

Dedicated to Prof. I.P. Beletskaya for her fundamental contributions to organometallic chemistry

Lithiation Reactions Catalyzed by Linear and Cross-Linked Arene-Based Polymers. Generation of Functionalized Organolithium Compounds*

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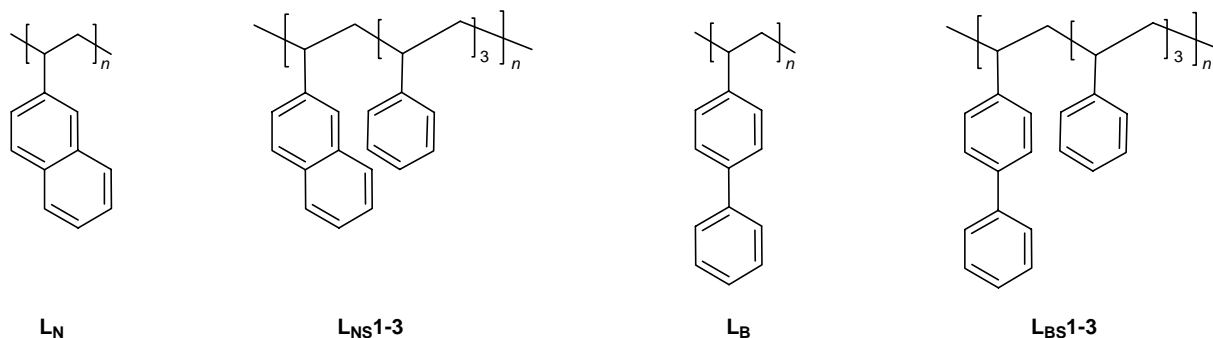
Abstract—Lithiation of various substrates, such as chlorinated acetals, α -chloro ether, dichloro derivatives, benzo-fused heterocycles, and allyl and benzyl derivatives, with excess lithium powder in the presence of a catalytic amount of soluble linear or insoluble cross-linked arene (naphthalene or biphenyl)-based polymers yields the expected organolithium intermediates. The latter react with electrophiles either in two steps or under Barbier-type reaction conditions to afford the corresponding adducts. The catalyst is easily recuperated by filtration at the end of the process, and the procedure can be regarded as a reasonable alternative to the use of free arenes as electron carrier in lithiation reactions.

Functionalized organometallic compounds [1] are interesting intermediates in synthetic organic chemistry due to their ability in reactions with electrophiles to transfer their own functionality on the electrophilic reagent. In this way, polyfunctional molecules become accessible in one reaction step. Among organometallic compounds, functionalized organolithium reagents [2] are of particular interest due to their high reactivity even under mild conditions, which originates from the high polarity of the lithium–carbon bond (~60%) [3]. In many cases, organolithium intermediates are fairly unstable; therefore, their preparation and further transformations should be performed at low temperature. With the goal of making the lithiation conditions milder we have recently developed a procedure based on the use of excess lithium powder in the presence of a catalytic (substoichiometric) amount of an arene [4–6], naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being used most commonly [7]. This arene-catalyzed lithiation allowed us to prepare simple organolithium reagents from halogen-free materials [8], functionalized organolithium intermediates [2] (in particular, via reductive ring opening of heterocyclic compounds [9]), and polylithium synthons [10], as well as to activate other metals [11], especially nickel, in

reduction processes [2]. In some cases, intermediates are very unstable, and the lithiation should be performed under Barbier-type reaction conditions, i.e., in the presence of an electrophilic reagent [13]. We have recently developed further extension of the arene-catalyzed lithiation with the use of an arene attached to a polymer [4]. In this case, the electron transfer agent is also added in a substoichiometric amount, but it can be reused many times without appreciable loss in efficiency. This polymer-supported methodology involving insoluble (cross-linked) polymers has been applied to lithiation of chlorinated materials and in some cases of allyl, benzyl, and silyl ethers [14], as well as to activation of nickel [15, 16]. In the present work we extended the scope of application of cross-linked polymers to ring opening of some heterocycles and formation of allyl- and benzyl lithium reagents from ethers and amides. In addition, we report here on the synthesis of soluble (linear) arene-containing polymers and their use in various lithiation reactions.

