Organolithium additions to styrene are synthetically viable

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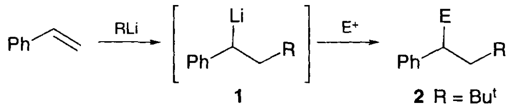
In diethyl ether at −78 to −25 °C, styrene undergoes efficient addition reactions with a range of alkyllithium reagents, and the intermediate benzyllithiums can be trapped (*e.g.* with carbon dioxide and chlorotrimethylsilane); two aryl-substituted styrenes are shown to react in a similar manner.

As part of a medicinal chemistry project we required a range of phenethyl compounds (*e.g.* **2–7**) and were intrigued by the possibility of preparing them *via* the carbolithiation of styrene as shown in Scheme 1.[1] Of course, the anionic polymerisation of styrene using organolithium reagents is a well-known process[2] and, presumably for this reason, there are few reports[1,3,4] in the literature of its organometallic addition reactions. Alkenyl-substituted derivatives of styrene do undergo synthetically useful organolithium addition reactions, although it is usually necessary to optimise the choice of reaction conditions to minimise oligomerisation.[1,5–7] We decided to investigate the organolithium addition–trapping reactions of styrene, as shown in Scheme 1, in order to determine their synthetic utility.

We anticipated that extensive experimentation would be necessary to devise conditions which would limit the degree of polymerisation. To our great surprise, this was not the case and a range of commercial and 'home-made' organolithium reagents underwent efficient addition to styrene in diethyl ether giving adducts **2–7** in good isolated yields (Table 1). Thus, treatment of styrene with *tert*-butyllithium or *sec*-butyllithium in diethyl ether as solvent at −78 °C followed by protonation using methanol gave the required adducts in almost quantitative yields (Table 1, entries 1 and 3). It seemed possible that the facility of these additions was due to the steric bulk of the secondary and tertiary substituents R; this could slow down the addition of **1** to a second molecule of styrene. However, the reactions of styrene with butyllithium and *iso*-butyllithium were also efficient (>80%), although the lower reactivity of these reagents required that a higher reaction temperature be employed (−25 °C) (Table 1, entries 5 and 10): compounds **8a,b**, resulting from the addition of a second molecule of styrene, were present as minor by-products in these reactions. In the addition of butyllithium to styrene a comparison of solvents was carried out (Table 1, entries 5, 7 and 8). No reaction was observed using hexane as solvent from −78 °C to room temperature. In contrast, with THF as solvent rapid polymerisation was observed on addition of the alkyllithium reagent, even at −78 °C. The absence of reaction in hexane was unsurprising[6,7] but the dramatic difference between diethyl ether and THF is noteworthy. These observations presumably indicate that the organolithium reagent must be sufficiently reactive to add to styrene but that the resulting lithiated intermediate **1** must be sufficiently stabilised to minimise oligomerisation.[‡] In the cases mentioned the use of diethyl ether as solvent appears to meet these requirements. This delicate balance is emphasised in the reaction of methyllithium with styrene (Table 1, entry 11). No reaction was observed in diethyl ether from −78 °C to room temperature but in this case changing to THF had no effect.[‡] The addition of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to the methyllithium in the diethyl ether reaction, however, produced polymerisation. Further studies are required to determine whether a suitable solvent can be found to effect this methylation without polymerisation occurring.[§] All of the above transformations were accomplished using commercial organolithium reagents. Entries 12 and 13 in Table 1 indicate that this is not a



2 R = Bu^t
3 R = Bu^s
4 R = Bu
5 R = Bu^i
6 R = $C_{10}H_{21}$
7 R = $PhCH_2CH_2$
a E = H; **b** E = CO_2H; **c** E = $SiMe_3$

Scheme 1

Table 1 Organolithium addition reactions with styrene

Entry	R	E	Solvent	*T*/°C	Product	Yield (%)
1	Bu^t	H	Et_2O	−78	**2a**	93[b]
2	Bu^t	CO_2H	Et_2O	−78	**2b**	92
3	Bu^s	H	Et_2O	−78	**3a**	94
4	Bu^s	CO_2H	Et_2O	−78	**3b**	86
5	Bu	H	Et_2O	−25	**4a**	85[c]
6	Bu	CO_2H	Et_2O	−25	**4b**	84
7	Bu	H	THF	−78	—[d]	—
8	Bu	H	hexane	−78 → room temp.	—[e]	—
9	Bu	Me_3Si	Et_2O	−25	**4c**	51
10	Bu^i	H	Et_2O	−25	**5a**	82[f]
11	Me	H	Et_2O	−78 → room temp.	—[g]	—
12	$C_{10}H_{21}$	H	Et_2O	−25	**6a**	82
13	$PhCH_2CH_2$	H	Et_2O	−25	**7a**	60

[a] All products were isolated and fully characterised by spectroscopy; new compounds were also characterised by HRMS or elemental analysis. [b] Styrene did not react with *tert*-butylmagnesium chloride, even at room temperature; $(Bu^t)_2CuLi$ gave **2a** in 85% yield. [c] Diadduct **8a** was also obtained (7%). [d] Polymer obtained. [e] No reaction. [f] Diadduct **8b** was also obtained (12%). [g] No reaction in diethyl ether or THF (polymerisation when TMEDA was added to ether reaction).

requirement. Decyllithium (entry 12) and 2-phenylethyllithium (entry 13), prepared by transmetallation of the corresponding iodides,[8] gave good to fair yields of the required adducts. In several cases trapping of intermediate **1** was attempted. Thus carboxylation of **1** (R = Bu^t, Bu^s, Bu) gave the expected acids **2**–**4b** in high isolated yields (Table 1, entries 2, 4 and 6 respectively), and trimethylsilylation of **1** (R = Bu) gave **4c** in 51% unoptimised yield (Table 1, entry 9).

A brief study was carried out to see if aryl substituted styrenes also participate in this type of reaction (Scheme 2). With 2-methoxystyrene **9** and a 2-amino derivative **11**, the expected adducts **10** and **12**, respectively, were obtained in high yields from the reaction with *tert*-buyllithium in diethyl ether. Further work is underway to determine the scope and limitations of this reaction and its applications in synthetic ventures.

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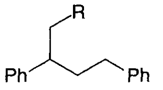
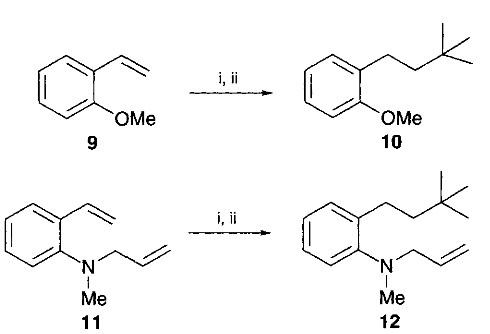


8a R = Bu
b R = Bu^i



Scheme 2 *Reagents and conditions*: i, Bu^tLi, Et_2O, −78 °C, 30 min; ii, MeOH, 83% (**10**), 90% (**12**)

Footnotes

† On leave from the Chemistry Department, Nanjing University, China.

‡ In addition reactions to 1,1-diphenylethene in diethyl ether it has been shown that methyllithium is *ca.* 4000 times less reactive than butyllithium.[7] In the same study it was demonstrated that benzyllithium is *ca.* 1700 times more reactive in THF than in diethyl ether.

§ Phenyllithium and cyclohexenyllithium gave no reaction in diethyl ether but polymerisation in THF. PhC≡CLi gave no reaction even in diethyl ether–TMEDA.

References

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