GENERAL STEREOSELECTIVE ROUTE TO (*E*)-3-HYDROXY-1-ALKENYL CHLORIDES AND PHENYL ETHERS†

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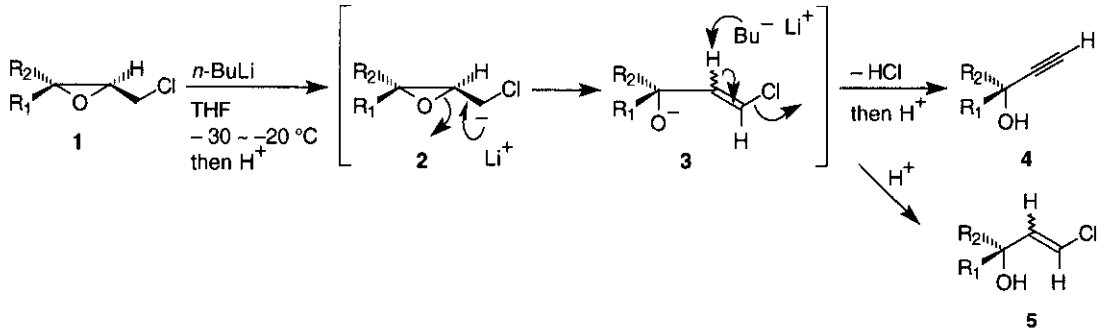
Abstract —— Treatment of 2,3-epoxyalkyl chlorides with potassium *tert*-butoxide affords the corresponding (*E*)-1-chloro-3-hydroxyalkenes stereoselectively when dicyclohexano-18-crown-6 is present. On the other hand, 2,3-epoxyalkyl phenyl ethers furnish (*E*)-3-hydroxy-1-alkenyl phenyl ethers stereoselectively upon exposure to *n*-butyllithium in the presence of hexamethylphosphoric triamide.

In 1989, we reported[1] an efficient general protocol for the construction of optically active 3-hydroxy-1-alkynyl functionalities (**4**) by *n*-butyllithium-induced elimination of optically active 2,3-epoxyalkyl chlorides (**1**), generated *via* the Katsuki-Sharpless asymmetric epoxidation [2] The reaction is presumed to involve a 1-chloro-3-hydroxyalkenyl intermediate (**5**) which can be often isolated as a by-product when insufficient amount of *n*-butyllithium is employed (**Scheme 1**). Because of the synthetic potential of optically active 1-chloro-3-hydroxyalkenyl derivatives (**5**), we have been trying to obtain these compounds selectively by treating the chloro-epoxides (**1**) with a limited amount of the base. However, a mixture of three compounds consisted of a desired chloroalkene (**5**), an acetylene (**4**), and a starting material (**1**) was always generated by using *n*-butyllithium as base. While our struggling, Yadav and coworkers[3] have disclosed successful stereospecific transformation of the chloro-epoxides (**1**) into the (*E*)-chloroalkenes [(*E*)-**5**] by employing one equiv. of LDA in THF or one equiv. of lithium amide in liquid ammonia. Unfortunately, a more practical one of the Yadav's procedures using LDA could not be reproduced by our hands which furnished a mixture of a chloro-alkene (**5**),

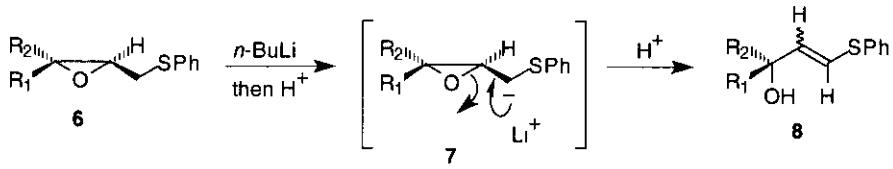
† Dedicated to Prof. Dr. Arnold Brossi on the occasion of his 70 birthday.

an acetylene (**4**), and a starting material (**1**) under the described conditions. Moreover, contrary to their claim, a chloro-alkene (**5**) generated under their conditions was often accompanied by a *Z*-isomer in our experiment (**Table 1**).



Scheme 1

In connection with this 3-hydroxy-1-alkyne formation reaction, we have also investigated the base-catalyzed reaction of 2,3-epoxyalkyl phenyl sulfides (**6**) and we have found[4] a facile generation of 3-hydroxy-1-alkenyl phenyl sulfides (**8**) *via* the α-thio-carbanion intermediate (**7**) on treatment with *n*-butyllithium in THF (**Scheme 2**).

