.2, 26.6, 25.3, 22.6, 14.0.

3-(3-Carbethoxypropyl)cyclohexanone (1c).[5f] ^{1}H NMR (500 MHz): 4.13 (q, J = 7.2 Hz, 2 H), 1.26–2.50 (m, 15 H including a triplet at 2.29, J = 7.2 Hz), 1.26 (t, J = 7.2 Hz, 2 H). ^{13}C NMR (125 MHz): 211.7, 173.4, 60.2, 47.9, 41.4, 38.7, 35.8, 34.2, 30.9, 25.1, 22.0, 14.2. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.28; H, 9.32.

3-(3-Cyanopropyl)cyclohexanone (1e).[5f] ^{1}H NMR (200 MHz): 2.36 (t, J = 6.9 Hz, 2 H), 1.22–2.50 (m, 13 H). ^{13}C NMR (125 MHz): 211.0, 199.3, 47.6, 41.2, 38.2, 35.3, 30.9, 24.9, 22.5, 17.1.

3-Cyclohexylcyclohexanone (1g).[2a] ^{1}H NMR (200 MHz): 2.47–0.84 (m, 20 H). ^{13}C NMR (125 MHz): 212.8, 45.5, 44.6, 42.6, 41.6, 29.9, 29.8, 28.4, 26.5, 26.4, 25.6.

3-Phenylcyclohexanone (1h).[28] ^{1}H NMR (200 MHz): 7.31–7.34 (m, 2 H), 7.21–7.25 (m, 3 H), 2.97–3.04 (m, 1 H), 2.34–2.61 (m, 4 H), 2.06–2.17 (m, 2 H), 1.75–1.89 (m, 2 H). ^{13}C NMR (125 MHz): 211.0, 144.3, 128.6, 126.6, 126.5, 48.9, 44.7, 41.1, 32.7, 25.5.

Ethyl 5-Methyl-7-oxononanoate (2a). ^{1}H NMR (200 MHz): 4.13 (q, J = 7.25 Hz, 2 H), 2.36–2.43 (m, 3 H), 2.03 (m, 1 H), 1.50–1.54 (m, 2 H), 1.15–1.34 (m, 5 H, contains a triplet at 1.26, J = 7.25 Hz, 3 H), 1.04 (t, J = 7.3 Hz, 3 H), 0.90 (d, J = 6.85 Hz, 3 H). ^{13}C NMR (125 MHz): 211.3, 173.6, 60.1, 49.5, 36.4, 36.2, 34.3, 28.9, 22.3, 19.7, 14.2, 7.7.

3-Phenylundecanal (3a). R_f = 0.28 in 10:1 (v/v) hexane and ethyl acetate, respectively. IR (neat): 2954, 2925, 2854, 1726, 1454, 761 cm^{-1}. ^{1}H NMR (500 MHz): 9.66 (s, 1 H), 7.18–7.32 (m, 5 H), 3.17 (m, 1 H), 2.71 (d, J = 7.4 Hz, 2 H), 1.64 (m, 1 H), 1.14–1.27 (m, 13 H), 0.87 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz): 202.1, 143.9, 128.6, 127.4, 126.5, 50.6, 40.0, 36.6, 31.8, 29.5, 29.4, 29.2, 27.2, 22.6, 14.1.

Ethyl 7-Oxo-5-phenylheptenoate (3b). R_f = 0.10 in 9:1 (v/v) hexane and ethyl acetate, respectively. ^{1}H NMR (500 MHz): 9.66 (t, J = 1.9 Hz, 1 H), 7.16–7.35 (m, 5 H), 4.09 (q, J = 7.2 Hz, 2 H), 3.11–3.26 (m, 1 H), 2.72 (dd, J = 7.3, 2.0 Hz, 1 H), 2.25 (t, J = 7.5 Hz, 3 H), 1.17–1.71 (m, 7 H). ^{13}C NMR (50 MHz): 201.6, 173.3, 143.3, 128.7, 127.4, 126.7, 60.2, 50.5, 39.8, 35.8, 33.9, 22.7, 14.2.

