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Preparation of Polymer-Supported Benzyllithium Reagents

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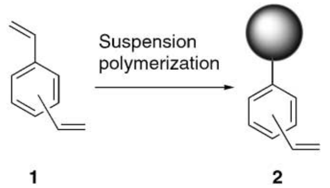
Abstract—Cross-linked polystyrenes (**2**, **8**, and **11**) possessing pendant double bonds conjugated with benzene ring were prepared by both polymerization method and chemical modification of pre-formed polymers. These double bonds were readily lithiated with *n*-butyllithium to give the benzyllithium species on the polymer. The polymer supported benzylic anions (**3** and **12**) are a versatile polymeric organometallic reagent that reacted with various kinds of electrophiles. © 2002 Elsevier Science Ltd. All rights reserved.

Organometallic compounds cover a broad range of reactivities, and are highly versatile reagents.[1] There is no doubt that many of organic synthesis require reactions including organometallics. Polymer supported organometallic compounds are also very important reactive polymers, which should be useful in solid-phase organic synthesis.[2] However, preparation of such polymers has not been developed extensively. One of the most useful methods to obtain organometallic species in solution system is oxidative metallation of organic halides, which is usually not applicable to cross-linked insoluble polymers. For example, Merrifield resins and other cross-linked polymers having haloalkyl group cannot be lithiated with lithium metal because of their solid–solid heterogeneous reactions.[3] The direct halogen–metal exchange on cross-linked polymer has only been achieved with magnesium/anthracene[4] and with activated calcium.[5] Although metal–halogen exchange reactions using soluble organolithium reagent are another important way to obtain organometallic species, limited success has been achieved on the insoluble polymer supports, since Wurtz-type coupling is always accompanied.[3,6] Polymer supported phenyllithium is an exception and may be generated by this method without a considerable amount of such side reactions. This polymer has actually been most frequently used organometallic polymer in solid-phase syntheses.[7] Polymeric thienyllithium was also generated by this method.[8] Metal–hydrogen exchange is another method to generate organometallic species on the polymer. Polymers having protons of relatively lower pK_a values can be metalated. A few examples are available using this strategy.[9–12] Some heteroatom-containing polymers were also lithiated by this method to give organometallic polymers such as polymeric phenyl-thiomethyllithium reagent,[13] lithiated imidazole,[14] furyllithium,[15] and thienyllithium reagents.[15] Reductive lithiation of polymer-supported phenyl thioethers with lithium naphthalenide is a method suitable for the preparation of polymeric alkyllithiums.[3]

Carbometallation reaction of organometallics with conjugated double bonds readily occurs to generate carbanionic species quantitatively, which has been successfully utilized for anionic polymerization of vinyl monomers.[16] However, it is surprising that no attempt of generation of benzyllithium species on the cross-linked polymers using this methodology has been reported. We have investigated the carbometallation reactions on the cross-linked polystyrene having pendant double bonds conjugated with benzene ring to generate benzylic carbanion. In this paper we describe a new method of obtaining cross-linked polystyrene having benzyllithium species based on the carbometallation.



Scheme 1. (Vinyl)polystyrene **2** prepared by suspension polymerization.

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We have prepared three types of cross-linked polystyrene containing styrenic double bonds (**2**, **8**, and **11**). They were readily available by the following methods. Some preparation methods have been proposed for the (vinyl)polystyrene **2** in the literature.[17,18] One of the convenient method to lead such polymer is suspension polymerization of divinylbenzene as shown in Scheme 1. Free-radical suspension polymerization of divinylbenzene gave cross-linked polymers,[19] which have been shown to still bear many unreacted pendant vinyl groups. Commercial divinylbenzene is usually contaminated with large amount of ethylstyrene (divinylbenzene/ethylstyrene, 55:45). We have prepared **2** from this divinylbenzene/ethylstyrene mixture and from divinylbenzene enriched monomer (divinylbenznene/ethylstyrene, 96:4)[20] as shown in Table 1. The double bonds in the polymer **2** can be used for the carbometallation.