1. Soluble (linear) arene-containing polymers (L). Homopolymers on the basis of 2-vinylnaphthalene (L_N) and 4-vinylbiphenyl (L_B) were synthesized in boiling benzene in the presence of a catalytic amount of 1,1'-azobis(isobutyronitrile) (AIBN) as initiator. The products were isolated by precipitation with cold methanol. Heteropolymers (L_{NS} and L_{BS}) containing

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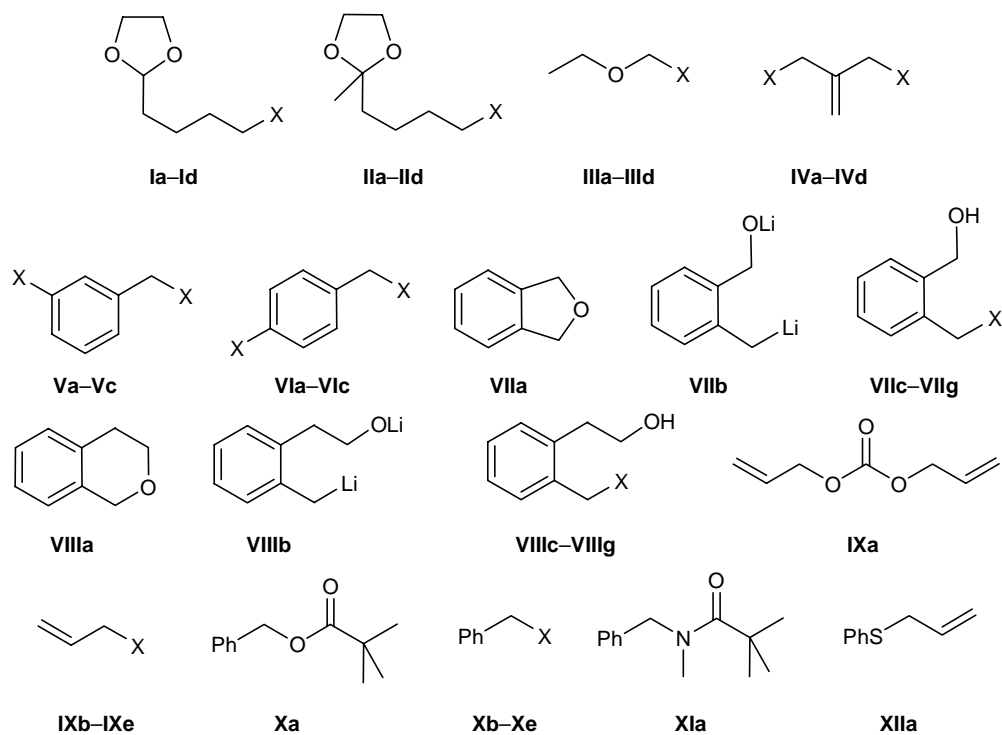


styrene as co-monomer (molar ratio 1:3) were synthesized according to the same procedure [17].

Dry polymers **L** were used in the catalytic lithiation of various chlorinated substrates, such as chloro acetals **Ia** and **IIa** and α -chloro ether **IIIa**. Compounds **Ia–IIIa** were treated with a suspension of lithium powder (molar ratio 1:7) and the corresponding polymer **L** (~5 mol %) in tetrahydrofuran (THF) at -78°C to generate intermediates **Ib–IIIb**. Hydrolysis of the latter at the same temperature afforded the expected products **Ic**, **Id**, **IIIc**, and **IIId** (Scheme 1; Table 1, run nos. 1–9) [18–20]. The reactions with dichloro sub-

strates **IVa–VIa** were carried out under Barbier-type reaction conditions to obtain products **IVc**, **IVd**, **Vc**, and **VIc**, presumably via dilithiated intermediates **IVb–VIb** (Scheme 1; Table 1, run nos. 10–17) [21, 22]. (A more reasonable mechanistic alternative includes a double tandem chlorine–lithium exchange– S_E reaction; in this case, the replacement of two chlorine atoms by the corresponding electrophilic fragment would be a stepwise process.) Finally, reductive ring opening of isobenzofuran (**VIIa**) and isochroman (**VIIIa**) in the presence of polymers **L** gave intermediates **VIIb** and **VIIIb**, respectively, which were

Scheme 1.