Typical Procedure for Intramolecular Epoxide-Opening Reactions of Phosphine-Based Epoxy Arylcopper Reagents, Table VI. Lithium (9.09 mmol) and naphthalene (9.97 mmol) in freshly distilled THF (20 mL) were stirred at ambient temperature for 2 h under argon. To this dark green preformed lithium naphthalenide solution was added via a cannula a cold (0 °C) solution of CuI/PBu_3, which was prepared by stirring the preformed CuI·PBu_3 complex (8.28 mmol) and excess PBu_3 (11.1 mmol) in THF (20 mL). After being stirred at 0 °C for 40 min, the reaction mixture was then cooled to −5 °C (acetone–ice bath). A solution of ethyl 3-bromo-4-(2,3-epoxybutoxy)benzoate (1.43 mmol) in THF (10 mL) was added to Cu* at −5 °C. The reaction mixture was stirred at −5 to 0 °C and monitored by thin-layer chromatography. The epoxide-opening reaction proceeded readily at −5 to 0 °C and was completed after stirring at −5 to 0 °C for 6 h. The reaction was quenched by adding $NH_4Cl_{(sat.)}$ at 0 °C. The reaction mixture was stirred at room temperature until it turned into two clear layers, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined ether layers were washed with H_2O (10 mL) and were dried over $MgSO_4$. Upon removal of organic solvent under reduced pressure, the resulting residue was chromatographed twice on silica gel (100 mL, eluted with hexane/EtOAc mixtures) to give **ethyl 2,3-dihydro-3-(1-hydroxyethyl)-5-benzofurancarboxylate** as a colorless oil (74% yield). IR (neat): 3100–3700, 2978, 1711, 1610, 1491, 1367, 1290, 1259, 1173, 1109, 769 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): 7.88–7.98 (m, 2 H), 6.80 (d, J = 8.0 Hz, 1 H), 4.71 (dd, J = 9.3, 5.8 Hz, 1 H), 4.64 (dt, J = 9.3, 1.0 Hz, 1 H), 4.33 (q, J = 7.1 Hz, 2 H), 4.05–4.15 (m, 1 H), 3.49 (m, 1 H), 1.84 (br s, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.26 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.4, 164.8, 131.7, 127.6, 126.7, 122.9, 109.3, 73.4, 68.7, 60.7, 48.7, 20.5, 14.3. MS (EI) m/e (relative intensity): 236 (M^+, 19.1), 192, 191, 163, 119, 91 (100). HRMS: calcd for $C_{13}H_{16}O_4$ m/e 236.1049, found m/e 236.1060.

2,3-Dihydro-3-benzofuranmethanol.[29] IR (neat): 3100–3600, 1595, 1480, 1225, 745 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 7.11–7.26 (m, 2 H), 6.89 (dd, J = 7.4, 1.0 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 4.64 (t, J = 9.0 Hz, 1 H), 4.48 (dd, J = 9.1, 5.3 Hz, 1 H), 3.81 (m, 2 H), 3.56–3.73 (m, 1 H), 1.60 (d, J = 5.9 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 160.5, 128.9, 127.0, 124.6, 120.4, 109.8, 74.0, 64.9, 44.6.

3,4-Dihydro-2*H*-1-benzopyran-3-ol.[30] Mp: 75–77 °C (lit.[28] mp 79 °C). IR (neat): 3100–3650, 1595, 1485, 1225, 745 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): 7.12 (t, J = 7.8 Hz, 1 H), 7.06 (d, J = 7.5 Hz, 1 H), 6.89 (t, J = 7.4 Hz, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 4.27 (m, 1 H), 4.05–4.16 (m, 2 H), 3.11 (dd, J = 16.6, 4.8 Hz, 1 H), 2.81 (dd, J = 16.6, 4.7 Hz, 1 H), 1.93 (d, J = 7.3 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 153.8, 130.5, 127.6, 121.1, 119.3, 116.6, 69.7, 63.3, 33.6.

2,3-Dihydro-5-carbethoxy-3-benzofuranmethanol. IR (neat): 3150–3650, 1711, 1612, 1288, 1257, 771 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 7.85–7.93 (m, 2 H), 6.75–6.83 (m, 2 H), 4.72 (t, J = 9.1 Hz, 1 H), 4.57 (dd, J = 9.2, 5.4 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 3.57–4.92 (m, 3 H), 2.43 (br s, 1 H), 1.37 (t, J = 7.1 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.5, 164.5, 131.7, 127.8, 126.4, 122.9, 109.3, 75.1, 64.6, 60.7, 43.9, 14.3. MS (EI) m/e (relative intensity): 222 (M^+, 42.1), 191 (100), 177, 163, 145, 119, 91. HRMS calcd for $C_{12}H_{14}O_4$ m/e 222.0892, found m/e 222.0891.

