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Chiral β-Lithio Enol Ethers: Synthesis and Properties

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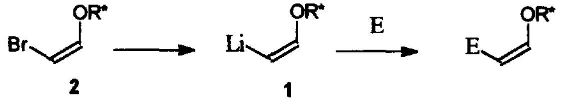
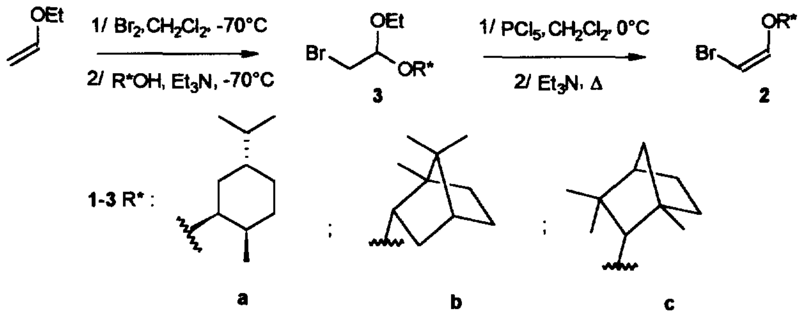
Abstract: Chiral lithio enol ethers **1** obtained from corresponding Z-bromo enol ethers react with alkyliodides, acylchlorides, leading to new chiral enol ethers of controlled configuration **5-8**.

Our interest in the field of organometallic vinylic reagents with a masked carbonyl function[1] prompted us to consider lithio enol ethers **1**, bearing a chiral moiety as valuable intermediates in asymmetric synthesis. In this paper, we report their preparation from bromo enol ethers **2** and their reactions with various electrophilic reagents (Scheme 1).



Scheme 1

We first developed a general and versatile procedure to chiral unknown bromo enol ethers **2**, precursors of reagents **1** (Scheme 2).Addition of bromine to ethyl vinyl ether in dichloromethane, followed by chiral alcohol R*OH led to mixed bromoacetals **3** (2 diastereomers) which were transformed into bromo enol ethers **2** upon treatment by phosphorus pentachloride, followed by triethylamine in dichloromethane at reflux. [2] For this last step, the transformation of the intermediate dihalo ethers was monitored by GC. We thus prepared three chiral bromo enol ethers **2a-c** in two steps with a good overall yield (59 < yd% <87) (Table 1).



Scheme 2

It is to be noted that the use of crude instead of freshly distilled dichloromethane led to significantly lower yields. Also to be underlined is the prominent Z configuration of bromo enol ethers **2** (9 < Z/E < 11.5). [3]

Table 1 : *Preparation of bromo enol ethers* **2**.

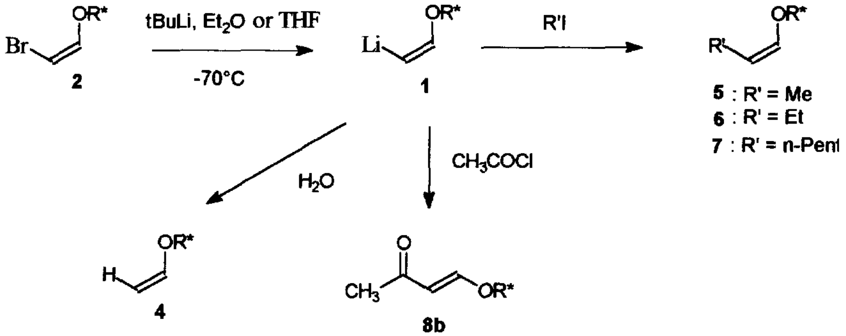
R*	yield[a] **3**	Reflux time **3→2**	yield[b] **2**	Global yield[a,b] **2**	Z/E **2**
Menthyl	**3a** 89%	4h	**2a** 98%	**2a** 87%	90/10
Bornyl	**3b** 80%	5h	**2b** 82%	**2b** 66%	92/8
Fenchyl	**3c** 78%	5h	**2c** 75%	**2c** 59%	92/8

[a]Yield in chromatographed product. [b]Based on ethyl vinyl ether.

The bromine-lithium exchange performed at -70°C in ether or tetrahydrofurane using *t*-butylithium was complete as shown by subsequent addition of H_2O leading to enol ethers **4** in quantitative yields (Scheme 3).

