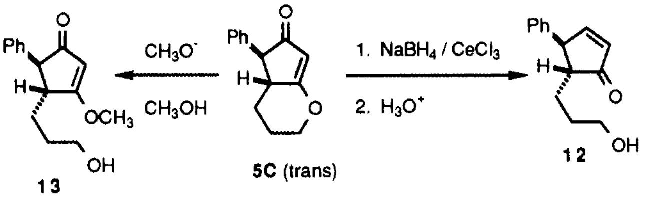
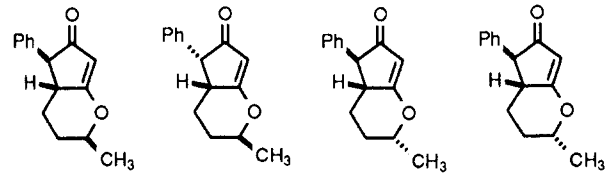
Scheme IV



in many prostaglandin synthesis intermediates,[9] proceeded in 51% yield. Addition of chromium hexacarbonyl to the reaction in entry C led to an increase in the trans:cis ratio. Thermolysis of complex **4J** in aqueous dioxane led to a 40:35:14:11 mixture of four stereoisomers in 61% yield. The major isomer (trans–trans) differs from the second-most abundant one (trans–cis) only in the configuration of the substituents on the five-membered ring. The methyl group apparently controls the overall stereochemistry of the reaction since the six-membered ring substituents are diequatorial in both of the two major isomers. Reactions involving terminal alkynes (entries B, E, H, I) were less efficient, and highly sensitive to ring size, giving reasonable yields of cycloadducts only in entry H. A similar dependence with regard to length of tether has been observed in the intramolecular reaction of terminal alkynes with arylcarbene–chromium complexes.[2,10]

5J



trans-trans trans-cis cis-trans cis-cis

The vinylogous ester functionality is susceptible to further synthetic manipulation.[12] Reaction of compound **5C** (trans) with sodium borohydride/cerium trichloride,[13] followed by aqueous acid, led to the enone alcohol **12** (trans) in 68% yield (93% based on recovered starting material) (Scheme IV). The corresponding cis isomer underwent the same conversion to give compound **12** as a 3:1 cis:trans mixture. Treatment of compound **5C** (trans) with sodium methoxide/methanol led to the vinylogous ester alcohol **13**; both the cis and the trans isomers of **5C** led to the trans compound **13**.

In summary, the intramolecular reaction between cyclopropylcarbene–chromium complexes and alkynes provides cyclopentane-fused oxygen heterocycles in good yield. The products obtained are further susceptible to ring opening reactions. We are actively exploring further the synthetic potential of these processes.

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Supplementary Material Available: Procedures for the above experiments and spectral data for the compounds reported in these studies (57 pages). Ordering information is given on any current masthead page.

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Direct Metalation of *p*-Bromopolystyrene Using Highly Reactive Copper and Preparation and Reaction of Highly Reactive Copper Bound to an Insoluble Polymer

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Summary: Polymeric organocopper reagents have been prepared involving highly reactive copper with cross-linked *p*-bromopolystyrene and phosphine-containing polymers.

Chemical transformations of insoluble materials such as polymers are normally possible only with soluble reagents present in a solvent system surrounding and permeating the polymer.[1] Accordingly, the direct metalation of a polymer such as the formation of a Grignard reagent from *p*-bromopolystyrene with magnesium metal is not possible even if the magnesium is highly reactive.[2] This problem was recently overcome by the use of the soluble reagent magnesium anthracene.[2] In this paper, we would like to report the first direct copper metalation of halogen-containing polymers using the soluble zero-valent copper reagent recently reported.[3] The resulting copper-derivatized polymers can be reacted with a variety of electrophiles to yield highly functionalized polymers. Also, we would like to report that the soluble zero-valent copper reagent can be prepared attached to a phosphine-containing polymer. This insoluble zero-valent copper will react with alkyl and aryl halides to generate organocopper