I–VI, X = Cl (**a**), Li (**b**); **I**, X = Et₂C(OH) (**c**); **II**, X = PhCH(OH) (**c**), (CH₂)₅C(OH) (**d**); **IV**, X = Et₂C(OH) (**c**), (CH₂)₅C(OH) (**d**); **V**, **VI**, X = Me₃Si (**c**); **VII**, X = Et₂C(OH) (**c**), (CH₂)₅C(OH) (**d**), *t*-BuCH(OH) (**e**), PhCH(OH) (**f**), PhC(OH)(Me) (**g**); **VIII**, X = *t*-BuCH(OH) (**c**), (CH₂)₅C(OH) (**d**), PhCH(OH) (**e**), Et₂C(OH) (**f**), PhC(OH)(Me) (**g**); **X**, X = Li (**b**), PhCH(OH) (**c**), (CH₂)₅C(OH) (**d**), Ph₂C(OH) (**e**); **X**, X = Li (**b**), *t*-BuCH(OH) (**c**), Et₂C(OH) (**d**), (CH₂)₅C(OH) (**e**).

Table 1. Lithiation of compounds **Ia–VIIIa** in the presence of linear arene-containing polymers and reactions of organolithium intermediates **Ib–VIIIb** with electrophiles

Run no.	Initial compound	Polymeric catalyst	Intermediate	Electrophile	Product ^a		
					no.	yield, ^b %	reference ^c
1	Ia	L _N	Ib	Et ₂ CO	Ic	59	[18]
2	Ia	L _N	Ib	(CH ₂) ₅ CO	Id	71	[18]
3	Ia	L _{NS} 1-3	Ib	(CH ₂) ₅ CO	Id	54	[18]
4	Ia	L _B	Ib	(CH ₂) ₅ CO	Id	69	[18]
5	Ia	L _{BS} 1-3	Ib	(CH ₂) ₅ CO	Id	44	[18]
6	IIa	L _N	IIb	PhCHO	IIc	45	[19]
7	IIa	L _N	IIb	(CH ₂) ₅ CO	IIId	41	[19]
8	IIIa	L _N	IIIb	PhCHO	IIIId	87	[20]
9	IIIa	L _N	IIIb	PhCOMe	IIIId	84	[20]
10	IVa	L _N	IVb	Et ₂ CO	IVc	64	[21]
11	IVa	L _N	IVb	(CH ₂) ₅ CO	IVd	92	[21]
12	IVa	L _N ^d	IVb	(CH ₂) ₅ CO	IVd	80 ^d	[21]
13	IVa	L _{NS} 1-3	IVb	(CH ₂) ₅ CO	IVd	73	[21]
14	IVa	L _B	IVb	(CH ₂) ₅ CO	IVd	65	[21]
15	IVa	L _{BS} 1-3	IVb	(CH ₂) ₅ CO	IVd	78	[21]
16	Va	L _N	Vb	Me ₃ SiCl	Vc	54	[22]
17	VIa	L _N	VIb	Me ₃ SiCl	VIc	55	[22]
18	VIIa	L _N	VIIb	Et ₂ CO	VIIc	62	[23]
19	VIIa	L _N	VIIb	(CH ₂) ₅ CO	VIIId	65	[23]
20	VIIa	L _{NS} 1-3	VIIb	(CH ₂) ₅ CO	VIIId	49	[23]
21	VIIa	L _B	VIIb	(CH ₂) ₅ CO	VIIId	72	[23]
22	VIIa	L _{BS} 1-3	VIIb	(CH ₂) ₅ CO	VIIId	63	[23]
23	VIIIa	L _N	VIIIb	<i>t</i> -BuCHO	VIIIc	37	[24]
24	VIIIa	L _N	VIIIb	(CH ₂) ₅ CO	VIIIId	56	[24]

^a All products **I–VIII** contained more than 95% of the main substance [according to the ¹H NMR (300 MHz) and/or GLC data] and were fully characterized by comparing their spectral and chromatographic parameters with those reported in the literature (see footnote ^c).

^b Yield of the product isolated by column chromatography (silica gel, hexane–ethyl acetate), calculated on the initial compound **Ia–VIIIa**.

^c Given are references to the reactions in the presence of the corresponding free arenes.

