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Organolithium Additions to Styrene Derivatives, Part IV: Tandem Intermolecular-Intramolecular Carbolithiation as a New Route to Tetralins

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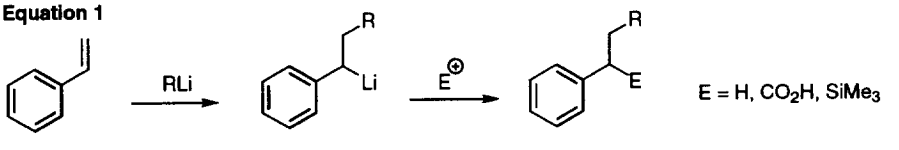
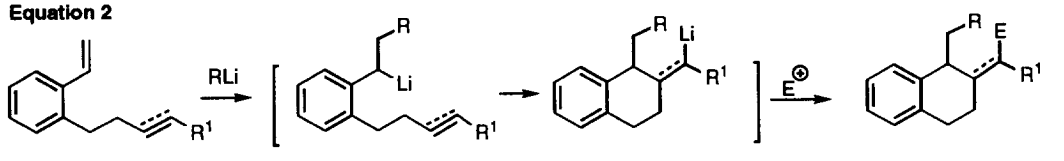
Abstract: Styrenes bearing unsaturated side chains at the 2-position undergo regioselective carbolithiation of the styrene unit followed by 6-*exo-trig* or 6-*exo-dig* cyclisation to produce 1,2- disubstituted tetralins or their unsaturated analogues. © 1997 Elsevier Science Ltd.

We recently reported that styrene[1] and 2-substituted styrenes[1,2] undergo efficient addition and addition-trapping reactions with a range of organolithium reagents providing diethyl ether is used as the solvent (Equation 1).[3] We also showed that when the addition-carboxylation reactions are carried out in the presence of (-)-sparteine, reasonable enantiomeric excesses (up to 72% with 2-methoxystyrene) can be obtained.[4] In view of our interest in the preparation of bioactive tetralins,[5] we decided to explore the tandem intermolecular carbolithiation-intramolecular carbolithiation approach to their synthesis outlined in Equation 2. The intramolecular cyclisation is obviously related to the work by Bailey *et al.* concerning organolithium cyclisations on to alkenes and alkynes.[6,7] Most published examples of this reaction are of the 5-*exo-trig* or 5-*exo-dig* type, although there are a limited number of 6-*exo-trig*[6a] and 6-*exo-dig*[7] processes known. The combination of this proven methodology with styrene carbolithiation would, in principle, provide a novel and versatile route to substituted tetralins.[8]

Equation 1

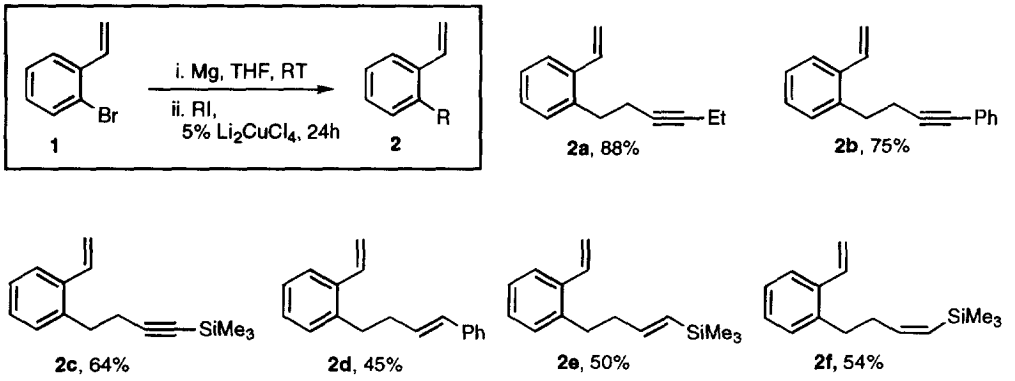


Equation 2



Suitable cyclisation precursors, designed to test the scope and limitations of the methodology outlined in Equation 2, were prepared from commercially available 2-bromostyrene **1** by the copper-catalysed Grignard procedure[9] shown in Scheme 1.[10] The alkylation yields, which are unoptimised, were considered acceptable given the potential for elimination from the homoallylic iodides.