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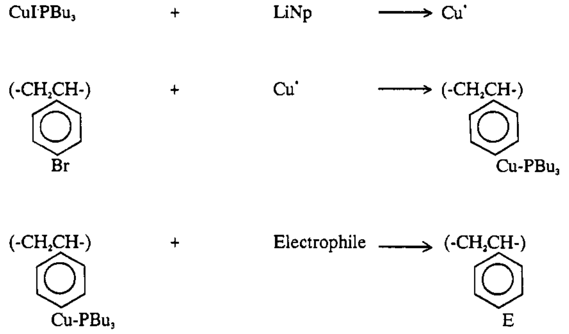
(1) For reviews concerning the functionalization of polymers and their uses: Sherrington, D. C., Hodge, P., Eds. *Synthesis and Separations using Functional Polymers*; John Wiley and Sons: New York, 1988; pp 43–122, and references therein.

(2) (a) Itsuno, S.; Darling, G. D.; Stover, H. D. H.; Frêchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4645 and references therein. (b) Harvey, S.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1988**, *10*, 652.

(3) (a) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. *High Energy Processes in Organometallic Chemistry*, ACS Symposium Series No. 333; American Chemical Society: Washington, DC 1987; Chapter 14, p 223. (b) Wu, T. C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5057. (c) Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056. (d) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513. (e) Wu, T. C.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 6753. (f) Rieke, R. D.; Wehmeyer, R. M.; Wu, T. C.; Ebert, G. W. Recent Developments in Organocopper Chemistry; Lipshutz, B. H., Ed.; Tetrahedron Symposia-in-print Number 35; *Tetrahedron* **1989**, *45*, 443.

Scheme I



reagents capable of reacting with a variety of electrophiles.

Functionalization of *p*-Bromopolystyrene. The preparation of copper-derivatized polymers has been limited to metathesis approaches. *p*-Bromopolystyrene, for example, was converted into the aryl cuprate by first forming the organolithium reagent by treatment with n-BuLi followed by the addition of a copper(I) salt.[4] We would like to report that direct copper metalation has been achieved by the reaction of insoluble polymers with the zero-valent copper reagent recently reported by our group.[3,5] The highly reactive soluble copper was prepared by the lithium naphthalenide reduction of a tributylphosphine/copper(I) iodide complex. An excess of this highly reactive copper was added to a 2% cross-linked *p*-bromopolystyrene[6] at room temperature in THF under inert atmosphere conditions. The resulting black solution was then stirred at room temperature for 80 h at which time the appropriate electrophile was added, the mixture was stirred for 80 h at room temperature, and, upon purification,[7] the functionalized polymer was obtained.

The arylcopper species is shown (Scheme I) as an arylcopper–phosphine complex. However, the exact nature of this species has not been determined by isolation or by spectral data. Rather the phosphine complex is inferred by the dependence of the reactivity of the organocopper reagent on the type of phosphine present. The more electron donating the phosphine the more nucleophilic the arylcopper reagent.[8,9]

Table I. Polymers Prepared from the Addition of an Electrophile to the Organocopper Reagent Formed from Cross-Linked *p*-Bromopolystyrene and Active Copper

			functional yield,[b] %	
entry	electrophile	product[a]	A	B
1	H_2O	PS—H	89	75
2	D_2O	PS—D	78	66
3	PhCOCl	PS—COPh	70	43
4	*p*-BrC_6H_4COCl	PS—COC_6H_4(*p*-Br)	40	26
5	*p*-ClC_6H_4COCl	PS—COC_6H_4(*p*-Cl)	25	22

[a] Elemental analyses, FT-IR, and EI-MS. See ref 10. [b] See ref 11. A: 2.2 mmol Br/g *p*-bromopolystyrene, DF = 0.31. B: 5.5 mmol Br/g *p*-bromopolystyrene, DF = 0.98.

