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# Enantioselective Carbolithiation of β-Alkylated Styrene.

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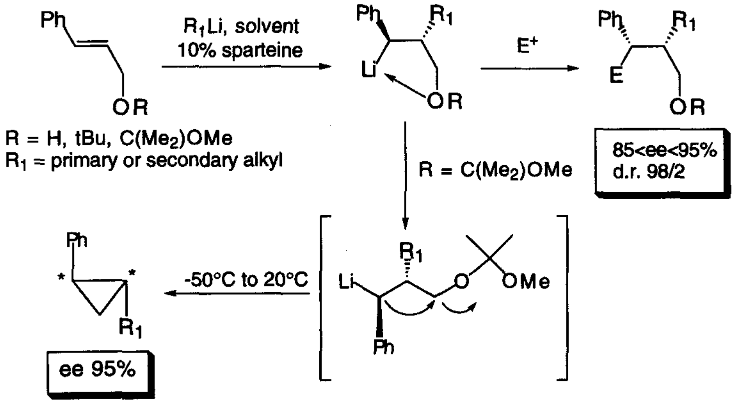
**Abstract**: Stoichiometric or catalytic amounts of (-) sparteine serve as promoter for enantioselective carbolithiation of β-alkylated, non functionalized styrene. © 1997 Published by Elsevier Science Ltd.

Key words: β-methyl styrene, sparteine, enantioselective carbolithiation.

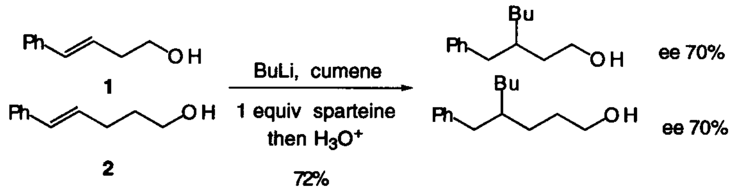
The addition of an organometallic reagent to an unsaturated olefin is generally difficult to control since such an addition may lead to polymerisation of the olefin[1] unless the final organometallic adduct is stabilized[2] or differs markedly from the starting one[3]. In this context, we have recently reported[4] an enantioselective carbolithiation[5] of cinnamyl derivatives, mediated by a stoichiometric or catalytic amount of (-) sparteine[6], leading to the chiral carbometalated product in 85% to 95% ee. Moreover, when the alcohol moiety is protected as a dimethyl methoxymethyl ether, the benzylic organolithium, when warmed to room temperature, undergoes a 1,3-elimination reaction to yield the pure chiral *trans* disubstituted cyclopropane in 95% ee[7].



Scheme 1

Cinnamyl amines also allowed a similar enantioselective addition of organolithium reagents[4]. From these studies, we thought that the intramolecular chelation of the benzylic organolithium by the heteroatoms was absolutely necessary to avoid the polymerisation reaction[2].

However, the additions of an alkyllithium in the presence of (-) sparteine to 4-phenyl-3-buten-1-ol **1** and to 5-phenyl-4-penten-1-ol **2** also lead to the carbometalated products of unknown absolute configuration in 70% ee[8] without a trace of polymeric product.

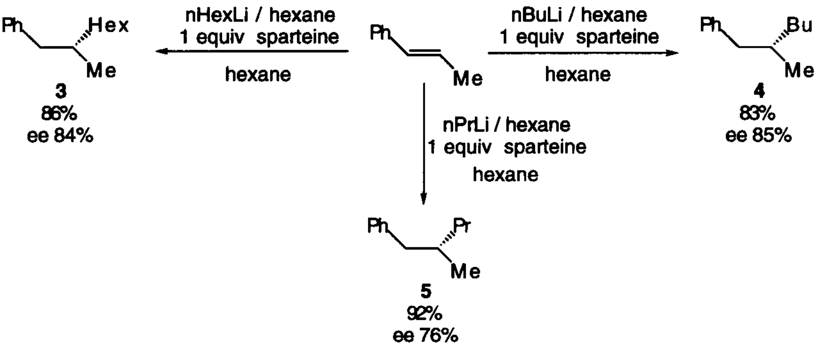


Scheme 2

These puzzling results let us to reconsider our basic idea on the necessary intramolecular chelation since in the carbolithiation reaction of **2**, a non favorable seven-membered metalacycle should be formed before hydrolysis. Moreover, recent reports have shown that the carbolithiation reaction of styrene derivative was also possible in good chemical yield without anionic polymerisation[9].