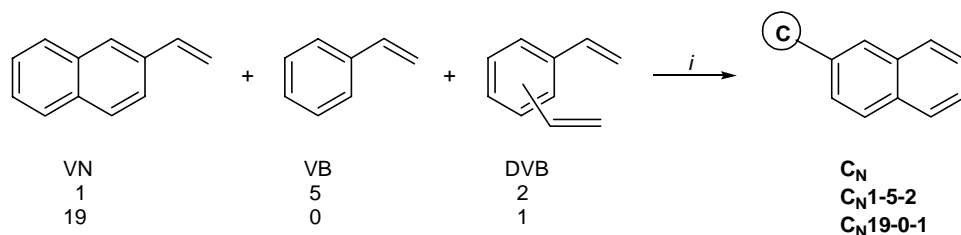
^d The reaction was performed with regenerated (once) polymeric catalyst.

treated with electrophiles; after hydrolysis with water, expected products **VIIc**, **VIIId**, **VIIIc**, and **VIIIId** were obtained (Scheme 1, Table 1, run nos. 18–24) [23, 24]. The data in Table 1 show that (1) homopolymers L_N and L_B are slightly more effective catalysts than heteropolymers L_{NS} and L_{BS} (cf. run nos. 2–5 and 19–22 in Table 1); (2) the obtained results are comparable (with slight variations) with those observed with free arenes as catalysts [18–24]; and (3) the polymeric catalyst can be recovered after hydrolysis with water by treatment with methanol (see Experi-

mental) and used repeatedly without appreciable loss in activity (Table 1, run nos. 11 and 12 and footnote ^d).

2. Insoluble (cross-linked) arene-containing polymers (C). Cross-linked polymers C_N were prepared according to the procedure described in [14], by treatment of a mixture of 2-vinylnaphthalene (VN) and divinylbenzene (DVB) in the presence or in the absence of vinylbenzene (VB) with an aqueous solution of polyvinyl alcohol in a benzene–THF mixture under reflux (Scheme 2).

Scheme 2.



i: Azobis(isobutyronitrile), THF, polyvinyl alcohol, H₂O, reflux.

Insofar as catalytic lithiation of some chlorinated materials like **Ia–VIa** was already reported [14] (see above), in the present work we examined ring opening of benzo-fused heterocycles **VIIa** and **VIIIa**. The reactions were carried out with excess lithium powder and a catalytic amount of insoluble polymer C (~10 mol %) in THF at 0°C [with isobenzofuran (**VIIa**)] or at room temperature [with isochroman (**VIIIa**)]. Treatment of the expected organolithium derivatives **VIIb** and **VIIIb** with electrophiles, followed by hydrolysis with water, afforded compounds **VIIc–VIIg** and **VIIIc–VIIIg** (Scheme 2; Table 2, run nos. 1–20) [23, 24]. The polymeric catalyst could be regenerated at the end of the process by simple filtration and reused up to four times, as we already reported in [14]. Insoluble polymers C were also used to catalyze deallylation and debenzylolation reactions, following an analogous procedure but under Barbier-type reaction conditions. Catalytic lithiation of compounds **IXa–XIIa** in the temperature range from –78 to 0°C gave intermediates **IXb** and **Xb** which reacted with electrophiles to afford (after hydrolysis) the corresponding products **IXc–IXe** and **Xc–Xe** (Scheme 2; Table 2, run nos. 21–29) [4, 25].

In general, the results given in Table 2, do not allow us to draw clear conclusions on the use of catalysts C_N1-5-2 and C_N19-0-1, the latter containing no styrene as co-monomer (Scheme 2). In some cases, C_N1-5-2 is less effective than C_N19-0-1 (cf. run nos. 5 and 6 in Table 2), while in the other cases, the opposite pattern is observed (run nos. 9, 10) or there is no difference in their efficiencies (run nos. 3, 4).

Thus the use of linear (L) or cross-linked (C) arene-containing polymers as lithiation catalysts provides a reasonable alternative to processes carried out under homogeneous conditions in the presence of free arenes, ensuring comparable yields of the products. The main advantage of the proposed procedure is that the catalyst can easily be regenerated and used in other catalytic lithiation reactions.