Electrophiles studied to date include protonation as well as benzoyl chlorides (Table I). Volhard analysis of the filtrate after reaction of *p*-bromopolystyrene with the active copper indicated that approximately 45–88% of the bromophenyl groups had been converted into the corresponding arylcopper species. There was a greater conversion to the arylcopper species in the less substituted *p*-bromopolystyrene (2.2 mmol Br/g, DF = 0.31) than in the more highly substituted *p*-bromopolystyrene (5.5 mmol Br/g, DF = 0.98). Addition of electrophiles resulted in approximately 65–95% of these groups being functionalized, again depending on the starting *p*-bromopolystyrene. The functional yields and characterization of the polymers were determined by elemental analyses, diffuse-reflectance FT-IR, and low-resolution EI-MS. Attempts to convert all the bromophenyl groups into arylcopper reagents have not been successful so far. As the active copper species is assumed to be a copper–phosphine cluster,[12] size exclusion within the polymer may prevent complete reaction. Studies are currently underway to further probe this observation. One consequence of the direct metalation is that polymers containing esters, nitriles, ketones, and less reactive halogens (as Cl) can now be converted into the organocopper reagent without involvement of the functional groups. Accordingly, highly functionalized polymers should now be possible using this approach.

Polymer-Supported Active Copper. While the exact nature of the highly reactive zero-valent copper reagent

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(4) Itsuno, S.; Darling, G. D.; Lu, P. Z.; Frèchet, J. M. J. *Polym. Mater. Sci. Eng.* **1987**, *57*, 570.

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(6) In a typical reaction, Li (10.36 mmol) and naphthalene (13.51 mmol) in freshly distilled THF (15 mL) were stirred at room temperature under argon for 2 h. CuI (9.08 mmol) and PBu_3 (12.31 mmol) in THF (15 mL) were stirred for 1 h at room temperature under argon. To this colorless, preformed CuI·PBu_3 solution was transferred via cannula at 0 °C the preformed lithium naphthalenide solution. The resultant reddish-black solution of active copper was stirred for 30 min at 0 °C and transferred via cannula to a solution of *p*-bromopolystyrene (2.24 mmol, based on 2.2 mmol Br/g polymer, DF = 0.31, 2% DVB cross-linking) in THF (35 mL) at room temperature. The polymer was stirred at room temperature under argon for 24 h prior to the addition of the active copper. The resultant black solution was stirred at room temperature for 80 h followed by the addition of benzoyl chloride (14.64 mmol) in THF (10 mL). The solution was stirred for an additional 80 h at room temperature at which time H_2O (10 mL) was added and stirred for an additional 24 h at room temperature. The polymer was then filtered and purified (see ref 7) to yield the functionalized polymer.

(7) Purification of the polymer included washing the polymer with several portions of THF, MeOH, and H_2O. The polymer was then stirred in MeOH for 24 h at room temperature and washed with THF, MeOH, $CHCl_3$, and H_2O. The polymer was dried under vacuum at room temperature for 24 h.

(8) The relationship between donating ability of the phosphine and reactivity of generated organocopper species has been found by Wehmeyer, see refs 3c and 3d.

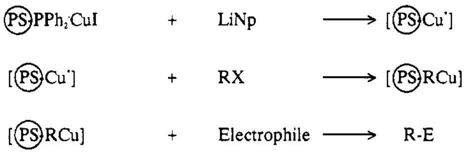
(9) (a) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953, 2956. (b) Tolman, C. A. *Chem. Rev.* **1977**,313. (c) *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Ed.; Pergamon Press: Oxford, 1979; Vol. 2, Chapter 10. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(10) The functionalized polymers showed distinctive peaks at 2260 cm^{-1} for the C–D stretch (entry 2) and 1660–65 cm^{-1} for the carbonyl stretching frequency (entries 3–5). A decrease in peak intensity for the carbon–bromine frequencies was observed at 1487, 1408, 1072, 1010, and 718 cm^{-1} when compared to the starting cross-linked *p*-bromopolystyrene (entries 1–3 and 5). Low-resolution EI-MS yielded M^+ peaks at 104 *m/e* (entry 1), at 105 *m/e* (entry 2), and at 208 *m/e* (entry 3) for the functionalized monomeric units. A fragment was observed at 105 *m/e* for $C_7H_5O^+$ (entry 3). The EI-MS of entries 4 and 5 did not yield M^+ peaks for the functionalized monomeric units but rather fragmentation patterns characteristic of the monomeric units. Entry 4 gave a fragment at 207 *m/e* for $C_{15}H_{11}O^+$ with the loss of HBr from the functionalized monomeric unit and at 183 *m/e* for a $C_7H_4OBr^+$ fragment. Another fragment was observed at 105 *m/e* for the loss of $C_7H_5O^+$. The EI-MS of entry 5 gave a fragment at 139 *m/e* for $C_7H_4OCl^+$ as well as at 105 m/e for $C_7H_5O^+$. The EI-MS of entries 1-5 also showed the molecular ion peaks for the 2% cross-linked monomer, the starting *p*-bromopolystyrene and polystyrene monomeric units.