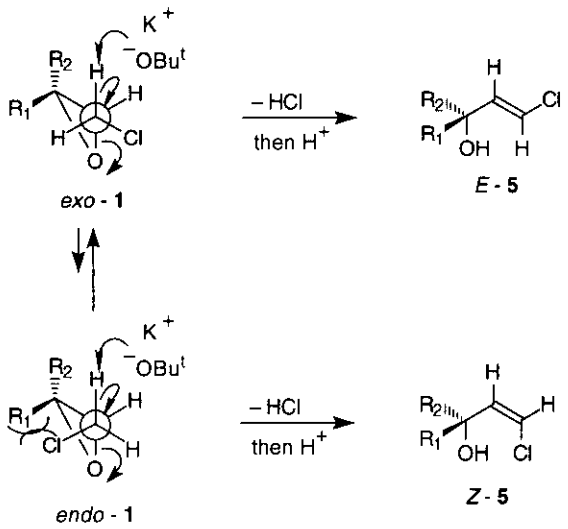


Scheme 2

In the present study, we first explored optimal conditions for the selective generation of the alkenyl chlorides (**5**) from the 2,3-epoxyalkyl chlorides (**1**) and next attempted to extend the α-thio-carbanion-mediated reaction[4] to the phenyl ether substrates (**9**) with expectation to initiate a similar ring-opening reaction to give 3-hydroxy-1-alkenyl ethers (**10**) *via* an α-oxy-carbanion intermediate. We now wish to report new conditions leading to stereoselective generation of (*E*)-3-hydroxy-1-alkenyl chlorides [(*E*)-**5**] from the 2,3-epoxyalkyl chlorides (**1**)

and the new procedure leading to stereoselective generation of (*E*)-3-hydroxy-1-alkenyl phenyl ethers [(*E*)-**10**] from the 2,3-epoxyalkyl phenyl ethers (**9**), respectively.

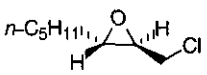
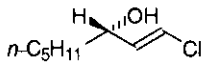
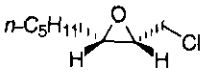
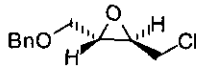
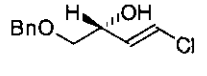
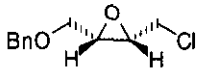
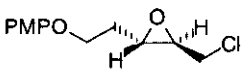
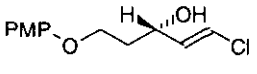
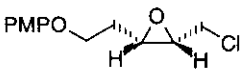
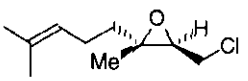
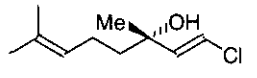
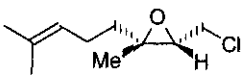
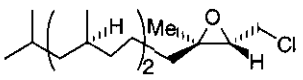
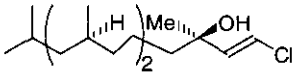
First, we found that (*E*)-3-hydroxy-1-alkenyl chlorides [(*E*)-**5**] were generated stereoselectively when the chloro-epoxides (**1**) were treated with 3 equiv. of potassium *tert*-butoxide in THF at –78 ~ –30 °C in the presence of 0.1 equiv. of dicyclohexano-18-crown-6. Under these conditions, a facile and clean reaction occurred to give rise to the (*E*)-olefins [(*E*)-**5**] stereoselectively in moderate to excellent yields without formation of the acetylenic by-products (**4**) though a minor amount of the starting materials were recovered unchanged in some cases. The reaction, however, did not proceed cleanly in the absence of the crown ether. In this transformation, the original optical integrity was virtually not changed which was deduced by the examination of ^{1}H nmr spectra of MTPA esters (500 MHz) (**Table 1**). We reasoned that the stereoselectivity observed was due to steric repulsion between the *syn*-β-substituent (R_1) on the epoxy ring and the chlorine atom which forced to take an *exo*-transition state (*exo*-**1**) rather than a more crowded *endo*-transition state (*endo*-**1**) to generate a chloro-olefin [(*E*)-**5**] having (*E*)-configuration (**Scheme 3**).



Scheme 3

In a typical example (Entry 7), the epoxyalkyl chloride [(*E*)-**1d**] (111 mg, 0.59 mmol) followed by dicyclohexano-18-crown-6 (22 mg, 59 μmol), was added to a stirred solution of potassium *tert*-butoxide (198 mg, 1.77 mmol) in THF (2.0 ml) at –78 °C, and the temperature was raised gradually to –30 °C. After stirring