EXPERIMENTAL

All reactions with organometallic reagents were carried out under nitrogen using oven-dried glassware. The IR spectra were obtained on a Nicolet Impact 400D Fourier transform spectrometer. The NMR spectra were recorded on a Bruker AC-300 instrument at 300 MHz (¹H) and 75 MHz (¹³C); CDCl₃ was used as solvent; the chemical shifts were measured relative to TMS (internal reference) or solvent signals. The electron impact mass spectra (70 eV) were run on a Shimadzu QP-5000 spectrometer. All solvents, 4,4'-di-*tert*-butylbiphenyl, and the electrophilic reagents were commercial products (Acros, Aldrich, Fluka) which were used without additional purification. Anhydrous tetrahydrofuran (Acros, stabilized) had a purity of 99.9%. Benzyl 2,2-dimethylpropanoate (**Xa**), *N*-benzyl-*N*,2,2-trimethylpropanamide (**IIa**), and allyl phenyl sulfide (**XIIa**) were synthesized by known methods [26]. Lithium powder was prepared by the procedure described in [27].

Preparation of linear polymers L (*general procedure*). A solution of 5 mmol of the corresponding monomer (901 mg of 2-vinylnaphthalene or 770 mg of 4-vinylbiphenyl) and 13 mg of 1,1'-azobis(isobutyronitrile) (AIBN) in 5 ml of benzene was degassed with argon over a period of 20 min under stirring and was then refluxed (85°C) for 40 h. The solution was poured at –40°C into 150 ml of methanol, and the precipitate was filtered off, washed with methanol (3×20 ml), and dried under reduced pressure (10 mm). Heteropolymers L_{NS}1-3 and L_{BS}1-3 were synthesized in a similar way using 1.7 ml (15 mmol) of styrene as co-monomer. The yields of the polymeric products were greater than 90%. Their spectral and analytical data are given below.

Poly[1-(2-naphthyl)ethylene] (L_N). IR spectrum (KBr), ν , cm⁻¹: 3049, 3017, 1631, 1599, 1507 (C=CH). ¹H NMR spectrum, δ , ppm: 1.46 br.s (CHCH₂); 1.86 br.s (CHCH₂); 6.56 br.s, 7.32 br.s, 7.59 br.s

Table 2. Lithiation of compounds **VIIa–XIIa** in the presence of cross-linked arene-containing polymers and reactions of organolithium intermediates **VIIb–Xb** with electrophiles

Run no.	Initial compound	Polymeric catalyst	Intermediate	Electrophile	Product ^a		
					no.	yield, ^b %	reference ^c
1	VIIa	C _N 1-5-2	VIIb	Et ₂ CO	VIIc	58	[23]
2	VIIa	C _N 19-0-1	VIIb	Et ₂ CO	VIIc	43	[23]
3	VIIa	C _N 1-5-2	VIIb	(CH ₂) ₅ CO	VIIId	78	[23]
4	VIIa	C _N 19-0-1	VIIb	(CH ₂) ₅ CO	VIIId	75	[23]
5	VIIa	C _N 1-5-2	VIIb	<i>t</i> -BuCHO	VIIe	57	[23]
6	VIIa	C _N 19-0-1	VIIb	<i>t</i> -BuCHO	VIIe	75	[23]
7	VIIa	C _N 1-5-2	VIIb	PhCHO	VIIIf	57	[23]
8	VIIa	C _N 19-0-1	VIIb	PhCHO	VIIIf	65	[23]
9	VIIa	C _N 1-5-2	VIIb	PhCOMe	VIIg	72	[23]
10	VIIa	C _N 19-0-1	VIIb	PhCOMe	VIIg	50	[23]
11	VIIIa	C _N 1-5-2	VIIIb	<i>t</i> -BuCHO	VIIIc	43	[24]
12	VIIIa	C _N 19-0-1	VIIIb	<i>t</i> -BuCHO	VIIIc	68	[24]
13	VIIIa	C _N 1-5-2	VIIIb	(CH ₂) ₅ CO	VIIIId	55	[24]
14	VIIIa	C _N 19-0-1	VIIIb	(CH ₂) ₅ CO	VIIIId	44	[24]
15	VIIIa	C _N 1-5-2	VIIIb	PhCHO	VIIIe	47	[24]
16	VIIIa	C _N 19-0-1	VIIIb	PhCHO	VIIIe	54	[24]
17	VIIIa	C _N 1-5-2	VIIIb	Et ₂ CO	VIIIIf	46	[24]
18	VIIIa	C _N 19-0-1	VIIIb	Et ₂ CO	VIIIIf	51	[24]
19	VIIIa	C _N 1-5-2	VIIIb	PhCOMe	VIIIg	33	[24]
20	VIIIa	C _N 19-0-1	VIIIb	PhCOMe	VIIIg	45	[24]
21	IXa	C _N 1-5-2	IXb	PhCHO	IXc	43 ^d	[25]
22	IXa	C _N 1-5-2	IXb	(CH ₂) ₅ CO	IXd	21 ^d	[25]
23	IXa	C _N 1-5-2	IXb	Ph ₂ CO	IXe	46 ^d	[25]
24	Xa	C _N 19-0-1	Xb	<i>t</i> -BuCHO	Xc	73	[25]
25	Xa	C _N 19-0-1	Xb	Et ₂ CO	Xd	71	[25]
26	Xa	C _N 19-0-1	Xb	(CH ₂) ₅ CO	Xe	34	[25]
27	XIa	C _N 19-0-1	Xb	<i>t</i> -BuCHO	Xc	61	[25]
28	XIa	C _N 19-0-1	Xb	(CH ₂) ₅ CO	Xe	34	[25]
29	XIIa	C _N 19-0-1	IXb	(CH ₂) ₅ CO	IXd	16	[25]

