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Polymer Supported Naphthalene-Catalysed Lithiation Reactions

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Abstract: The reaction of functionalised mono or dichlorinated materials **1a-6a** with an excess of lithium and a catalytic amount of a naphthalene supported polymer (P-152, easily prepared by radical copolymerisation of 2-vinylnaphthalene, styrene and divinylbenzene) in THF either in the presence (Barbier-type conditions) or not of different electrophiles [Me_3SiCl, Bu^nCHO, Bu^iCHO, PhCHO, Et_2CO, $c(C_3H_5)_2CO$, $Pr^i{}_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe, PhCH=NPh] leads, after hydrolysis, to the expected products **1c-6c**. The catalyst is quantitatively recovered and can be reused several times without any loss of its activity.

One inherent problem when a lithiation reaction has to be carried out at low temperature to prepare unstable organolithium compounds is that is necessary to activate the lithium metal in order to achieve the desired metallation.[1] For this purpose, the use of a stoichiometric amount of an arene as electron carrier in tetrahydrofuran as solvent allows the preparation of a solution of lithium-arene (or lithium arenide), naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most commonly used:[2] this solution is active enough to perform a chlorine-lithium exchange at temperatures even below -78°C, thus unstable functionalised organolithium compounds[3] are accessible using this methodology. A further step refining the lithiation procedure was the discovery that using a catalytic amount (<10%) of the mentioned arenes the lithiation was more effective. The reaction was far cleaner and shorter, and at the end of the process it was not necessary to remove important amounts of the arene, which could in some cases suffer side-reactions in the stoichiometric version.[4] By means of this arene-catalysed lithiation we have been able to prepare for the first time organolithium reagents starting from non-halogenated precursors[5a] as well as very reactive functionalised organolithium compounds (by chlorine/lithium exchange[5b] or by reductive opening of heterocyclic compounds[5c]) or polylithium synthons.[5d] Probably the ideal situation, even using a catalytic amount of the arene for the lithiation process, would be the use of a polymer supported naphthalene, which could be filtered at the end of the reaction without contaminating the final product with the electron carrier. In this paper we report the preparation of such a supported catalyst containing naphthalene units and its use in the preparation of very reactive organolithium intermediates.[6]

The preparation of the polymer supported naphthalene was carried out using the Itsuno methodology[7] to give cross-linked polymers. Thus, a solution of 2-vinylnaphthalene (1 mmol scale), styrene and divinylbenzene (1:5.2 molar ratio) in benzene containing a catalytic amount of AIBN (30 mol %) was treated with a solution of poly(vinyl alcohol) (*ca.* 80 mg) in water and the mixture was heated at 80°C for *ca.* 36 h, to give after filtration, washing (MeOH, H_2O, H_2O-THF, Et_2O) and drying *in vacuo* a quantitative yield of the polymer catalyst (Ⓟ-152).[8]

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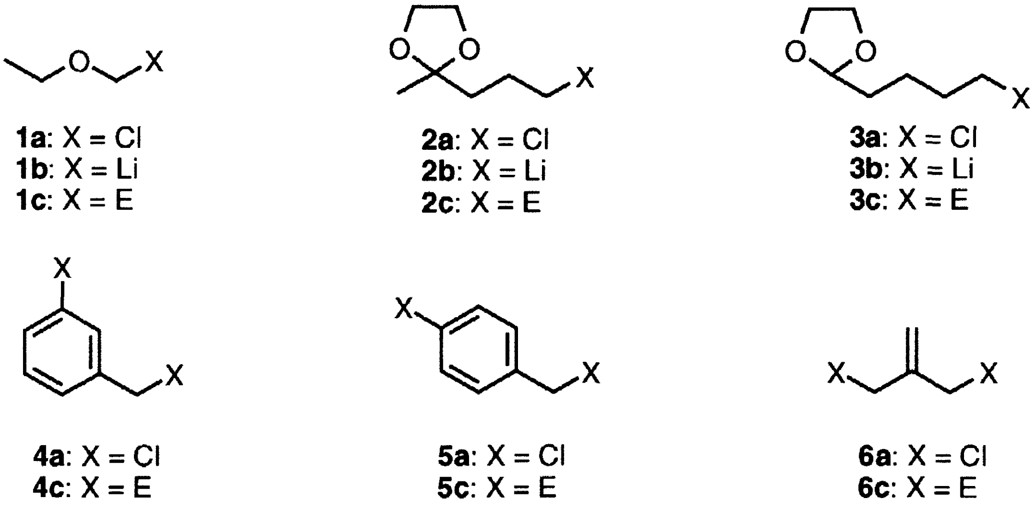
The reaction of the functionalised chlorinated materials **1a-3a** with an excess of lithium powder and a catalytic amount of the polymer Ⓟ-152 (*ca.* 10 mol %)[9] in tetrahydrofuran at temperatures ranging between -90 and -78°C for 1 h led to a solution of the corresponding lithium intermediates **1b-3b**, which on treatment with different electrophiles [Bu^nCHO, Bu^iCHO, PhCHO, $c(C_3H_5)_2CO$, Pr^i_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe, PhCH=NPh] at -78 to 20°C led, after hydrolysis, to the expected products **1c-3c**[10] (Chart 1 and Table 1). At the end of the work-up the solid polymer was filtered off , washed and dried (see above) being then quantitatively recovered and reused two or three times without apparent loss of efficiency (Table 1, entries 2, 3 and 8; see also below).