6-Carboethoxy-3,4-dihydro-2*H*-1-benzopyran-3-ol. ^{1}H NMR (360 MHz, $CDCl_3$): 7.81 (m, 2 H), 6.87 (d, J = 8.3 Hz, 1 H), 4.35 (m, 2 H), 4.07–4.23 (m, 3 H), 3.13 (dd, J = 16.3, 4.4 Hz, 1 H), 2.85 (dd, J = 16.3, 4.9 Hz, 2 H), 1.96 (d, J = 5.9 Hz, 1 H), 1.26 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.4, 157.8, 132.3, 129.2, 122.7, 119.3, 116.2, 69.9, 62.4, 60.4, 33.1, 14.0.

(26) Known compound; spectral data match those published in *Sadtler*, ^{13}C NMR 8626.

(27) Known compound; spectral data match those published in *Sadtler*; IR, 8632; ^{1}H NMR 3620; ^{13}C NMR 1758.

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2,3-Dihydro-5-methyl-3-benzofuranmethanol.[29] IR (neat): 3100–3650, 1595, 1245, 805 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.03 (br s, 1 H), 6.96 (dm, J = 8.1 Hz, 1 H), 6.70 (d, J = 8.1 Hz, 1 H), 4.62 (t, J = 9.0 Hz, 1 H), 4.45 (dd, J = 9.1, 5.4 Hz, 1 H), 3.80 (m, 2 H), 3.61 (m, 1 H), 2.29 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 158.0, 129.5, 129.0, 127.1, 125.0, 109.0, 74.0, 64.6, 44.5, 20.5.

2,4-Dihydro-6-methyl-2*H*-1-benzopyran-3-ol. IR (neat): 3100–3650, 1590, 1495, 1245, 1215, 805 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 6.93 (dm, J = 8.2 Hz, 1 H), 6.87 (br s, 1 H), 6.75 (d, J = 8.2 Hz, 1 H), 4.24 (m, 1 H), 4.02–4.12 (m, 2 H), 3.07 (dd, J = 16.6, 4.7 Hz, 1 H), 2.77 (dd, J = 16.6, 4.6 Hz, 2 H), 2.26 (s, 3 H), 2.01 (d, J = 6.2 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 151.4, 103.5, 130.0, 128.0, 119.0, 116.0, 69.4, 63.0, 33.2, 20.2.

2,3-Dihydro-3-(1-hydroxyethyl)benzofuran. IR (neat): 3130–3620, 1595, 1485, 1230, 750 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.22 (d, J = 7.4 Hz, 1 H), 7.16 (t, J = 7.8 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 4.62 (dd, J = 9.1, 5.6 Hz, 1 H), 4.55 (t, J = 9.1 Hz, 1 H), 4.07 (m, 1 H), 3.47 (m, 1 H), 1.51 (br s, 1 H), 1.25 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 160.7, 128.8, 127.0, 124.9, 120.2, 109.6, 72.3, 68.8, 49.3, 20.4. MS (EI) m/e (relative intensity): 164 (M^+, 33.6), 146, 120 (100), 91. HRMS: calcd for $C_{10}H_{12}O_2$: m/e 164.0837, found m/e 164.0838.

5-Chloro-2,3-dihydro-3-(1-hydroxyethyl)benzofuran. IR (neat): 3100–3650, 2970, 2895, 1481, 1236, 1108, 812 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 7.19 (d, J = 2.2 Hz, 1 H), 7.11 (dd, J = 8.5, 2.2 Hz, 1 H), 6.71 (d, J = 8.5 Hz, 1 H), 4.62 (dd, J = 9.2, 5.8 Hz, 1 H), 5.58 (t, J = 9.1 Hz, 1 H), 4.06 (m, 1 H), 3.46 (m, 1 H), 1.49 (d, J = 3.9 Hz, 1 H), 1.24 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 159.3, 129.1, 128.5, 125.0, 124.8, 110.4, 72.9, 68.5, 49.1, 20.2. MS (EI) m/e (relative intensity): 200 (M^+, 9.9), 198, 154, 125 (100). HRMS: calcd for $C_{10}H_{11}O_2{}^{37}Cl$ m/e 200.0418, found m/e 200.0415.