Reaction of reagents **1** with alkyliodides R'I in THF gave chiral enol ethers **5-7** of exclusive Z configuration. [4] The condensation yields were improved in the presence of lithium bromide and using concentrated solutions (Table 2). Chiral enol ethers are reported to be choice partners for [2+2][5], [3+2][6], [4+2][7] cycloadditions and lewis acid catalysed condensations with acetals. [8] The synthesis of monosubstituted chiral enol ethers **5-7** of controlled configuration proposed here represents an attractive alternative to the three main methods of literature : isomerisation of allylic ethers[5a], reduction of α-alkoxy enol phosphates[9], reduction of ynol ether. [10, 11]

Reaction of **1b** with acetylchloride in ether led to the β-keto enol ether **8b** (68%) isolated (after elimination of products by Kugelrohr distillation) under its E configuration. As retention of the configuration of lithio enol ethers is observed in similar cases [1, 3], we presume that an isomerisation of the initial Z isomer occurs during the work-up.



Scheme 3

Table 2 : *Chiral Z-enol ethers* **5-7** *by condensation of* **1** *with alkyl iodides.*

Starting **1**	Yields **5-7**[a]		
	R'= Me	R'= Et	R'= n-Pent
1a	**5a** quant	**6a** 51%[b, c]	
1b	**5b** 92%		**7b** 54%[b, d]
1c	**5c** 91%		**7c** 35%[b]

[a] Yields from **2** ; **5-7** were purified by chromatography on silicagel or Kugelrohr distillation (for hydrolysis compounds **4**). [b] Alkylation in the presence of LiBr (5eq).[c] 13% Alkylation without LiBr (determined by GC).[d] Using 4.5 M *t*-BuLi for the bromine lithium exchange; 44% yd using 1.7 M *t*-BuLi.

Experimental details are reported in reference 12.

The synthesis of new chiral bromo enol ethers **2** and the study of related products are currently under investigation.

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(11) See : Dujardin, G.; Rossignol, S.; Brown, E.; *Tetrahedron Lett.* **1995**, *36*, 1653-1656, for the preparation of chiral 2-alkoxy propenes isomers of **5a** and **5b**.

(12) Bromo enol ethers **2** : To a stirred solution of ethyl vinyl ether (38 mmol, 2.8g) in freshly distilled dichloromethane (20 ml), under argon at -70°C was added bromine (38 mmol, 6.2 g) until persistent color. A few drops of ethyl vinyl ether were then added until the mixture faded. The chiral alcohol (47.2 mmol) in triethylamine (50.5 mmol, 5.1g) was then added under stirring within 20 minutes. The reaction mixture was maintained at this same temperature for 15 minutes, at 0°C for 1 hour, diluted with dichloromethane, and poured into ice-water. The organic layer was washed with 0.1N HCl, 2N NaOH, saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silicagel (98/2 petroleum ether-ether) to give bromoacetal **3**.

Bromoacetal **3** (22.9 mmol) in freshly distilled dichloromethane (10 ml) was added to a suspension of phosphorus pentachloride (22.9 mmol, 4.75 g) in dichloromethane (20 ml) at 0°C under argon, within 15 minutes. The mixture was stirred at 0°C for 45 minutes and triethylamine (114 mmol, 11.5 g) was then added. The mixture was heated at reflux (see table 1) and poured into cold water. The organic layer was washed with 0.5N HCl, 2N NaOH, saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was finally chromatographed on deactivated silicagel (0.5% triethylamine in petroleum ether) affording bromo enol ether **2**.

1-bromo-2-menthoxy ethylene **2a** (Z/E = 90/10).

Characteristic peaks in **^{1}H-NMR** Z isomer : (200 MHz, $CDCl_3$) 4.87 (d, 1H, J=4 Hz), 6.14 (d, 1H, J=4 Hz); E isomer : 4.42 (d, 1H, J=12 Hz), 6.51 (d, 1H, J=12 Hz).

$[\alpha]_D^{20}$: -40 (EtOH, c=1.07).

Enol ethers **5** To bromo enol ether **2** (0.96 mmol) in THF (3.85 ml) under argon was added *t*-butyllithium (1.8M in pentane, 1.07 ml, 1.93 mmol) within 10 minutes at -70°C. After 90 minutes at -70°C, freshly distilled methyl iodide (1.93 mmol, 0.275g) at -70°C was added. After 2-3 hours at -70°C the mixture was slowly warmed up to room temperature (~12 hours). The solution was then cooled down back to -70°C and 5% aqueous Na_2CO_3 was added. The aqueous layer was extracted with ether. The organic solution was dried ($MgSO_4$) and concentrated to provide enol ether **5**.

Enol ethers **6-7** : Lithium bromide (4.78 mmol, 0.42g) was introduced in a flask and dried by heating under vacuum. THF (2.5 ml) was then added. The solution was cooled down to -70°C before adding *t*-butyllithium (1.54M in pentane, 2.20 mmol, 1.43 ml), then bromo enol ether **1** (0.96 mmol) in THF (1.35 ml). After stirring for 90 minutes at -70°C, alkyliodide (1.93 mmol) was added and the mixture worked up as in the case of enol ethers **5**.

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