(11) The functional yields were based on elemental analyses of the polymers with a 2% DVB cross-linking, partial retention of bromine on the rings (2.2 mmol, DF = 0.31, 10–40%; 5.5 mmol; DF = 0.98, 25–50%), partial formation of the polystyrene monomer (2.2 mmol, 10–25%; 5.5 mmol, 20–45%) and formation of the functionalized monomer.

(12) Rieke, R. D.; Wu, T. C.; Stinn, D. E.; Wehmeyer, R. M. *Synth. Commun.* **1989**, *19*, 1833.

Scheme II



is not known, it has proven to be a valuable new synthetic approach to many novel functionalized organocopper reagents.[3] However, in some instances the presence of the phosphine causes considerable separation problems in the final workup. In an attempt to circumvent this problem, we prepared the zero-valent copper reagent bound to a phosphine-containing polymer. The basic approach involved the reduction of a phosphine-bound polymer loaded with CuI. The preparation of a polymer-bound triphenylphosphine copper(I) iodide has been reported by Schwartz and San Filippo.[13] We developed a simpler approach by stirring a 1:1 solution of copper(I) iodide and the polymer-bound triphenylphosphine[14] in THF at room temperature for 1 week. Both methods resulted in a 88–96% incorporation of the CuI into the polymer as determined by elemental analyses. The analyses indicated a 1:1 ratio of CuI per polymer-bound PPh_3 that suggests a single-site attachment of the CuI with the phosphine.

The polymer-bound triphenylphosphine/copper(I) iodide complex is a tan solid and upon reduction by lithium naphthalenide in THF yielded a black solid. The reduction was accomplished at 0 °C for 1 h using 1.10 equiv of lithium naphthalenide. The polymer containing the active copper was washed with several portions of THF at room temperature using Schlenk glassware. This removed any traces of naphthalene, which has also been found to hinder product purification in some instances. Elemental analyses of the polymer containing the active copper species suggested a quantitative amount of copper in the polymer.[15] For the reactions,[16] the polymer containing the active copper was suspended in THF and cooled to −35 °C. The alkyl halide was added to the black solution and then stirred at −35 °C for 30 min. Aryl halides required warming to 0 °C as well as longer reaction times. The electrophile was added to the organocopper species at −35 °C. The reaction was stirred for 90 min at −35 °C and then at room temperature for an additional 60 min. The reaction mixture was quenched with saturated $NH_4Cl(aq)$, the polymer was filtered, and the filtrate was extracted with diethyl ether. The product was purified via column chromatography. Preliminary results suggest the organocopper species may exist in an equilibrium between the polymer-bound species and the free species in solution. However, the reactions with the electrophiles are most likely occurring with the polymer-bound species as RCu reagents are normally not considered very reactive in these cross-coupling reactions. Stereo- as well as regioselective effects induced by the polymer-bound phosphine are being examined (Scheme II, Table II).

Table II. Functionalized Products Formed from the Reaction of the Polymer Containing Active Copper with Various Alkyl/Aryl Halides and Electrophiles

entry	RX	electrophile	product[a]	yield,[b] %
1	$Br(CH_2)_7CH_3$	PhCOCl	$PhCO(CH_2)_7CH_3$	78
2	$Br(CH_2)_3CO_2Et$	PhCOCl	$PhCO(CH_2)_3CO_2Et$	63
3	$Br(CH_2)_3CN$	PhCOCl	$PhCO(CH_2)_3CN$	73
4	$Br(CH_2)_6Cl$	PhCOCl	$PhCO(CH_2)_6Cl$	65
5	$Br(CH_2)_3CO_2Et$	$ClCO_2Et$	$EtO_2C(CH_2)_3CO_2Et$	43
6	$Br(CH_2)_7CH_3$	PhCHO	$PhCH(OH)(CH_2)_7CH_3$	45[c]
7	$Br(CH_2)_7CH_3$	2-cyclohexen-1-one	3-octylcyclohexanone	10[d]
8	7-bromo-1,2-epoxyheptane		cycloheptanol	22
9	$Br(CH_2)_7CH_3$	1,2-epoxybutane	3-dodecanol	79
10	$p\text{-}IC_6H_4CO_2Et$	PhCOCl	$p\text{-}EtO_2CC_6H_4COPh$	45[e]
11	$p\text{-}BrC_6H_4CH_3$	PhCOCl	$p\text{-}CH_3C_6H_4COPh$	56[d,f]