^a All products **VII–X** contained more than 95% of the main substance [according to the ¹H NMR (300 MHz) and/or GLC data] and were fully characterized by comparing their spectral and chromatographic parameters with those reported in the literature (see footnote ^c).

^b Yield of the product isolated by column chromatography (silica gel, hexane–ethyl acetate), calculated on the initial compound **VIIa–XIIa**.

^c Given are references to the reactions in the presence of the corresponding free arenes.

^d Yield corresponding to introduction of one allyl group into the electrophile.

(H_{arom}). ¹³C NMR spectrum, δ_C, ppm: 40.7 (CHCH₂); 43.2 (CHCH₂); 125.3, 125.5, 127.5, 127.7 (CH_{arom}); 132.0, 133.3, 142.1 (C_{arom}). Found, %: C 90.18; H 6.44. (C₁₂H₁₀). Calculated, %: C 93.46; H 6.54.

Poly[1-(2-naphthyl)-3,5,7-triphenylocta-methylene] (L_{NS}1-3). IR spectrum (KBr), ν, cm⁻¹: 3057, 3024, 1631, 1599, 1492 (C=CH). ¹H NMR spectrum, δ, ppm: 1.41 br.s (CHCH₂); 1.80 br.s (CHCH₂);

6.55 br.s, 7.01 br.s, 7.36 br.s, 7.71 br.s (H_{arom}). ^{13}C NMR spectrum, δ_{C} , ppm: 40.3 (CHCH_2); 43.8 (CHCH_2); 125.6, 125.7, 127.5, 127.9 (CH_{arom}); 132.1, 133.3, 145.2 (C_{arom}). Found, %: C 92.08; H 7.18. (C_8H_8)₃($\text{C}_{12}\text{H}_{10}$). Calculated, %: C 92.66; H 7.18.

Poly[1-(4-biphenyl)ethylene] (L_B). IR spectrum (KBr), ν , cm^{-1} : 3052, 3024, 1599, 1485 ($\text{C}=\text{CH}$). ^1H NMR spectrum, δ , ppm: 1.48 br.s (CHCH_2); 1.90 br.s (CHCH_2); 6.60 br.s, 7.50 br.s (H_{arom}). ^{13}C NMR spectrum, δ_{C} , ppm: 40.1 (CHCH_2); 42.8 (CHCH_2); 126.8, 126.9, 128.7 (CH_{arom}); 138.2, 140.8, 144.1 (C_{arom}). Found, %: C 91.50; H 6.66. $\text{C}_{14}\text{H}_{12}$. Calculated, %: C 89.66; H 8.09.

Poly[1-(4-biphenyl)-3,5,7-triphenyloctamethylene] (L_{BS1-3}). IR spectrum (KBr), ν , cm^{-1} : 3080, 3058, 3024, 1600, 1486 ($\text{C}=\text{CH}$). ^1H NMR spectrum, δ , ppm: 1.43 br.s (CHCH_2); 1.86 br.s (CHCH_2); 7.04 br.s, 7.30 br.s; 7.41 br.s; 7.52 br.s (H_{arom}). ^{13}C NMR spectrum, δ_{C} , ppm: 40.3 (CHCH_2); 43.8 (CHCH_2); 125.6, 126.9, 127.6, 128.0, 128.7 (CH_{arom}); 138.3, 141.1, 145.2 (C_{arom}). Found, %: C 91.87; H 7.23. (C_8H_8)₃($\text{C}_{14}\text{H}_{12}$). Calculated, %: C 92.64; H 7.36.