1a: X = Cl
1b: X = Li
1c: X = E

2a: X = Cl
2b: X = Li
2c: X = E

3a: X = Cl
3b: X = Li
3c: X = E

4a: X = Cl
4c: X = E

5a: X = Cl
5c: X = E

6a: X = Cl
6c: X = E

Chart 1.

Another type of arene-catalysed reaction carried out in solution required the use of Barbier-type reaction conditions[11] (lithiation in the presence of the electrophile) due to the high instability of the organolithium intermediates generated. This is the case when polychlorinated materials are submitted to a lithiation process, for example compounds **4a-6a**. With these compounds and working under the above mentioned conditions (-50°C for **4a** and **5a**, and -78°C for **6a**), but in the presence of double amount of the electrophile [Me_3SiCl, Et_2CO,$c(C_3H_5)_2CO$, $(CH_2)_4CO$], lithium and the polymeric catalyst (the starting material contains two chlorine atoms) during the lithiation step, the expected products **4c-6c** were isolated after final hydrolysis.[10] (Chart 1 and Table 2). In these cases the catalyst was also quantitatively recovered. As a test of the catalyst activity, after recovery from the reaction with dichlorinated material **6a**, the reaction with 3-pentanone was carried out five times using the same reused catalyst. The yield in each case was found to be in the same range of 80-82% (Table 2, entry 3).

From the results described in this paper we conclude that the use of a naphthalene supported polymer (easily prepared by described methodologies) as catalyst in lithiation processes represents an advantageous version of the same process in solution due to the easy recovery of the catalyst, the yields being similar in both reactions.

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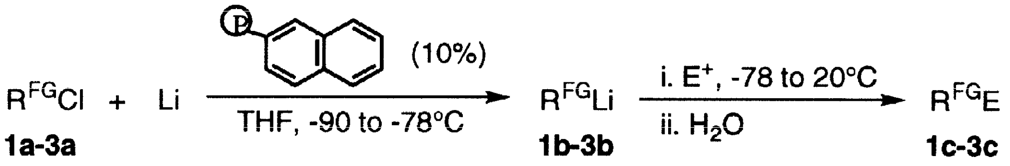
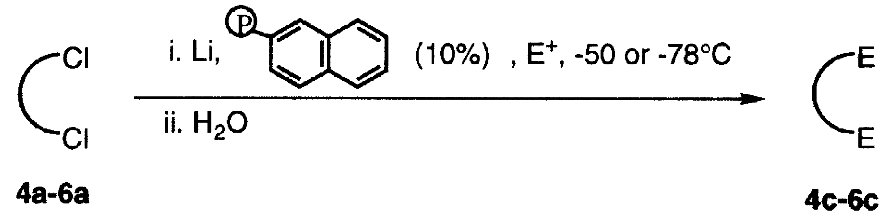
Table 1. Polymer Supported Naphthalene-Catalised Lithiation Reactions in a Two-step Process



