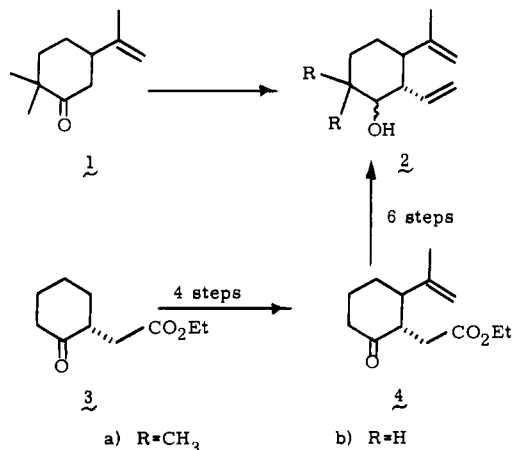


Reductive Vinylation  $\alpha$  to Ketones

Sir:

Our independent interest in effecting tandem Cope-Claisen rearrangements of the sort recently discussed by Ziegler and Piwinski<sup>1</sup> has made us painfully aware of the paucity of methodology for introducing a vinyl group at a primary or secondary center adjacent to a ketone.<sup>2,16</sup> Especially in the case of carvone derivative **1**, several attempted transformations into vinyl alcohol **2a** proved unsuccessful due to the hindered nature of this molecule.



Ziegler's synthesis of the less hindered alcohol **2b**<sup>1</sup> was effected in ten steps from keto ester **3**, six of these steps involving formation of the vinyl alcohol substructure from **4**. Considering the potential importance of such vinyl alcohols for the tandem Cope-Claisen process, as well as the occurrence of vinyl substituents in many natural products, there exists a definite need for a good general method of effecting  $\alpha$ -vinylation. Herein we report two closely related procedures which efficiently achieve reductive vinylation adjacent to ketones (e.g., **1**  $\rightarrow$  **2a**).

Our first method (A) works well for introducing vinyl substituents which are at least somewhat hindered (Table I: **2a, b, 11**). As illustrated below for the lithium diisopropylamide derived anion **5a** of ketone **1**, this approach involves kinetic aldol condensation of a ketone enolate (in THF at  $-78^\circ\text{C}$ ) with (phenylseleno)acetaldehyde (**6**).<sup>3</sup> The intermediate  $\beta$ -hydroxy selenide

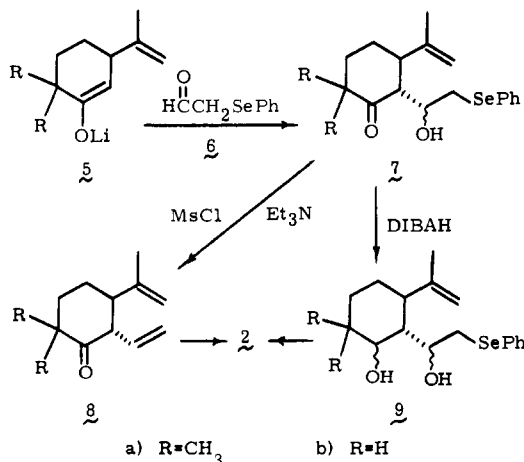


Table I

Starting Ketone	Method <sup>a</sup>	Products (yield <sup>b</sup> / $\beta$ : $\alpha$ -OH <sup>c</sup> )
<b>1</b> <sup>8</sup>	A	<b>2a</b> <sup>9</sup> (88%/3:1)
<b>10</b> <sup>10</sup>	A	<b>11</b> <sup>9</sup> (65%/9:1)
<b>12</b>	A, d, e	<b>2b</b> <sup>1</sup> (60%/9:1)
<b>12</b>	B <sup>d</sup>	<b>2b</b> (59%/2:3)
<b>13</b>	B	<b>14</b> <sup>11</sup> (65%/1:1)
<b>13</b>	A, e, f	<b>15</b> <sup>11</sup> R=H (25%) <b>16</b> R=PhSe (10%) CH <sub>2</sub> R
<b>17</b>	B	<b>18</b> <sup>12</sup> (72%)
<b>17</b>	A, e, f	<b>19</b> <sup>13</sup> (73%)
<b>20</b>	B	<b>21</b> <sup>14</sup> (65%)
<b>22</b> 2-octanone	B	<b>23</b> <sup>14</sup> (78%)

<sup>a</sup> Method A: LDA, THF, PhSeCH<sub>2</sub>CHO; MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; LAH, ether. Method B: LDA, PhSeCH<sub>2</sub>CHO, THF; DIBALH, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^\circ\text{C}$ ; (CF<sub>3</sub>CO)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>3</sub>CN/(MeO)<sub>3</sub>P/H<sub>2</sub>O, NaOH. <sup>b</sup> Chromatographed product. <sup>c</sup>  $\beta$ -Alcohol, trans to vinyl group;  $\alpha$ -alcohol cis. <sup>d</sup> Enolate obtained via conjugate addition to enone. <sup>e</sup> Cleaner products were obtained in these cases if the crude mesylate in CH<sub>2</sub>Cl<sub>2</sub> was washed with water and then returned to the Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> solution for elimination. <sup>f</sup> LAH reduction was not performed.