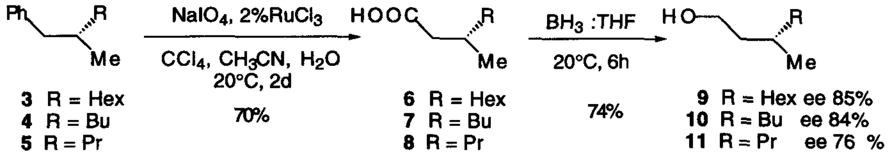
So, we decided to investigate the enantioselective carbolithiation of β-substituted, non functionalized styrenes.

Addition of β-methyl styrene to a solution of various alkyl lithiums in hexane in the presence of 1 equiv of (-) sparteine in 4 hours at -15°C leads, after hydrolysis, to the corresponding carbometalated product in good yield and good enantioselectivity without polymerisation as described in Scheme 3.



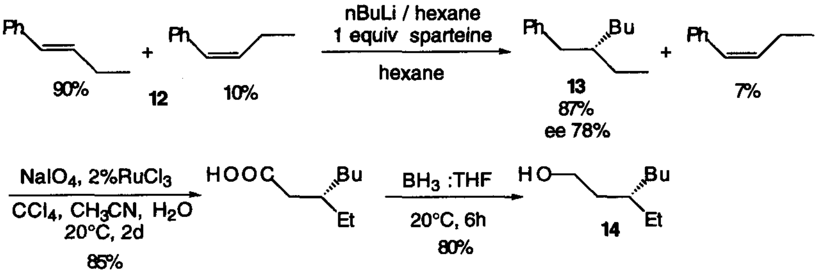
Scheme 3

From this Scheme, we can deduce that the intramolecular chelation is not necessary to prevent the polymerisation (at least in hexane as solvent). The optical purities as well as the absolute configurations of **3** and **4** were determined by comparison with authentical samples[10], except for **5**, the correlation of which was made according to Scheme 4. In the case of the addition of nPrLi, the enantiomeric excess is lower (76% instead of 85%) since the preparation of this reagent required $Et_2O$ as solvent, and in order to have good enantioselectivities it was necessary to stripp off $Et_2O$ before adding hexane as solvent[4]. Moreover, these three carbometalated products were also derivatized into the corresponding known acids[11] **6**, **7** and **8**, then reduced into the alcohols[11b,12] **9**, **10** and **11** in order to corroborate their optical purities *via* the NMR method described in reference 8.



**Scheme 4**

A slightly lower enantiomeric excess, 70%, is obtained for **4** when the reaction is performed in the presence of a catalytic amount of (-) sparteine (10%) after 12 hours at 0°C. As we have previously described[4], the stereochemistry of the olefin is crucial for the enantioselectivity of the carbolithiation. Indeed, whereas the carbometalation of the E-β-methyl styrene gives the *S* alkylated product in 4 hours at -15°C (see Scheme 3), the same reaction on the Z-β-methyl styrene leads to the opposite enantiomer (*R* )with a low enantiomeric excess (28%) in 50% yield after 8 hours at O°C. The fact that the carbometalation reaction on the Z isomer (8 hours at 0°C) differs markedly in rate from the carbometalation on the E isomer (4 hours at -15°C) led us to undertake a kinetic resolution to other β-alkylated styrene derivatives, such as β-ethyl styrene. Indeed, the addition of nBuLi on this latter substrate **12** in a E/Z ratio of 90/10, leads to the carbometalated derivative at -10°C. After hydrolysis, the corresponding product **13** is obtained in 87% yield with an enantiomeric excess of 78%, and the Z isomer is still present in the crude reaction mixture in an extent of 7% (see Scheme 5). The *S* absolute configuration as well as the enantiomeric excess of **13** were determined after derivatization into **14** and by comparison with an authentical sample[13].



**Scheme 5**

Thus, both **13** and **14** can be easily prepared in an enantioselective way, which represents an interesting entry to the elaboration of the West fragment of a potent tripeptide immunomodulator[13].

The easy and straightforward enantioselective carbolithiation of β-substituted, non functionalized styrenes allows the preparation of various chiral β-alkylated benzyl derivatives in good enantiomeric excess without a trace of polymeric product. We are currently exploring this reaction on different substrates and studying the diastereoselectivity generated at the benzylic center by reaction with different electrophiles.

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10 (a) Watson, M.B.; Youngson, G.W. *J. Chem. Soc.* **1968**, 258-262 (b) Letsinger, R.L. *J. Am. Chem. Soc.* **1948**, *70*, 406-409.**3** $[\alpha]_D^{25}$ = -10.08 (4.96, $Et_2O$); **4** $[\alpha]_D^{25}$ = -7.72 (5.01, $Et_2O$); **5** $[\alpha]_D^{25}$ = -4.96 (4.98, $Et_2O$).
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