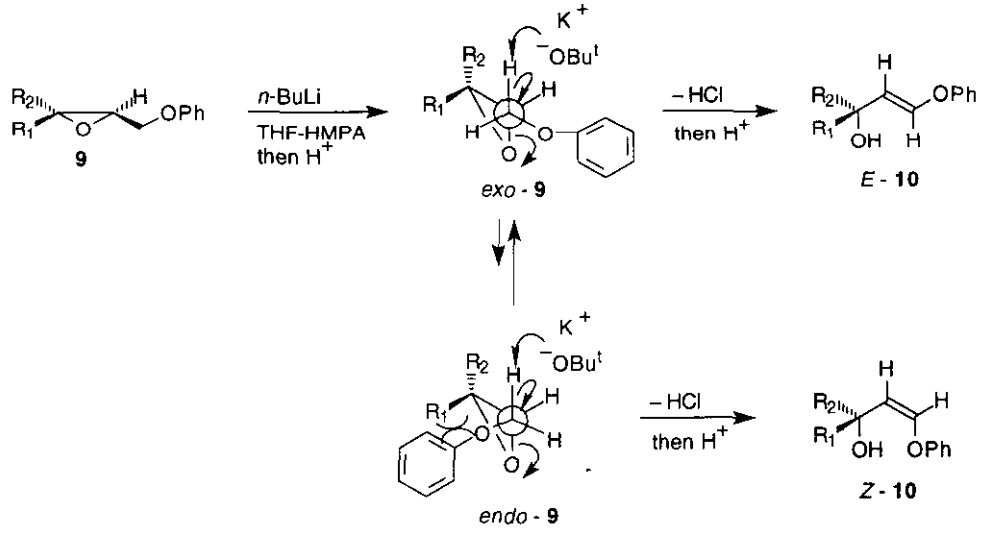
Table 1: Formation of (*E*)-Alkenyl Chloride (**5**) from 2,3-Epoxyalkyl Chloride (**1**)

Entry	Substrate (**1**)	Product[a] [(*E*)-**5**]	Yield[b] (%)	Recovery[b] of **1** (%)	LDA in THF[c] (*E*)-**5**:(*Z*)-**5**:**4**:**1** (%)
1			54.6	10.0	5:7:7 55
	(*E*)-**1a**[d]	**5a**			
2		**5a**	53.8	19.8	6 5:0:0:71
	(*Z*)-**1a**[d]				
3			59.9	0	19:10:13:49
	(*E*)-**1b**[e]	**5b**[f]			
4		**5b**[f]	71.2	6.1	21.5:0:10:60.5
	(*Z*)-**1b**[e]				
5			41.5	31 8	15:26.5:9:49
	(*E*)-**1c**[d]	**5c**			
6		**5c**	45.6	19.8	30:0:6:52
	(*Z*)-**1c**[d]				
7			100	0	28:0:0:62
	(*E*)-**1d**[e]	**5d**			
8		**5d**	79.8	0	27:0:0:49
	(*Z*)-**1d**[e]				
9			85.4	0	0:0:0:96
	(*E*)-**1e**[e]	**5e**			

a. *E*/*Z*-Ratio (>99:1) was determined by ^{1}H-nmr (500 MHz). b. Isolated yield after SiO_2 chromatography. c. Our results based on the Yadav's conditions.[3] d. Racemic material was used. e. Optically active material was used. f. Optical integrity of the epoxide precursor was preserved (MTPA esters, 500 MHz ^{1}H-nmr).

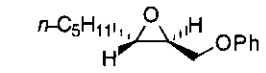
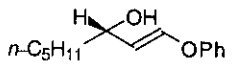
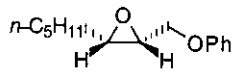
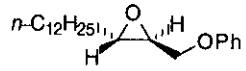
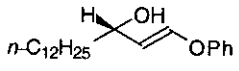
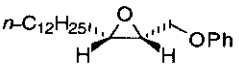
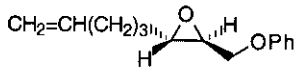
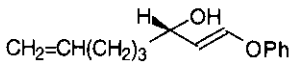
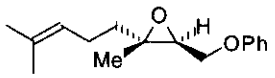
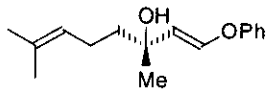
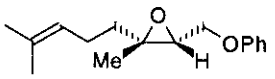
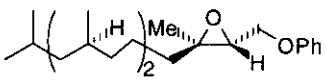
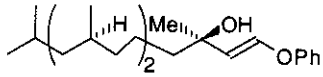
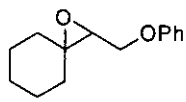
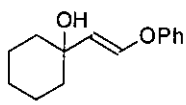
at the same temperature for 1 h, the reaction was quenched by addition of brine and the mixture was extracted with Et_2O. Purification of the crude product by silica gel column chromatography yielded the (*E*)-1-chloro-3-hydroxyalkene [(*E*)-**5d**] (111 mg, 100%) as a single product.