	Starting material		Electrophile	Product[a]		
Entry	$R^{FG}Cl$	Intermediate	E+	No.	E	Yield (%)[b]
1	**1a**	**1b**	Bu^nCHO	**1c**	Bu^nCHOH	59
2	**1a**	**1b**	Bu^iCHO	**1c**	Bu^iCHOH	87[c]
3	**1a**	**1b**	PhCHO	**1c**	PhCHOH	66[d]
4	**1a**	**1b**	$(CH_2)_4CO$	**1c**	$(CH_2)_4COH$	78
5	**1a**	**1b**	$(CH_2)_5CO$	**1c**	$(CH_2)_4COH$	66
6	**1a**	**1b**	Pr^i_2CO	**1c**	Pr^i_2COH	69
7	**1a**	**1b**	PhCOMe	**1c**	PhC(OH)Me	79
8	**1a**	**1b**	PhCH=NPh	**1c**	PhCHNHPh	58[d]
9	**2a**	**2b**	Bu^iCHO	**2c**	Bu^iCHOH	79
10	**2a**	**2b**	$(CH_2)_4CO$	**2c**	$(CH_2)_4COH$	71
11	**2a**	**2b**	$(CH_2)_5CO$	**2c**	$(CH_2)_5COH$	64
12	**2a**	**2b**	PhCOMe	**2c**	PhC(OH)Me	80
13	**2a**	**2b**	Pr^i_2CO	**2c**	Pr^i_2COH	87
14	**3a**	**3b**	$(CH_2)_5CO$	**3c**	$(CH_2)_5COH$	90

[a] All crude products **1c-3c** were >90% pure and were characterised (GLC-MS) by comparison with authentic pure samples (see ref 9). [b] Isolated crude yield based on the starting material **1a-3a**. [c] The catalyst was reused twice. [d] The catalyst was reused once.

Table 2. Polymer Supported Naphthalene-Catalysed Lithiation Reactions under Barbier-Type Conditions



	Starting material	Electrophile	Product[a]		
Entry		E+	No.	E	Yield (%)[b]
1	**4a**	Me_3SiCl	**4c**	Me_3Si	98
2	**5a**	Me_3SiCl	**5c**	Me_3Si	70
3	**6a**	Et_2CO	**6c**	Et_2COH	82[c]
4	**6a**	$(CH_2)_4CO$	**6c**	$(CH_2)_4COH$	69
5	**6a**	$(c\text{-}C_3H_5)_2CO$	**6c**	$(c\text{-}C_3H_5)_2COH$	76

[a] All crude products **1c-3c** were >90% pure and were characterised (GLC-MS) by comparison with authentic pure samples (see ref 9). [b] Isolated crude yield based on the starting material **4a-6a**. [c] The catalyst was reused four times.

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6. (a) When the developement of this idea was in course, a communication appeared in which the authors obtained a polymer supported lithium naphthalenide using a silicon mediated junction between the arene and the polymeric structure. One drawback of the starting material is that *it does not react with lithium powder*, so it is necessary to use lithium biphenyl as lithiating agent. In addition, the lithiation polymer *has to be used in stoichiometric amounts*, so considerable amount of the polymeric material has to be used: van den Ancker, T. R.; Hanson, G. R.; Lee, F.-C.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1997**, 125-126. (b) For the use of a polymer-attached magnesium-anthracene complex for preparing organomagnesium compounds, see: Harvey, S.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1988**, 652-653 and Itsuno, S.; Darling, G. D.; Stöver, H. D. H.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4644-4645.
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8. The name of the polymer comes from the relative molar ratio of 2-vinylnaphthalene:styrene: divinylbenzene (1:5:2) used in its preparation.
9. This percent was calculated from the relative molar proportions of 2-vinylnaphthalene in the polymer coming that the stoichiometric amount would need 2 eq of naphthalene per chlorine atom in the starting chlorinated material, according to the equation: $RCl + 2LiC_{10}H_8 \rightarrow RLi + LiCl + C_{10}H_8$.
10. For the corresponding catalytic lithiation in solution of compounds **1a**,$^{10a-c}$ **2a**,^{10d} **3a**,^{10e,f} **4a**,^{10g} **5a**^{10g} and **6a**,$^{10h-j}$ see: (a) Guijarro, A.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 3487-3490. (b) Guijarro, A.; Mancheño, B.; Ortiz, J.; Yus, M. *Tetrahedron* **1996**, *52*, 1643-1650. (c) Ortiz, J.; Guijarro, A.; Yus, M. *An. Quim. Int. Ed.* **1997**, *93*, 44-48. (d) Yus, M.; Ramón, D. J. *J. Org. Chem.* **1992**, *57*, 750-751. (e) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 4923-4938. (f) Gil, J. F.; Ramón, D. J.; Yus, M. *Tetrahedron* **1994**, *50*, 7307-7314. (g) Gómez, C.; Huerta, F. F.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 687-690. (h) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 2217-2220. (i) Gómez, C.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 4117-4126. (j) Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187-2190.
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