

# A Highly Stereoselective Synthesis of $\alpha$ -Halo Vinyl Ethers and Their Applications in Organic Synthesis<sup>1</sup>

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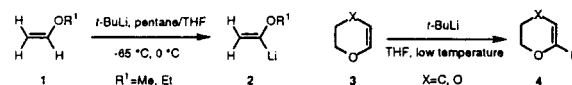
The use of acyl anion equivalents in the formation of C–C bonds is a powerful strategy in the development of new synthetic methods.<sup>2</sup> Among all the acyl anion equivalents, the  $\alpha$ -alkoxy vinyl anions are notable for their low cost, high reactivity, and easy deprotection of the resultant vinyl ether functionality.  $\alpha$ -Alkoxyvinylolithiums can be prepared by metalation of the commercially available methyl vinyl ether or ethyl vinyl ether using *t*-BuLi or super base (BuLi/KO-*t*-Bu).<sup>3</sup> This methodology was subsequently extended to cyclic systems (Scheme 1) by Boeckman.<sup>4</sup> In addition, metalation of 1,3-dienyl ethers, 1,3,5-trienyl ethers, and alkoxyallenes was also realized under the similar conditions.<sup>5</sup>

Chemical applications of more substituted acyclic  $\alpha$ -alkoxy vinyl anions is still in its infancy compared to other acyl anion equivalents. The reason for the underdevelopment in this field is that clean metalation of a variety of acyclic vinyl ethers with  $\beta$ -alkyl substituents is quite difficult.<sup>6</sup> Although (*Z*)-1-propenyl 2-tetrahydropyranyl ether and 2-methyl-1-propenyl 2-tetrahydropyranyl ether react with *s*-BuLi/KO-*t*-Bu to give the corresponding anions, it only works in the case of tetrahydropyranyl ether for additional chelation and stability of such reagents.<sup>7</sup> Metalation of (*Z*)-1-ethoxy-propene required 24 h at  $-30$  °C and gave only 70% yield of the corresponding anion. Metalation of compounds bearing more sterically demanding alkyl groups were uniformly unsuccessful even employing super bases.<sup>6</sup>

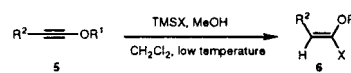
To solve this problem, Kocienski and co-workers developed a procedure to prepare  $\alpha$ -alkoxy vinylstannanes as the precursor of  $\alpha$ -alkoxy vinyl anions.<sup>6</sup> However, this method suffered from low yields due to the formation of the undesired regioisomer and the decomposition of the products during column chromatography.

In connection with a project in our laboratories, we required to generate  $\beta$ -alkyl substituted  $\alpha$ -alkoxy vinyl cuprates.  $\alpha$ -Alkoxy vinylolithium was envisaged to be generated by lithium–halogen exchange between butyllithium and  $\alpha$ -halo vinyl ether. However, we were surprised to find that there was no general literature procedure for the regio- and stereoselective preparation of  $\alpha$ -halo vinyl ethers. Thus, our first task was to secure a new method for the preparation of  $\alpha$ -halo vinyl ethers.

## Scheme 1



## Scheme 2



It is known that many reagents can undergo electrophilic addition to acetylenic ethers.<sup>8</sup> However, the addition of HX to acetylenic ethers has not been systematically studied. The problem associated with this type of reactions lies in the difficulty of accurate addition of commercially available HX and the formation of a mixture of stereoisomers and side products caused by excess of HX.<sup>8c,18d</sup> In addition,  $\alpha$ -halo vinyl ethers are quite labile and are prone to decomposition during aqueous workup and silica gel column chromatography. We have found that hydrogen halide generated *in situ* by addition of 0.99 equiv of trimethylsilyl halide<sup>9</sup> to a solution of 1.0 equiv of acetylenic ether<sup>10</sup> and 0.99 equiv of MeOH in  $\text{CH}_2\text{Cl}_2$  at low temperature exclusively gave  $\alpha$ -halo vinyl ether in a completely regio- and stereospecific manner (Scheme 2). The yield was nearly quantitative (excess of acid resulted in poorer selectivity). Since MeOTMS could be evaporated easily, neither work up nor column chromatography was necessary.

