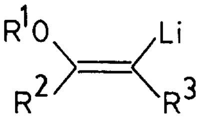
Tetrahedron Letters,Vol.25,No.52,pp 5977-5980,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

HETEROATOM DIRECTED β-LITHIATION OF A VINYL ETHER

Patrick G. McDougal* and Joseph G. Rico
Department of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332

Abstract: Oxygen directed β-deprotonation of a vinyl ether leads to Z substituted enol ethers. The stereoselective elaboration to a naturally occuring threo 1,3-diol is described.

While the α-lithiation of vinyl ethers has enjoyed extensive use in organic chemistry[1,2], most notably for the generation of acyl anion equivalents[2], direct β-lithiation of a vinyl ether containing no additional activating groups has yet to be reported[1]. β-Lithiated enol ethers, such as **1-3**, have been prepared by either metal-halogen exchange [3] or transmetallation[4]. The unsubstituted lithiated vinyl ethers 1[3b] and 2[3c] have been introduced as nucleophilic acetaldehyde equivalents, while Kowalski has demonstrated the enhanced nucleophilicity of dianions 3 in comparison to simple enolates[3d]. In this communication we wish to report the first direct β-deprotonation of a simple vinyl ether and to outline some unique advantages associated with β-lithiated vinyl ethers.



1 R^1=Et; R^2,R^3 = H
2 R^1=Si≡; R^2,R^3 = H
3 R^1=Li; R^2,R^3 = variety of substituents

Heteroatom facilitated deprotonations have played a major role in the development of new stratagies for C-C bond formation[1,5]. The enol ether **4**[6] has two sites which could benefit from oxygen assisted deprotonation. While ortho deprotonation (H_a) directed by a benzyl heteroatom has ample precedent[1,7], the removal of the cis-vinyl proton (H_b) would be unique[8] and would represent a novel entry into β-lithiated vinyl ethers. In the event treatment of enol ether **4** with 1.4 equivalents of s-BuLi at -78° forms a deep orange solution which upon quenching with a variety of electrophiles (E) leads to the substituted enol ethers **6** in good to moderate yields (Table I)[9,10]. No products arising from aromatic deprotonation (H_a) could be detected by NMR spectroscopy (300 MHz).

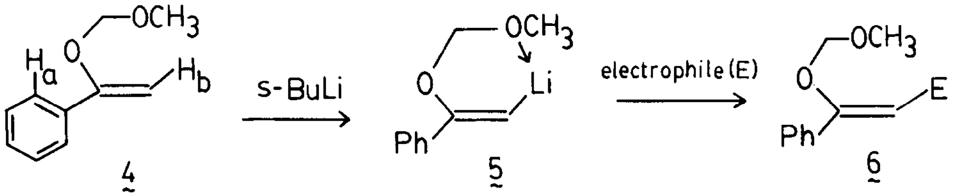
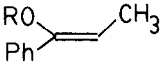
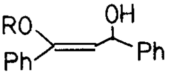
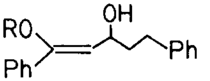
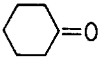
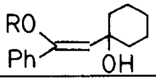
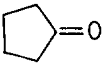
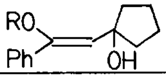
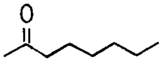
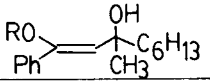
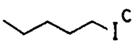
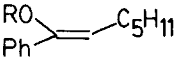


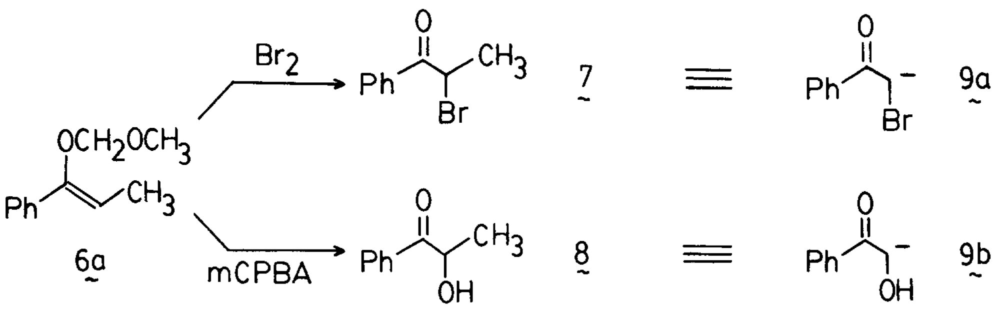
Table I: Reactions of Vinyl Anion **5** with Various Electrophiles[9,10]