Although many precedents appeared for the functionalization of the vinyl groups of a (vinyl)polystyrene **2**, no example has ever been reported for the carbometallation.[21] First, we treated **2** prepared from suspension polymerization of divinylbenzene containing 4% ethylstyrene[20] with *n*-butyllithium at −78 °C (Table 1, run 1). The polymer beads turned deep red color indicating the formation of benzylic anion on the polymer **3**. The lithiated polymer **3** was then quenched with 4-chlorobenzyl chloride **4** to give polymer **5** (Scheme 2).

Chlorine analysis of **5** showed that 14% of benzene rings of polystyrene resin was functionalized with this method (run 1). When *n*-butyllithium was added at 0 °C, degree of functionalization increased to 20% (run 2).[22] Only 4.1% of functionalization was obtained if the temperature was raised to 25 °C (run 3). The same divinylbenzene monomer was polymerized for longer reaction time (2 h) to afford more highly cross-linked and less double bond content polymer (run 4). Lithiation of this polymer showed somewhat lower loading%. When 55:45 divinylbenzene/ethylstyrene mixture was polymerized residual double bonds could be functionalized with lower degree of functionalization (6.5%) mainly due to anionic oligomerization occurred in the polymer having relatively flexible network structure (run 5).

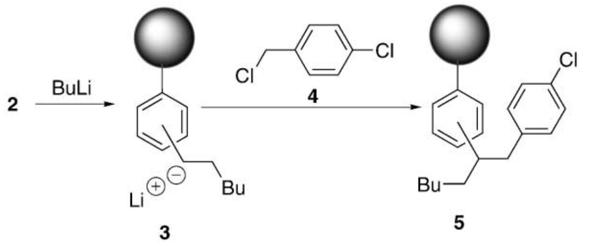
Next, we employed **8** as a starting polymer for the carbometallation. Cross-linked polystyrene having vinylphenyl pendant group **8** was prepared from Merrifield resin **6** and 4-vinylbenzyl alcohol **7** (Scheme 3). Lithiation of this polymer, however, resulted in low degree of functionalization (<5%), since lightly cross-linking (2%) and flexible pendant structure of **8** may cause anionic oligomerization within the polymer bead as a side reaction. Another side reaction of benzylic anion induced 1,6-elimination is also possible in this case.[23]

Table 1. Lithiation of **2** followed by reaction with 4-chlorobenzyl chloride

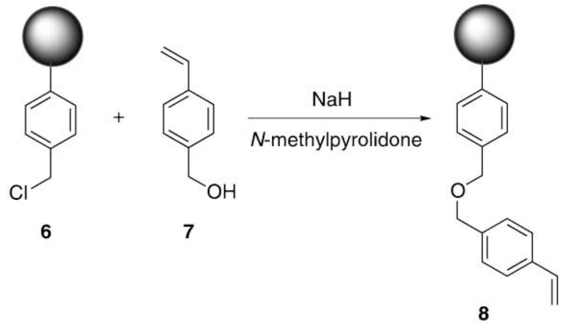
Run	**2**		Lithiation temperature °C	Loading %[a] of **5**
	Divinylbenzene/ ethylstyrene	Polymerization time (h)		
1	96:4	1	−78	14
2	96:4	1	0	20
3	96:4	1	25	4.1
4	96:4	2	0	16
5	55:45	2	0	6.5

[a] Determined by chlorine analysis.

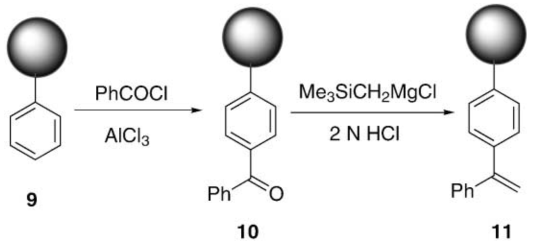
Another structure of double bond conjugated with benzene ring is diphenylethylene moiety (**11**), which was easily introduced into the cross-linked polystyrene by the chemical modification route described in Scheme 4.[24] Friedel–Crafts acylation of cross-linked polystyrene with benzoyl chloride afforded **10**. Loading of benzophenone moiety in **10** was estimated by nitrogen analysis of its oxime derivative. Peterson olefination of **10** led to **11** in quantitative conversion confirmed by IR spectroscopy. Although several transformation methods of ketone to olefin have been known in the literature,[25] complete conversion without side reaction and with easy work up was achieved with this method. Loading of diphenylethylene group in **11** was controlled by the amount of benzoyl chloride used in benzoylation reaction. In this study, we used 2% cross-linked micro-