Table 1 summarized the preparation of a variety of  $\alpha$ -halo vinyl ethers using our procedure. It should be noted that the reaction employing *in situ* generation of HCl was not only faster than that using commercially available HCl in ether (entries 4 and 5), but also gave better stereoselectivity (entry 3). We believe that this is due to the solvent effect. In addition, higher temperature gave better stereoselectivity (entries 3 and 5). Although  $\alpha$ -halo vinyl ethers are prone to decomposition to the corresponding esters, they can be stored in frozen benzene for a month. Because of the simplicity of our procedure, we often prepare them before use.

We next examined the reaction between  $\alpha$ -bromo vinyl ethers and BuLi.<sup>11</sup> *t*-BuLi reacted with  $\alpha$ -bromo vinyl ethers very quickly at  $-78$  °C and afforded  $\alpha$ -alkoxy vinylolithiums quantitatively.<sup>12</sup> The geometry of the double bond was fully retained in all instances. Entries 1–4 in Table 2 are several examples of the application of this type of acyl anions for organic synthesis.

The quantitative generation of the  $\alpha$ -alkoxy vinylolithium enabled us to study the formation of organo copper reagents.<sup>13</sup> Low-order,<sup>13</sup> high-order,<sup>14</sup> and mixed-high-order cuprates<sup>15</sup> have

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**Table 1.** A Stereoselective Synthesis of  $\alpha$ -Halo Vinyl Ethers

Entry	Substrates <sup>a</sup>	Conditions <sup>b</sup>	Products <sup>c</sup>	Yield <sup>d</sup>
1		Method A,		99%
2	<b>7</b>	Method B,	<b>8-I</b> X=I	97%
3	<b>7</b>	Method C,	<b>8-Cl</b> X=Cl	97%
4	<b>7</b>	HCl in ether, 25 °C, 30min	<b>8-Cl</b>	90%
5	<b>7</b>	HCl in ether, -30 °C, 7h	<b>8-Cl</b>	E:Z=2:1 99%
6	<b>9</b>	Method A		89%
7	<b>9</b>	Method B	<b>10-Br</b> X=Br	91%
8	<b>9</b>	Method C,	<b>10-I</b> X=I	91%
9	<b>11</b>	Method A		99%
10	<b>11</b>	Method B	<b>12-Br</b> X=Br	99%
11	<b>11</b>	Method C,	<b>12-I</b> X=I	99%
12	<b>13</b>	Method A		99%
13	<b>13</b>	Method B	<b>14-Br</b> X=Br	99%
14	<b>13</b>	Method C,	<b>14-I</b> X=I	96%
15	<b>15</b>	Method A		99%
16	<b>15</b>	Method B	<b>16-Br</b> X=Br	98%
17	<b>15</b>	Method C,	<b>16-I</b> X=I	98%

<sup>a</sup> R<sup>3</sup> = (-)-menthol, R<sup>4</sup> = [(1*S*)-endo]-(-)-Borneol. <sup>b</sup> All reactions were run in CH<sub>2</sub>Cl<sub>2</sub>. <sup>c</sup> The geometry of double bonds were determined by NOESY spectra. <sup>d</sup> All yields are isolated yields. The *Z/E* ratios were measured by integration of well-resolved signals in the <sup>1</sup>H NMR. Method A: TMSBr (0.99 equiv), MeOH (0.99 equiv), -40 °C, 10 min; Method B: TMSI (0.99 equiv), MeOH (0.99 equiv), -78 °C, 10 min; Method C: TMSCl (0.99 equiv), MeOH (0.99 equiv).

been successfully prepared from  $\alpha$ -alkoxy vinylolithium, and their conjugate additions to  $\alpha,\beta$ -unsaturated ketones were examined (Table 2, entries 5–7). All reactions afforded excellent yields and retention of the stereochemistry of the double bond.