ENTRY	electrophile (E)	PRODUCT(**6**)[a]	YIELD[b]
1	CH_3I	 6a	80%
2	PhCHO	 6b	84%
3	$PhCH_2CH_2CHO$	 6c	67%(80%)
4		 6d	65%(79%)
5		 6e	49%(75%)
6		 6f	55%(80%)
7	 [c]	 6g	55%(75%)

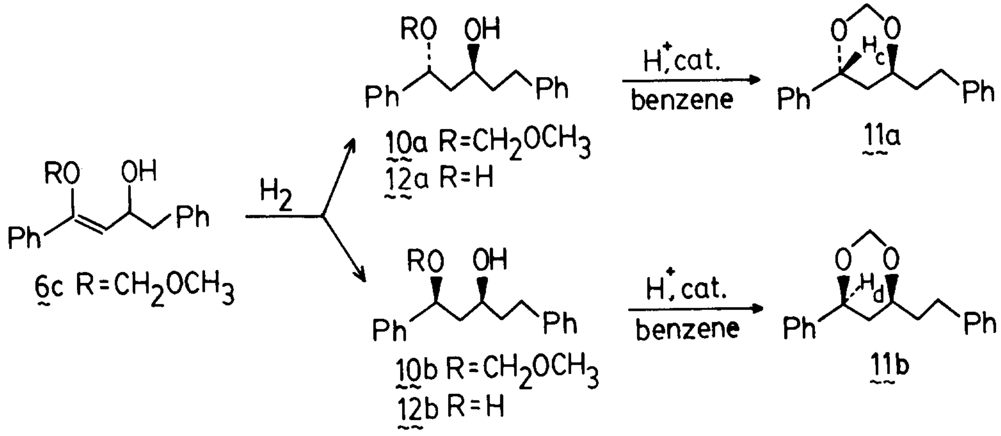
[a] $R=CH_2OCH_3$. [b] Yields are for isolated product. Yields in the parentheses are based on unreacted starting material **4**. [c] Reaction run in the presence of CuI (0.5 equi) and HMPA.

Certain features of this reaction deserve comment. First, anionic systems such as **5** are prone to alkoxide elimination[11] so that in some of our reactions small amounts (~5%) of acetylenic compounds were isolated. Second, reactions with alkyl halides, other than methyl iodide, required copper catalysis (entry 7). Third, deprotonation does compete with nucleophilic addition when the carbonyl electrophile possesses acidic protons (entries 3-6) as evidenced by recovery of the starting enol ether **4**. However, in contrast to the reaction of acetophenone enolate with cyclopentanone or the α-keto dianions **3** with 2-octanone in which only deprotonation was observed[3d], our system does yield addition products with both ketones (entries 5 and 6) albeit with some concomitant deprotonation. Finally, only one geometrical isomer, presumably the Z-isomer[11], was isolated in all cases. This allowed for a stereoselective synthesis of 1,3-diols as described below.

The adducts **6** can serve a number of useful functions. For example oxidation of the enol ether **6a** with either bromine or mCPBA leads to the substituted propiophenone derivatives **7** and **8** respectively. As such the original vinyl anion can be considered equivalent to the anion of α-bromo (**9a**) or α-hydroxy (**9b**) acetophenone. The Z-allylic alcohols (**6b-6f**) are ideally suited for stereoselective elaboration as exemplified by the transformation of **6c** into the naturally



occuring diols **12a** and **12b**[12]. Catalytic hydrogenation of the allylic alcohol **6c** furnished a 3:1 mixture of **10a** and **10b**[13]. The stereochemistry of **10a** and **10b** was easily ascertained by conversion into the 1,3-dioxane derivatives **11a** and **11b**. In accord with published data[14], the *trans*-4,6-disubstituted-1,3-dioxane (**11a**) exhibited a doublet of doublets (J=6.9,4.2 Hz) for the benzyl proton (H_c) while the *cis* derivative (**11b**) recorded a doublet of doublets (J=10.5, 3.5 Hz) for its benzyl proton (H_d). The *threo* selectivity observed for this hydrogenation nicely complements the *erythro* selectivity observed in the sodium borohydride reduction of acyclic 1,3-diones[12a]. The acetals **10a** and **10b** were hydrolyzed (aq. HCl, THF) to yield the diols **12a** and **12b**, both constituents of the Australian scented maple[12]. That the methoxy acetal moiety acts as both a directing group for the original deprotonation and a protecting group for an alcohol is noteworthy.