**7a** is not purified but rather eliminated under the conditions of Reich<sup>4</sup> (4 equiv of MsCl and 5 equiv of Et<sub>3</sub>N in CH<sub>2</sub>Cl<sub>2</sub> at  $0^\circ\text{C}$  for 30 min) to afford only the *trans*-dialkenyl ketone **8a**. Under these conditions, no olefin isomerization to the conjugated enone occurs for this hindered compound, and the purified ketone **8a** may be isolated in 73% yield. In this particular case, silica gel chromatography does not effect complete separation and some product is lost in mixed fractions. Purification of alcohol **2a** is more efficient; thus, reduction of crude **8a** with lithium aluminum hydride affords the desired vinyl alcohol **2a** in 88% overall yield (from **1**), as a purified 3:1 mixture of the  $\beta$  (*trans*) and  $\alpha$  (*cis*) hydroxy compounds. Similarly, ketone **10** affords the alcohol mixture **11** in 65% overall yield.<sup>17</sup>

Especially noteworthy is the generation and trapping of enolate **5b** derived from cyclohexenone (**12**). Conjugate addition of the isopropenyllithium-derived<sup>5</sup> cuprate (1.5 equiv, with 15 equiv of

(1) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880.

(2) At tertiary centers adjacent to a ketone one can readily introduce the dichlorovinyl substituent (Kende, A. A.; Benechie, M.; Curran, D. P.; Fludzinski, P. *Tetrahedron Lett.* **1979**, 4513), and in certain cases the vinyl group itself (Bruhn, J.; Heimgartner, H.; Schmid, H. *Helv. Chem. Acta* **1979**, *62*, 2630, employing the method of: Koppel, G. A.; Kinnick, M. D. *J. Chem. Soc., Chem. Commun.* **1975**, 473). Such methods succeed at tertiary centers since the product olefin cannot conjugate with the ketone carbonyl, as it can in vinylation at primary or secondary centers.

(3) We routinely prepare distilled aldehyde **6** [bp  $110^\circ\text{C}$  (0.5 mm)] in 80% yield by treating a solution of phenylselenenyl bromide<sup>15</sup> in THF with 2 equiv of ethyl vinyl ether for 15 min at  $0^\circ\text{C}$  and then with 5% HCl for 30 min without cooling. A two-step procedure for obtaining **6** was recently reported by: Petrizilka, M.; Baudat, R. *Helv. Chim. Acta* **1979**, *62*, 1406.

(4) Reich, H. J.; Chow, F. J. *Chem. Soc., Chem. Commun.* **1975**, 790. See also: Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

dimethyl sulfide in ether at  $-25^{\circ}\text{C}$  for 20 min) to enone **12** produces a solution of **5b**. Addition of (phenylseleno)acetaldehyde (**6**; 1.5 equiv) to this enolate (at  $-78^{\circ}\text{C}$ ) affords crude alcohol **7b** upon workup. Treatment of **7b** with mesyl chloride and triethylamine in methylene chloride<sup>6</sup> generates trans-ketone **8b** in 65% yield after chromatography. In contrast with the nine-step literature route,<sup>1</sup> this two-step synthesis of ketone **8b** from cyclohexenone dramatically illustrates the utility of our new vinylation procedure.

For less hindered ketones, e.g., **13** and **17**, method A fails; deprotonation  $\alpha$  to the carbonyl leads both to conjugation of the initially formed olefin products (producing **15** and **19**) and to mesylate elimination without selenium loss (affording **16**). Such problems are avoided in method B by diisobutylaluminum hydride reduction (4 equiv at  $-78^{\circ}\text{C}$  in methylene chloride) of the aldol product to a diol (e.g., **7b**  $\rightarrow$  **9b**) prior to olefin formation. The diol (e.g., **9b**) is treated with 4 equiv of trifluoroacetic anhydride and 6 equiv of triethylamine (in  $\text{CH}_3\text{CN}$  at  $\sim 15^{\circ}\text{C}$ ) to form the bis(trifluoroacetate); then trimethyl phosphite (3 equiv) is added and the solution refluxed (11 h) to unmask the olefin via this modified procedure of Krief.<sup>7</sup> Finally the reaction mixture is quenched with aqueous sodium hydroxide solution (excess, 2 h at room temperature) to hydrolyze the remaining trifluoroacetyl group. The 59% overall yield of alcohols **2b** obtained via this three-step procedure compares well with the 60% yield from method A.