Lithiation of compounds Ia–IIIa, VIIa, and VIIIa in the presence of linear arene-containing polymers (general procedure). To a suspension of 0.10 g (14 mmol) of lithium powder and the corresponding soluble polymer L (5 mol %) in 4 ml of THF we added 2 mmol of the substrate at -78°C (compounds Ia–IIIa), 0°C (VIIa), or 20°C (VIIIa), and the mixture was stirred for 1 h at the same temperature. The corresponding electrophile, 2.2 mmol, was then added at -78°C , and the mixture was stirred for 1 h at -78°C and hydrolyzed with 1 ml of water. The polymeric catalyst was precipitated by adding 10 ml of methanol and was filtered off. The solvent was removed from the filtrate, and the residue was extracted with ethyl acetate (3×10 ml). The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure (10 mm). The product yields are summarized in Table 1. Compounds Ic, Id [18], IIc, IID [19], IIIc, IIId [20], VIc, VIId [23] VIIC, and VIId [5] were reported by us previously. They were identified by comparing their spectral parameters with those of authentic samples.

Lithiation of compounds IVa–VIa in the presence of linear arene-containing polymers under Barbier-type reaction conditions (general procedure). A solution of 2.2 mmol of electrophilic reagent and 1 mmol of dichloro derivative IVa, Va, or VIa,

was added at -78°C to a suspension of 0.10 g (14 mmol) of lithium powder and the corresponding soluble polymer L (5 mol %) in 4 ml of THF. The cooling bath was removed, and the mixture was stirred until it warmed up to room temperature and was hydrolyzed by adding 1 ml of water. The polymeric catalyst was precipitated with 10 ml of methanol, and the subsequent procedure was the same as in the two-step process. The yields are given in Table 1. Previously described compounds IVc, IVd [21], Vc, and VIc [22] were identified by comparing their spectral parameters with those of authentic samples.

Cross-linked polymers C_N1-5-2 and $\text{C}_N19-0-1$ were synthesized as described in [14].

Lithiation of compounds VIIa and VIIIa in the presence of crossed-linked arene-containing polymers (general procedure). Compound VIIa or VIIIa, 1 mmol, was added at 0 or 20°C , respectively, to a suspension of 0.070 g (10 mmol) of lithium powder and the corresponding polymer C (10 mol %) in 4 ml of THF. The mixture was stirred for 1 h at the same temperature and cooled to -78°C , 1.2 mmol of electrophilic reagent was added, and the mixture was stirred for 1 h at -78°C and was hydrolyzed with 1 ml of water. The polymeric catalyst was filtered off and washed with methanol, water, and diethyl ether. The resulting solution was extracted with ethyl acetate (3×10 ml), and the extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure (10 mm). The product yields are given in Table 2. Previously described compounds VIIC–VIIG [23] and VIIC–VIIG [24] were identified by comparing their spectral parameters with those of authentic samples.

Lithiation of compounds IXa–XIIa in the presence of cross-linked arene-containing polymers under Barbier-type reaction conditions (general procedure). A solution of 2.2 mmol of electrophilic reagent and 1 mmol of compound IXa–XIIa was slowly (over a period of ~ 1 h) added at -78°C (at 0°C for IXa) to a suspension of 0.035 g (5 mmol) of lithium powder and the corresponding polymer C_N1-5-2 or $\text{C}_N19-0-1$ (10 mol %) in 4 ml of THF. The cooling bath was removed (Xa–XIIa), and the mixture was stirred until it warmed up to room temperature or (with compound IXa) was stirred for 1 h at 0°C . Water, 1 ml, was then added, the polymeric catalyst was filtered off and washed with methanol, water, and diethyl ether, and the filtrate was treated as described above for the two-step procedure. The yields are given in Table 2. Compounds IXc–IXe and Xc–Xe [25] were

reported by us previously. They were identified by comparing their spectral parameters with those of authentic samples.

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