Having demonstrated both the preparation and synthetic potential of β-lithiated vinyl ethers, we are presently attempting to extend this methodology to other substituted enol ethers including dienyl enol ethers. Our efforts toward this goal will be the subject of a future publication.

Acknowledgement: Acknowledgement is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Georgia Institute of Technology is also recognized for their generous support of our research program.

References and Notes

1. For review, see: Gschwend, H.W.; Rodriguez, H.R. Org. React. **1979**, 26,1.
2. Boeckman, Jr., R.K.; Bruza, K.J. Tetrahedron **1981**, 37, 3997 and references therein.
3. (a) Ficini, J.; Kahn, P.; Falou, S.; Touzin, A.M. Tetrahedron Lett. **1979**, 67. (b) Lau, K.S.Y.; Schlosser, M. J. Org. Chem. **1978**, 43, 1595. (c) Duhamel, L.; Tombret, F. J. Org. Chem. **1981**, 46, 3741. (d) Kowalski, C.J.; Fields, K.W. J. Am. Chem. Soc., **1982**, 104, 1777.
4. Wollenberg, R.H.; Albizati, K.F.; Peries, R. J. Am. Chem.Soc. **1977**, 99, 7365.
5. *For a recent example, see:* Mills, R.J.; *Snieckus,* V. *Tetrahedron* Lett. **1984**, 25, 483.
6. The enol ether **4** (b.p. 86-89°(2.0mm)) can be prepared in four steps (80%) from methyl mandelate: (a) $CH_3OCH_2OCH_3$, P_2O_5 (b) $LiAlH_4$ (c) CH_3I, NaH (d) s-BuLi, THF, -78° → 0°.
7. For a review of benzamide assisted ortho deprotonations, see: Beak, P.; Snieckus, V. Accts. Chem. Research **1982**, 15, 306.
8. Deprotonation of enol ethers where the β-directing effecting of oxygen is of secondary importance are known, see: (a) Ficini, J.; Depezay, J.C. Tetrahedron Lett. **1968**, 937. (b) Vlattas, I.; Della Vecchia, L.; Lee, A.O. J. Am. Chem. Soc. **1976**, 98, 2008.
9. A typical experiment is as follows. To the enol ether **4** (21.3 mmol) in THF (25 ml) was added s-BuLi (1.3 M(cyclohexane), 31.9 mmol) at -78°C. Following the addition the resulting orange solution was stirred for 30 min at -78° and then quenched with hydrocinnamaldehyde. After another 30 min at -78° the mixture was allowed to warm to RT, diluted with ether and washed with sat'd $NaHCO_3$. Flash chromatography (20% ethyl acetate-hexane) yielded **6c** (66%) as a crystalline solid (mp 52-53°).
10. All new compounds have been fully characterized by IR, 'H NMR and mass spectroscopy. High resolution MS and/or microanalysis established molecular composition.
11. Lau and Schlosser (ref. 3b) determined that the Z enol ether **1** was stable up to -30°C, while the E isomer spontaneously decomposed to acetylene at -80°C. The thermal stability of our reagent as well as the directing influence of the oxygen are the bases for assigning the Z configuration to the enol ether products (**6a**-**6**g).
12. (a) Breen, G.J.W.; Ritchie, E.; Taylor, W.C. Aust. J. Chem. **1962**, 15, 819. (b) Picker, K.; Ritchie, E.; Taylor, W.C. Aust. J. Chem. **1976**, 29 , 2023.
13. *The selectivity using* Wilkinson *catalyst was* 9:1 *in favor of the* threo product (**10a**). Unfortunately this was a sluggish reaction and the yield of product was variable. We have yet to experiment with iridium catalysts where precedent exists for such stereoselective reductions, see: Stork, G; Kahne, D.E. J. Am. Chem. Soc. **1983**, 105, 1072.
14. (a) Eliel, E.L.; Knoeber, M.C. J. Am. Chem. Soc. **1968**, 90, 3444. (b) Anteunis, M.; Tavernier, D.; Swaelens, G. Rec. Trav. Chim. Pays. - Bas. **1973**, 92, 531. (c) Burkert, U. Tetrahedron **1979**, 35, 691.

(Received in USA 22 August 1984)