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STEREO- AND REGIOSELECTIVE FORMATION OF SILYL ENOL ETHERS VIA OXIDATION OF VINYL ANIONS

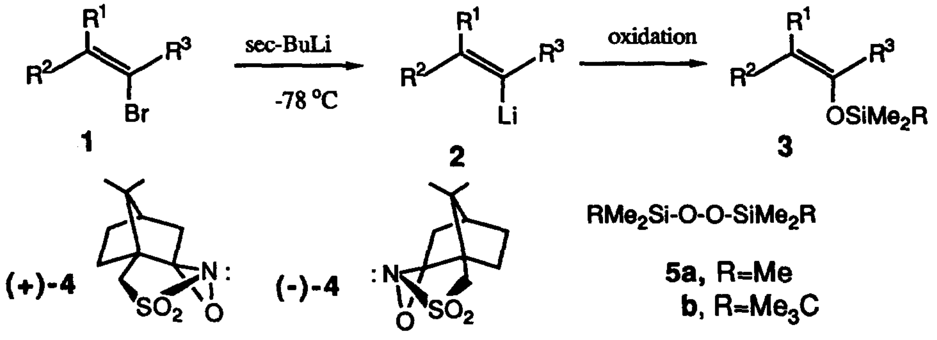
Franklin A. Davis,* G. Sankar Lal and Jia Wei
Department of Chemistry, Drexel University, Philadelphia, PA 19104

Summary: Oxidation of E- and Z-vinyl lithiums with silyl peroxides **5** affords silyl enol ethers **3** in good to excellent yield with retention of configuration. This methodology represents a useful new procedure for the stereo- and regioselective synthesis of ketone enolates.

Over the past two decades, a considerable degree of effort has been focused on the synthesis of acyclic ketone enolates of well defined structure.[1,2] This is due to the enormous synthetic utility of enolates in carbon-carbon bond forming reactions, i.e. alkylation and aldol condensation reactions. The stereostructure of the enolate is of particular importance in the aldol reaction because it defines the relative configurations of the two new chiral centers in the product.[3] There are two primary concerns in the generation of stereodefined enolates.[4] First is the formation of a specific E- or Z-enolate geometric isomer. While one of the enolate geometric isomers can generally be obtained in high purity by proper choice of solvent and base, it is frequently very difficult to obtain the other isomer.[5] One of the strategies used to circumvent this problem has been to trap the mixture of E- and Z-enolates as their silyl enol ethers. The E and Z-silyl enol ethers are separated, often with difficulty, and the enolates regenerated by treatment with methyllithium.[2,5] The second problem is the generation of a specific enolate regioisomer from acyclic ketones where the two α-positions are relatively similar.[2,6] Attempts to solve this problem have employed hindered bases,[7,8] activating groups[9], specific silylating reagents[10] and ester enolate transformations[11] with limited degrees of success.

In connection with our interest in the oxidation of carbanions,[12,13] we thought that the stereoselective oxidation of vinyl anions **2** could provide a solution to the difficulty of stereo- and regioselective enolate formation (Scheme). The stereoselective synthesis of vinyl lithiums from vinyl halides **1** is well documented.[14] We were further encouraged by a

Scheme



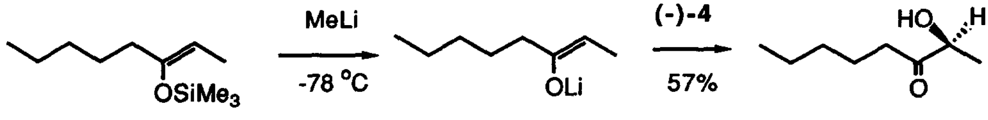
l977 report of Whitesides and co-workers in which they described the oxidation of E- and Z-1-lithio-1-propenes to the corresponding lithium enolates with retention of configuration using lithium *tert*-butyl peroxide .[15] Preliminary results of a simple procedure for the stereo- and regioselective formation of enolates involving the stereospecific oxidation of vinyl lithiums are described in this letter.

Typically, the vinyl anions **2** were generated by treatment of 1.0 mmol of the vinyl bromides **1** with one equivalent of *sec*-butyllithium or two equivalents of *tert*-butyllithium in THF at -78 or -110 °C. After 15 minutes the vinyl anions **2** were oxidized with (+)-(camphorylsulfonyl)oxaziridine (**4**),[13,16] bis(trimethylsilyl) peroxide (**5a**)[17,18] or bis(*tert*-butyldimethylsilyl) peroxide (**5b**).[17] In the former case the enolates were trapped with trimethylsilyl chloride (Table). The E- and Z-vinyl bromides were prepared by the general methods of Brown et al.[19] and by Miller and McGarvy.[20] The silyl enol ethers **3** were isolated as oils by flash chromatography (silica gel) eluting with dry n-pentane. The E/Z ratios of **3** were determined by ^{1}H NMR. While the geometry of the silyl enol ethers **3** were not rigorously established the reasonable assumption is made that major isomer is the one formed with retention of configuration. Consistent with this interpretation are the larger coupling constants observed for the E-2-phenyl silyl enol ethers **3** (19 and 12 Hz) compared to the Z-2-phenyl silyl enol ethers **3** (15 and 7 Hz) (Table, entries 5-8).