5-Chloro-2,3-dihydro-3-(1-hydroxy-1-phenylethyl)benzofuran. Mp: 100–101 °C. IR (neat): 3100–3650, 3064, 3032, 2958, 2895, 1481, 1466, 1240, 814, 766, 702, 687 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 7.22–7.43 (m, 5 H), 7.03 (ddd, J = 8.5, 2.3, 0.7 Hz, 1 H), 6.65 (d, J = 8.5 Hz, 1 H), 6.36 (dd, J = 2.3, 0.9 Hz, 1 H), 4.72 (dd, J = 7.2, 2.7 Hz, 1 H), 4.71 (dd, J = 9.3, 5.3 Hz, 1 H), 4.53 (t, J = 9.2 Hz, 1 H), 3.72 (m, 1 H), 2.24 (d, J = 2.7 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 159.4, 141.4, 128.6, 128.6, 128.4, 128.4, 126.7, 125.4, 124.6, 110.4, 75.7, 74.1, 49.6. MS (EI) m/e (relative intensity): 262 (0.3), 260 (0.7), 154, 128, 107 (100). HRMS: calcd for $C_{15}H_{15}O_2{}^{35}Cl$ m/e 260.0604, found m/e 260.0604. Anal. Calcd for $C_{15}H_{13}O_2Cl$: C, 69.10; H, 5.03. Found: C, 68.70; H, 5.00.

6-Chloro-4-phenyl-2*H*-1-benzopyran-3-ol. Mp: 67–69 °C. IR (neat): 3130–3700, 3062, 3030, 2960, 2931, 1485, 1257, 1232, 816, 752, 702 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 7.08–7.40 (m, 6 H), 6.83–6.90 (m, 2 H), 3.94–4.22 (m, 4 H), 2.30 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 152.8, 141.8, 130.6, 129.0, 128.8, 128.2, 127.3, 126.0, 123.9, 118.0, 69.3, 66.9, 50.0. MS (EI) m/e (relative intensity): 262 (10.6), 260 (30.1), 215 (100), 181, 152, 107. HRMS: calcd for $C_{15}H_{13}O_2{}^{35}Cl$ m/e 260.0604, found m/e 260.0608.

6-Chloro-4-phenyl-2*H*-1-benzopyran-3-ol. IR (neat): 3130–3610, 2974, 2931, 1487, 1250, 1180, 1120, 1038, 816 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 7.05 (dd, J = 8.6, 2.5 Hz, 1 H), 6.99 (m, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 3.90 (dd, J = 11.0, 2.1 Hz, 1 H), 3.78 (dt, J = 11.0, 1.0 Hz, 1 H), 2.81 (d, J = 16.6 Hz, 1 H), 2.71 (br d, J = 16.6 Hz, 1 H), 2.40 (br s, 1 H), 1.31 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 151.7, 129.7, 127.5, 125.7, 121.8, 117.8, 73.6, 65.6, 38.9, 24.7. MS (EI) m/e (relative intensity): 200 (17.8), 198 (57.0), 155, 141, 77, 57 (100). HRMS: calcd for $C_{10}H_{11}O_2{}^{35}Cl$ m/e 198.0448, found m/e 198.0444.

Ethyl 2,3-Dihydro-3-(2-hydroxy-2-propyl)-5-benzofurancarboxylate. IR (neat): 3180–3620, 2978, 1711, 1610, 1288, 1265, 773, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 8.01 (m, 1 H), 7.91 (ddd, J = 8.4, 1.9, 0.5 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 4.68 (dd, J = 9.6, 4.7 Hz, 1 H), 4.60 (t, J = 9.3 Hz, 1 H), 4.32 (qm, J = 7.1 Hz, 2 H), 3.47 (dd, J = 8.8, 4.7 Hz, 1 H), 2.23 (br s, 1 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.25 (s, 3 H), 1.19 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): 166.5, 164.8, 131.5, 127.8 (2 C), 122.6, 109.1, 74.4, 72.2, 60.6, 52.5, 26.6, 14.3. MS (EI) m/e (relative intensity): 250 (M^+, 0.5), 235, 192 (100), 163, 146, 118, 91, 59. HRMS: calcd for $C_{14}H_{18}O_4$ m/e 250.1205, found m/e 250.1209.

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