$\alpha$ -Halo vinyl ethers can undergo many important transformations catalyzed by transition metals such as palladium and nickel.<sup>16</sup> In the presence of a catalytic amount of palladium catalyst, compound **8-Br** underwent Stille coupling<sup>17</sup> with tributylvinyltin to provide functionalized 1,3-diene **22** which could not be easily access *via* known procedures, and can be used in asymmetric Diels–Alder reactions (Table 2, entry 8). It was interesting to observe that the geometry of the double bond was cleanly inverted.  $\alpha$ -Bromo vinyl ether **10-Br** could also undergo Sonogashira coupling<sup>18</sup> to give enyne **23** in excellent yield with complete retention of the geometry of the double bond (Table 2, entry 9). Palladium(0)-catalyzed carbonylation<sup>19</sup> between  $\alpha$ -bromo vinyl ether **12-Br** and CO in the presence of methanol gave  $\alpha$ -methoxy- $\alpha,\beta$ -unsaturated ester **24** in nearly quantitative yield (Table 2, entry 10). In this case, the geometry of the double bond was stereospecifically inverted.  $\alpha$ -Halo vinyl ethers also couple with Grignard reagents catalyzed by an organonickel catalyst. Compound **12-Br** reacted with EtMgBr in the presence of a catalytic amount of NiCl<sub>2</sub>dpppp<sub>2</sub> to give **25** in 71% after hydrolysis the enol ether (Table 2, entry 11). The same reaction also worked with

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**Table 2.** Application of  $\alpha$ -Halo Vinyl Ethers in Organic Synthesis

Entry	Substrates <sup>a</sup>	Conditions	Products <sup>b</sup>	Yield <sup>c</sup>
1	<b>10-Br</b>	1) <i>n</i> -BuLi, THF, -78 °C 2) PhCHO, 3) Ac <sub>2</sub> O		99%
2	<b>16-Br</b>	1) <i>t</i> -BuLi, THF, -78 °C 2) ClCO <sub>2</sub> Bn		87%
3	<b>8-Br</b>	1) <i>t</i> -BuLi, THF, -78 °C 2) TMSCl		97%
4	<b>8-Br</b>	1) <i>t</i> -BuLi, THF, -78 °C 2) Me <sub>3</sub> SnCl		98%
5	<b>14-Br</b>	1) <i>t</i> -BuLi, ether, -78 °C 2) CuI, Me <sub>2</sub> S, -40 °C, 3) 2-cyclohexen-1-one, -78 °C,		78%
6	<b>14-Br</b>	Method A	<b>21</b>	88%
7	<b>14-Br</b>	Method B	<b>21</b>	84%
8	<b>8-Br</b>	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , CH <sub>3</sub> CN, Bu <sub>3</sub> Sn-, reflux,		91%
9	<b>10-Br</b>	≡Me, PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> , CuI, piperidine, THF, 0-25 °C,		94%
10	<b>12-Br</b>	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , Et <sub>3</sub> N, CO, MeOH, DMF, 70 °C		98%
11	<b>12-Br</b>	1) NiCl <sub>2</sub> dpppp <sub>2</sub> , EtMgBr, 25 °C, C <sub>6</sub> H <sub>6</sub> , 2) H <sub>3</sub> O <sup>+</sup>		71%
12	<b>8-Br</b>	NiCl <sub>2</sub> dpppp <sub>2</sub> , PhMgBr, 25 °C, C <sub>6</sub> H <sub>6</sub>		86%

<sup>a</sup> R<sup>3</sup> = (-)-menthol, R<sup>4</sup> = [(1*S*)-endo]-(-)-Borneol. <sup>b</sup> The geometry of double bonds were determined by NOE or NOESY spectra. <sup>c</sup> All yields are isolated yields. Method A: (1) *t*-BuLi (2 equiv., ether, -78 °C). (2) CuCN, LiCl (2 equiv), THF, -40 °C, 30 min. (3) 2-cyclohexen-1-one, -78 °C, 5 min. Method B: (1) *t*-BuLi, ether, -78 °C. (2) CuCN, MeLi, THF, -40 °C, 30 min. (3) 2-cyclohexen-1-one, -78 °C, 5 min.

PhMgBr to afford **26** with retention of the geometry of the double bond (Table 2, entry 12).<sup>20</sup>

In summary, we have successfully developed a highly regio- and stereoselective method for the synthesis of  $\alpha$ -halo vinyl ethers. We have demonstrated that  $\alpha$ -halo vinyl ethers can serve as excellent latent acyl anions for carbon–carbon bond formation. The quantitative generation of  $\alpha$ -alkoxyvinylolithium enables the formation of a variety of cuprates that were not accessible via the previous known literature procedures. Furthermore, we have also discovered that  $\alpha$ -halo vinyl ethers are highly versatile substrates for transition metal catalyzed cross-coupling reactions. Currently, we are studying the asymmetric reactions employing the substrates bearing a chiral R<sup>1</sup> group as chiral auxiliary. Application of these methodologies to the total synthesis of natural products is underway, and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all the compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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