Scheme 1



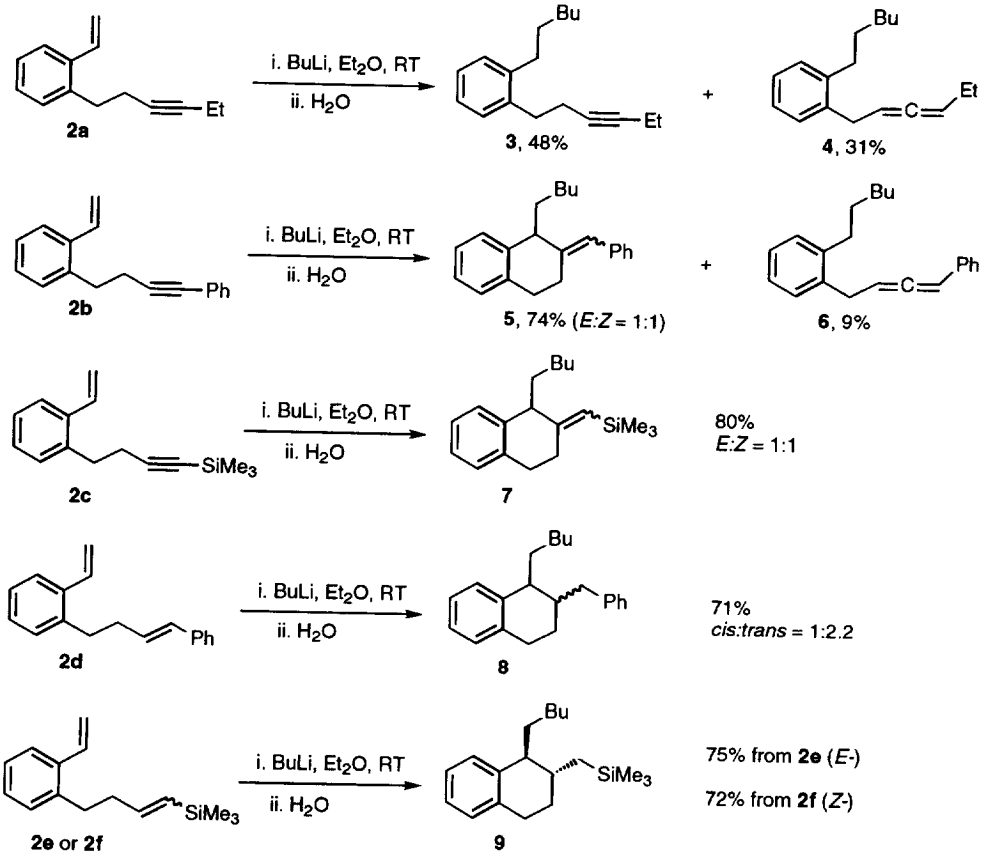
The organolithium addition reactions of **2a** - **2f** were then explored (Scheme 2). Alkynes **2a-c** were studied first, commencing with the dialkyl alkyne **2a**. Addition of butyllithium to a solution of **2a** in diethyl ether gave two separable adducts in a combined yield of 79%. The adducts were shown to be alkyne **3** and allene **4**. This result confirmed our belief that organolithium addition reactions to compounds **2** would occur preferentially at the styrene site, but indicated that the 6-*exo*-cyclisation was not facile with an unactivated alkyne. We therefore moved on to look at phenylalkyne **2b**. In this case butyllithium addition again occurred regioselectively at the styrene site but, most pleasingly, cyclisation then followed to produce, after protonation, tetralin **5** (74%), accompanied by allene **6** (9%). With trimethylsilylalkyne **2c** the cyclisation was even more efficient with vinylsilane **7** being isolated in 80% yield as the only product. In both of these successful examples, the adducts **5** and **7** were isolated as 1:1 mixtures of *E*- and *Z*-alkenes; the rapid equilibration of α–phenyl and α–trimethylsilyl vinyllithium reagents has been noted before.[7b]

Having demonstrated the viability of the tandem intermolecular carbolithiation-intramolecular 6-*exo-dig* cyclisation we moved on to examine the corresponding 6-*exo-trig* process with the activated alkenes **2d-f**. Treatment of styrene **2d** with butyllithium gave, after protonation, the 1,2-dialkylated tetralin **8** in 71% yield with a 2.2:1 predomominance of an isomer tentively assigned as having the *trans*-configuration. With the corresponding vinylsilanes **2e** and **2f**, the reactions were efficient and they were also stereoselective as tetralin **9** was isolated regardless of which silane was employed.[11] The 1,2-*trans*-configuration was tentatively assigned to **9** by comparison of ^{1}H- and ^{13}C-chemical shifts with the published values for the 1,2-dimethyltetralins,[5a] and because no nOe could be observed between the methine protons.