In order to extend the α-thio-carbanion-mediated reaction to the phenyl ether substrates, we next prepared some 2,3-epoxyalkyl phenyl ethers (**9**) staring from the 2,3-epoxyalkanols by employing the Mitsunobu reaction.[5] The reaction did occur in an expected way when the ethers (**9**) were treated with *n*-butyllithium in the presence of HMPA to give rise to the alkenyl phenyl ethers stereoselectively presumably *via* the α-oxy-carbanion intermediates.[6] Thus, upon exposure to five equiv. of *n*-butyllithium in THF containing five equiv. of HMPA, the phenyl ethers (**9**) furnished the (*E*)-3-hydroxy-2-alkenyl phenyl ethers [(*E*)-**10**] in good to excellent yields without losing the original chiral integrity (**Table 2**) Noteworthy in **Table 2** are Entries 2, 4, 6, 7, 8 and 9 wherein virtually complete *E*-selection was attained where *cis*- and tri-substituted epoxy substrates were used. This stereochemical outcome was apparently due to the steric interference between the phenoxy group and the *syn*-β-substituent (R_1) on the epoxide ring as similar as for the chloro-epoxides (**1**) which forced to take an less congested *exo*-transition state (*exo*-**9**) rather than a more congested *endo*-transition state (*endo*-**9**) leading to selective formation of an (*E*)-olefin [(*E*)-**10**] (**Scheme 4**).



Scheme 4

Table 2 Formation of (*E*)-3-Hydroxy-1-alkenyl Phenyl Ethers (**10**) from 2,3-Epoxyalkyl Phenyl Ethers (**9**)

Entry	Substrate (**9**)	Product (*E*-**10**)	Yield[a] (%)	Ratio (*E*/*Z*)[b]	**9** (%)[a]
1			71.8	15.5:1	21.6
	(*E*)-**9a**	**10a**			
2		**10a**	61.3	>99:1	23.5
	(*Z*)-**9a**[c]				
3			60.0	6.2:1	0
	(*E*)-**9b**	**10b**			
4		**10b**	89 4	>99:1	0
	(*Z*)-**9b**[c]				
5			58.3	3.8:1	0
	(*E*)-**9c**	**10c**			
6			87.7	>99:1	0
	(*E*)-**9d**[c]	**10d**			
7		**10d**	95.3	>99:1	0
	(*Z*)-**9d**				
8			88.5[e]	>99:1	0
	(*E*)-**9e**[c]	**10e**			
9			85.3	>99:1	0
	9f	**10f**			

a. Isolated yield after SiO_2 column chromatography. b. Ratio was determined by ^{1}H-nmr (300 or 500 MHz). c. Optically active material was used. Optical purities of the substrates and the products were determined by a hplc using a chiral column (Chiralcel OD, 1% v/v *i*-PrOH-hexane for substrates and 2% v/v *i*-PrOH-hexane for products). Original optical integrity was virtually not changed under the reaction conditions.

In general, the reaction was completed within 30 min under these conditions, however, the presence of HMPA was found to be essential [7] Since the products can be taken as the less accessible aldol enol ethers,[8] the present transformation may be useful in particular for the construction of a variety of the polyketide natural products.[9]

In a typical example (Entry 4), to a stirred solution of the epoxyalkyl phenyl ether [(Z)-**9b**] (114 mg, 0.26 mmol) and HMPA (0.48 ml, 2.76 mmol) in THF (3.0 ml) was added *n*-butyllithium (1.6 M solution in hexane, 1.73 ml, 2.77 mmol) at –78 °C. After stirring at the same temperature for 1 h, the reaction was quenched by addition of brine and the mixture was extracted with Et_2O. Purification of the crude product by silica gel column chromatography yielded the vinyl ether [(*E*)-**10b**] (102 mg, 89.4%) as a single product.

In conclusion, two carbanion-mediated elimination reactions developed in the present investigation may be highly useful for the enantio- and stereocontrolled construction of a wide variety of optically active molecules in combination with the Katsuki-Sharpless asymmetric epoxidation reaction.[2]

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2. R. A. Johnson and K. B Sharpless, In 'Comprehensive Organic Synthesis,' B. M Trost, Ed., Pergamon, Oxford, 1991, Vol. 7, 389.
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4. (a) S Takano, Y. Sugihara, and K. Ogasawara, *Synlett*, 1992, 668. (b) S. Takano, Y. Sugihara, and K. Ogasawara, *Tetrahedron Lett* , 1993, **34**, 845.
5. O. Mitsunobu, *Synthesis*, 1981, 1; D. L. Hughes, *Org. Reactions*, 1992, **42**, 335.
6. cf. J. F. Biellmann and J. -B. Ducep, *Org. Reactions*, 1982, **27**, 1
7. During the present investigation an interesting α-oxy-carbanion-mediated cleavage reaction of 2,3-epoxyalkyl methoxymethyl ethers using the Schlosser base has been disclosed, see: A. Degl'Innocenti, A. Mordini, S. Pecchi, D. Pinzani, G. Reginato, and A. Ricci, *Synlett*, 1992, 753.
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