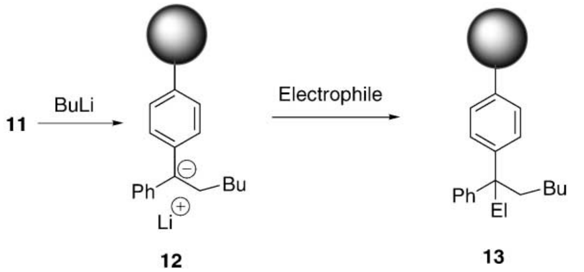
Scheme 2. Lithiation of (vinyl)polystyrene **2** followed by addition of electrophile.



Scheme 3. Preparation of cross-linked polystyrene containing vinylbenzyl ether.



Scheme 4. Preparation of cross-linked polystyrene having diphenylethylene moiety **11**.



Scheme 5. Lithiation of **11** followed by reaction of various electrophiles.

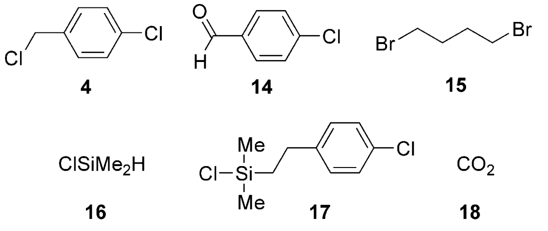
Table 2. Polymer supported diphenylhexyllithium **12** with various electrophiles

Electrophile	% Conversion to functional polymer **13**
4	93[a]
14	91[a]
15	92[a]
16	96[b]
17	99[a]
18 (dry ice)	94[c]

[a] Determined by halogen analysis.
[b] Hydrosilylation to 4-chlorostyrene followed by halogen analysis.
[c] Determined by acid-base titration.

porous polystyrene **9** as a starting resin to prepare diphenylethylene polymers **11** with loading of 35%.

As mentioned in the case of lithiation of **2** and **8**, competing anionic oligomerization within the polymer bead sometimes disturbs reaching high loading %. On the other hand, diphenylethylene has no possibility of anionic polymerization.[26] Diphenylethylene polymer **11** was then treated with *n*-butyllithium at 0 °C.[27] Immediate color change of the polymer beads to deep red was observed, indicating the formation of lithiated polymer **12** (Scheme 5). Although the polymer beads are lightly cross-linked and swellable in THF, diphenyl-alkyllithium generated in the polymer cannot react with other diphenylethylene moieties in the bead because of steric hindrance. Quantitative conversion without side reaction was achieved with this type of polymer. In general, the decreased basicity and increased steric requirements of diphenylalkyllithiums can suppress the undesired side reactions in many cases of the reaction with electrophiles and have been effectively used as a regio- and chemoselective nucleophilic reagent.[26,28] To test the reactivity of polymer supported diphenylhexyllithium **12** and explore its application to the preparation of polystyrene resins containing various functional groups, the resulting diphenylhexyllithium **12** was then treated with various kinds of electrophiles such as 4-chlorobenzyl chloride (**4**), 4-chlorobenzaldehyde (**14**), 1,4-dibromobutane (**15**), chlorosilanes (**16** and **17**), and carbon dioxide (**18**).[29] In all cases, high conversion was attained (Table 2). High reactivity of these polymers towards electrophiles would make it possible to allow application to previously inaccessible structures. It is also noticed that the generated anion in the polymer **12** was quite stable even at room temperature at least for 20 h under argon atmosphere.