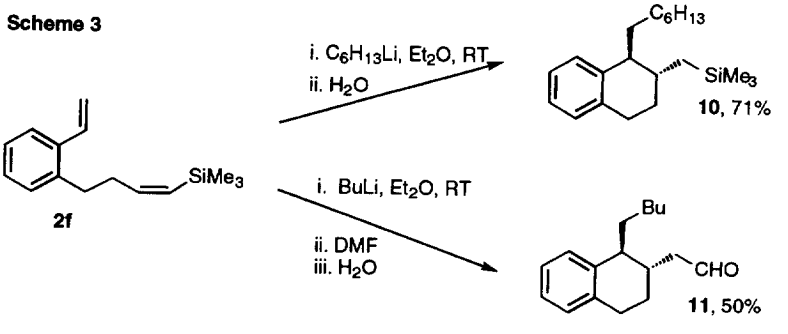
The reactions shown in Scheme 2 were all carried out using butyllithium as initiating nucleophile and protonation at the completion of the reaction. The methodology is extremely versatile in that a range of nucleophilic organolithium reagents and electrophiles can be employed. Thus (Scheme 3), with styrene **2f** hexyllithium followed by protonation gave tetralin **10**, and butyllithium followed by formylation with DMF gave **11** (desilylation occurring during work-up).

We are currently exploring further the synthetic potential of these processes with particular emphasis on asymmetric variants[4] and applications in medicinal chemistry.

Scheme 2



Scheme 3



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References and Notes

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   (c) see also Koppang, M. D.; Ross, G. A.; Woolsey, N. F.; Bartak, D. E. *J. Am. Chem. Soc.* 1986, **108**, 1441.
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   (b) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* 1993, **115**, 3080.
8. Substituted indane and indoline systems have been prepared by organolithium 5-*exo-trig* cyclisation processes: see references 6b and 6c and Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* 1996, **61**, 2594.
9. Friedman, L.; Shani, A. *J. Am. Chem. Soc.* 1974, **96**, 7101.
10. All new compounds were fully characterised by high field ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.
11. Representative experimental procedure; preparation of tetralin **9**:
    Under a nitrogen atomosphere at room temperature, a solution of diene **2f** (69 mg, 0.3 mmol) in diethyl ether (3 mL) was added dropwise to a stirred solution of butyllithium (1.6 *M*in hexanes, 0.25 mL, 0.4 mmol) in diethyl ether (12 mL) by a syringe pump over 1 h. On completion of the addition, the reaction was stirred for 5 min and then quenched with water. Ether (25 mL) was added to the solution and the ether layer was separated and washed with water (20mL), brine (20 mL) and dried over sodium sulphate. Evaporation of solvent and column chromatography (silica gel, petroleum ether as eluant) gave **9** (63 mg, 72%) as a colourless oil, R_f 0.5 (petroleum ether); ν_{max} (neat) 2929, 1602, 1458, 1248, 860, 837 cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.02 (9 H, s, $SiMe_3$), 0.61 (2 H, m, CH_2Si), 0.85 (3 H, t, *J* 7Hz, CH_3), 1.27 (7 H, m, CH_2), 1.56-1.71 (3 H, m, CH_2), 1.98 (1 H, m, ArCHC<u>H</u>), 2.47 (H, m, ArCH), 2.83 (H, m, CH_2Ar), 7.05 (H, m, ArH); δ_C (67.9 MHz, $CDCl_3$): -0.6, 14.2, 20.5, 22.7, 27.0, 28.0, 28.2, 29.6, 32.4, 33.9, 45.3, 124.6, 125.7, 129.0 (x 2), 135.9, 142.7; *m/z* (EI): 288 (M^+), 273, 217, 73 [HRMS: 288.2282. $C_{19}H_{32}Si$ requires 288.2273 (3 ppm error)].

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