[a] All products were compared with authentic samples. [b] Isolated yields. [c] Reaction also yielded a minor amount of the oxidized product, 1-phenyl-1-nonanone, after isolation. [d] Yield was determined by GC based on chromatographically pure sample. [e] Aryl iodide was added to polymer active copper at −35 °C for 30 min and then warmed to 0 °C for 30 min before addition of electrophile. [f] Aryl bromide was added to polymeric active copper at 0 °C for 2.5 h before addition of electrophile.

The isolated yields are compatible with previous results obtained using highly reactive copper involving the formation of functionalized ketones. However, lower yields were observed for 1,4-conjugate additions and intramolecular epoxide-opening reactions.[3c–e] This correlates with what was observed when using the PPh_3-based active copper instead of the PBu_3-based active copper (entries 7 and 8). Studies using polymer-bound trialkylphosphines are underway.

In conclusion, we have prepared polymers containing highly reactive copper under mild conditions which will undergo oxidative addition to organic halides. The resulting organocopper reagents can be cross-coupled with various electrophiles. Second, we have carried out the direct formation of organocopper reagents on an insoluble polymer by treating a cross-linked *p*-bromopolystyrene with highly reactive copper.

Acknowledgment. The financial support provided by the National Institutes of Health (Grant GM35153) is gratefully acknowledged. We would like to thank Dr. Dean E. Stinn and Dr. T. C. Wu for their helpful suggestions.

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[13] (a) Schwartz, R. H.; San Filippo, J., Jr. *J. Org. Chem.* **1979**, *44*, 2705. (b) Mulalidharan, S.; Freiser, H. *Inorg. Chem.* **1988**, *27*, 3251.

[14] The polymer-bound triphenylphosphine; (PS)-PPh_2, 9.5% P, 3.06 mmol PPh_3/g polymer with 2% DVB cross-linking, was purchased from Aldrich.

[15] The amount of active copper in the polymer was based on elemental analyses and the percent CuI incorporation into the polymer (2.69 mmol CuI/g polymer). This correlates to 2.69 mmol Cu^*/g polymer.

[16] In a typical reaction, Li (2.17 mmol) and naphthalene (2.53 mmol) in freshly distilled THF (15 mL) were stirred under argon at room temperature for 2 h. The polymer-bound triphenylphosphine/copper(I) iodide complex (1.76 mmol CuI, based on 2.69 mmol CuI/g polymer) was stirred in THF (30 mL) overnight prior to use. The lithium naphthalenide solution was transferred via cannula to the complex and stirred for 1 h at 0 °C. A Schlenk apparatus was used to isolate the polymer containing the active copper. The black solid was washed with several portions of THF (10 mL), and later THF (20 mL) was added. The solution was cooled to −35 °C at which time 1-bromooctane (0.57 mmol) was added with THF (10 mL) and stirred for 30 min. At this time, benzoyl chloride (2.57 mmol) was added with THF (10 mL) and stirred for 90 min at −35 °C followed by a warming to room temperature for 60 min. The reaction mixture was quenched by adding saturated $NH_4Cl(aq)$ (15 mL) and stirring for 15 min. The solution was then added to 50 mL of saturated NH_4Cl and allowed to stand overnight. The resultant solution was filtered to recover the polymer while the filtrate was extracted with anhydrous Et_2O and dried over anhydrous $MgSO_4$. Silica gel chromatography (hexanes followed by mixtures of hexanes/ethyl acetate) provided 1-phenyl-1-nonanone in 78% isolated yield.