Electrophile

In summary, we have prepared cross-linked polymers containing double bonds conjugated with benzene ring. Treatment of (vinyl)polystyrene **2** with *n*-butyllithium yielded polymeric benzyllithium reagent **3**. We have also prepared cross-linked polymer containing diphenylethylene moiety **11** which was lithiated smoothly at 0 °C without significant side reactions. Obtained lithiated polymer **12** was reactive toward various kinds of electrophiles in high conversion. These reactive organolithium polymers may be useful for number of solid phase organic syntheses including combinatorial synthesis.

Acknowledgements

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22. Lithiation of **2** followed by reaction with electrophile: To a THF suspension of (vinyl)polystyrene **2** (0.1 g), prepared from divinylbenzene and ethylstyrene (96:4), was added *n*-butyllithium (1.6 M in hexane, 0.5 mL, 0.8 mmol) at 0 °C. The polymer beads turned deep red color indicating the formation of benzylic anion on the polymer (**3**). After 30 min at 0 °C, the mixture was cooled to −78 °C and a THF (1 mL) solution of 4-chlorobenzyl chloride (0.16 g, 1 mmol) was added. After the resins became colorless, stirring was continued for another 20 min. The polymer was then collected by filtration and washed several times with THF/water (1:1), THF, CH_2Cl_2, and MeOH, yielding 0.1 g of polymer **5**. Microanalysis for Cl indicated 20% loading (1.20 mmol Cl/g).

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24. Synthesis of **11**: To a mixture of cross-linked polystyrene **9** (2% cross-linked, microporous resin) (2.0 g) and benzoyl chloride (0.89 mL, 7.7 mmol) in 1,2-dichloroethane (20 mL) at 0 °C was added $AlCl_3$ (1.2 g, 9 mmol) and the resulting suspension was heated to reflux and the reaction was stirred for 12 h. The reaction mixture was then cooled to room temperature and the polymer was collected by filtration and washed several times with dioxane/2 N HCl (2:1), dioxane/water (3:1), THF, $CHCl_3$, and MeOH, yielding 2.7 g of **10**. The IR spectrum of **10** had strong absorbance at 1658 cm^{-1}. Loading of benzoyl group in **10** (35%) was estimated from nitrogen analysis of its oxime derivative. To a solution of trimethylsilylmethylmagnesium chloride/THF solution, prepared from chloromethyltrimethylsilane (460 mg, 3.75 mmol) and magnesium (0.1 g) was added the benzoylated resin **10** (0.5 g, 1.25 mmol C=O) and stirred for 24 h at room temperature. The reaction was quenched with water and the polymer was collected by filtration and washed several times with THF, THF/water (1:1), MeOH, CH_2Cl_2, and MeOH, yielding 0.6 g of silylmethylated resin. FTIR (KBr) 3400 (OH) and 1247 (Si–C) cm^{-1}, peak absent at 1658 cm^{-1}. To a suspension of the silylmethylated resin (0.4 g) in THF (2 mL) was added 2 N HCl (2 mL) and stirred for 6 h at room temperature. The polymer was collected by filtration and washed several times with THF/water (1:1), THF, CH_2Cl_2, and MeOH, yielding 0.3 g of **11**. FTIR (KBr) 901($C{=}C\mathit{H}_2$) cm^{-1}, peaks absent at 3400 and 1247 cm^{-1}.

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29. Reaction of **12** with electrophile: To a suspension of polymer supported diphenylethylene **11** (0.2 g, 0.5 mmol $C{=}CH_2$) in THF (1 mL) was added *n*-butyllithium (1.6 M in hexane, 0.5 mL, 0.8 mmol) at 0 °C. The polymer beads turned deep red color, which indicated the formation of diphenylhexyllithium on the polymer (**12**). After 20 min at 0 °C, a THF solution of silylchloride **17** (0.23 g, 1 mmol) was added to the suspension at the same temperature. After the resins became colorless, stirring was continued for another 20 min. The polymer was then collected by filtration and washed several times with THF/water (1:1), THF, CH_2Cl_2, and MeOH, yielding 0.3 g of silyl substituted polymer **13**. FTIR (KBr) 1249 (Si–C) cm^{-1}. Microanalysis for Cl indicated 35% loading (1.53 mmol Cl/g).