Vinyl anion oxidations using (+)-(camphorylsulfonyl)oxaziridine (**4**) followed by trapping of the enolate with trimethylsilyl chloride gave the corresponding silyl enol ethers in moderate yield (Table: entries 1, 3, 11). Oxidation of **2** by (+)-**4** did not proceed with complete retention of configuration giving 15 to 20 percent of the isomerized silyl enol ethers. We reasoned that the oxidation time as well as the necessity for trapping with trimethylsilyl chloride may have caused some localized heating, resulting in isomerization of the vinyl anion. Quenching of the vinyl anion by the sulfonimine product derived from (+)-**4** is likely responsible for the lower yields observed with this oxidizing reagent.[12]

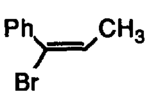
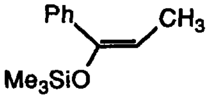
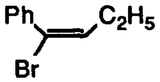
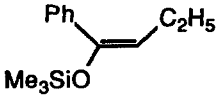
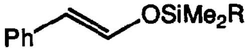
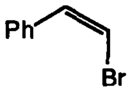
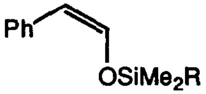
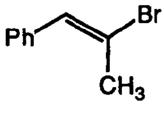
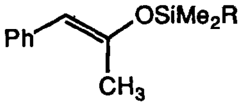
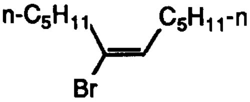
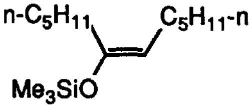
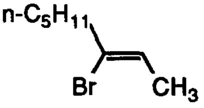
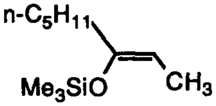
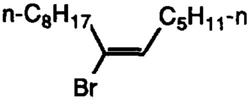
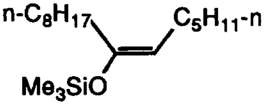
In 1978 Neumann and Seebach reported that the oxidation of E-1-lithio-1-hexene with bis(trimethylsilyl) peroxide (**5a**) gave the silyl enol ether in less than 7 percent.[17] Nevertheless we felt that **5a** should be a more effective reagent than (+)-**4** for vinyl anion oxidation because of its greater reactivity and the fact that **3** is formed directly, affording less opportunity for isomerization. Indeed, use of **5a** not only gave better yields than (+)-**4** but, more importantly, resulted in near complete retention of configuration (Table). Lower temperatures (-110 °C) and the use of bis(*tert*-butyldimethylsilyl) peroxide (**5b**) gave improved yields for the oxidation of the vinyl anions derived from 2-bromostyrene and 2-bromophenyl-2-propene, probably because of lower losses in the isolation step (Table: entries 6, 8, 10).

This methodology has obvious application to the regioselective formation of enolates from ketones where the two α-positions are similar. An illustration is the synthesis of (+) (S)- 2-hydroxy-3-octanone (**8**), one of the components of the two component grape-borer pheromone.[21] Treatment of silyl enol ether **6** (Table: entry 13) with methyllithium in THF at 0 °C for 15 minutes gave the enolate **7** which was cooled to -78 °C and oxidized by addition of 1.0 equivalent of (-)-**4**. The reaction mixture was warmed to 0 °C, quenched by addition of saturated NH$_4$I solution, and (+)-**8** isolated by flash chromatography (ether-pentane elution) in 57% yield. The optical purity, 12% ee, was determined using the chiral shift reagent Eu(hfc)$_3$ and by comparison of its optical rotation with literature values.[21]



6 **7** (+)(S)-**8** (12% ee)

Table: Stereoselective Oxidation of Vinyl Bromides to Enolates at -78 °C in THF

Entry	Vinyl Bromide (1) (ref.)	Oxidizing reagent conditions	Silyl Enol Ether (3)	% Isolate Yield (E:Z)
1	 (a)	(+)-4/TMSCl		48 (82:18)
2		5a		70 (92:8)
3	 (b)	(+)-4/TMSCl		41 (84:16)
4		5a		78 (92:8)
5	 (c)	5a -110° (t-BuLi)		11 (100:0)
6		5b -110° (t-BuLi)		43 (100:0)
7	 (d)	5a -110° (t-BuLi)		18 (0:100)
8		5b -110° (t-BuLi)		35 (0:100)
9	 (e)	5b		28 (100:0)
10		5b -110°		45 (100:0)
11	 (f)	(+)-4/TMSCl		25 (100:0)
12		5a		75 (100:0)
13	 (g)	5a		82 (0:100)
14	 (f)	5a		76 (70:30)

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In summary the stereoselective oxidation of vinyl lithium reagents represents useful new methodology for the stereo- and regioselective synthesis of silyl enol ethers which are precursors of stereodefined enolates.

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