The results shown in Table I<sup>8-14</sup> illustrate the generality of method B, which effects conversion of ketones **13**, **17**, **20**, and **22** into vinyl alcohols in overall yields of 65–78%. It should be noted that, while vinyl ketones are not intermediates in this procedure (as they are in method A), simple Jones oxidation of the homoallylic alcohols affords the nonconjugated enones in nearly quantitative yield for those cases examined (**2a,b**, **23**). Thus both methods A and B, while intended to effect reductive vinylation to the homoallylic alcohols, can be used to obtain the vinylated ketones as well. Use of these procedures should provide ready access to a variety of substituted Cope–Claisen precursors, and natural products, not easily synthesized by other means; such applications are currently under way.

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## Alkylaluminum Chloride Induced Cyclization of Unsaturated Carbonyl Compounds

Sir:

We have recently reported that alkylaluminum chlorides are useful catalysts for ene and Diels–Alder reactions<sup>1</sup> and cation–olefin cyclizations,<sup>2</sup> since they are proton scavengers as well as Lewis acids. We report here studies of the alkylaluminum chloride induced cyclization of unsaturated aldehydes and ketones which indicate the advantages of these reagents in Lewis acid initiated reactions. Proton-catalyzed reactions do not occur, the alkyl group can enter into the reaction in a synthetically useful manner, and the type of reaction can often be controlled by variation of the temperature and the strength and amount of Lewis acid. These reactions should be of considerable value in synthesis, as illustrated by the synthesis of the CD ring system of androstanone.

The reactions of 2,6-dimethyl-5-heptenal (**1**) (in the text **1**–**9** refer to the alcohol or carbonyl compounds obtained after workup from the structures shown in Scheme I), which are shown in Table I, indicate that either concerted or stepwise reactions can be made to occur selectively. With 1 equiv of  $\text{Me}_2\text{AlCl}$  at  $-80^{\circ}\text{C}$ , a concerted Lewis acid catalyzed ene reaction, which gives **2a** and **2b** in a 3:1 ratio, is the predominant process.<sup>3,6</sup> The ene adduct- $\text{Me}_2\text{AlCl}$  complex loses  $\text{CH}_4$  to give the aluminum alkoxide, thereby preventing reversal of the ene reaction and decomposition of **2**.<sup>1</sup> We believe that **2** is formed by a concerted process since ene reactions of 1,6-dienes have been shown to give mainly cis-substituted cyclopentanes<sup>4,6</sup> and **3** has the wrong stereochemistry to give **2**.

With 2 equiv of  $\text{Me}_2\text{AlCl}$  a more electrophilic aldehyde- $(\text{Me}_2\text{AlCl})_2$  complex is formed, so that formation of **3** by a more rapid reaction becomes the major process. At  $-80^{\circ}\text{C}$ , a high yield of chloro alcohol **4** is isolated. At  $0^{\circ}\text{C}$ , formation of **4** is reversible, so that products obtained from **3** by three competing irreversible reactions are obtained. A 1,5-methyl shift gives **6**,<sup>7</sup> a reversible 1,5-proton shift gives **5**, which irreversibly loses  $\text{CH}_4$ ,<sup>1</sup> and two 1,2-hydride shifts give **8**.<sup>8,9</sup>

Treatment of **1** with 2 equiv of  $\text{MeAlCl}_2$  at  $-80^{\circ}\text{C}$  gives mainly **8**. This is due to the greater acidity of  $\text{MeAlCl}_2$ , which makes

(5) Seebach, D.; Newmann, H. *Chem. Ber.* **1974**, *107*, 847.

(6) See Table I, note e.

(7) Addition of trimethyl phosphite is essential to effect olefin formation on these bis(trifluoroacetates); this extra reagent was not employed in the mono(trifluoroacetate) systems investigated by: Rémon, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, 1385.

(8) Ketone **1** was obtained from *l*-carvone in 75% yields by conventional reductive methylation in ammonia; a related preparation was recently reported by: Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647.

(9) Obtained for these new compounds were IR and NMR spectral data consistent with the assigned structures, as well as satisfactory combustion or exact mass spectral analyses.

(10) Edwards, H. N.; Wycpoleki, A. F.; Corbin, N. C.; McChesney, J. D. *Synth. Commun.* **1978**, 563.

(11) Crandall, J. K.; Arrington, J. P.; Hen, J. *J. Am. Chem. Soc.* **1967**, *89*, 6208.

(12) Akenhaim, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* **1969**, 4038.

(13) Chau, T. M.; Beaute, C.; Thoai, N.; Niemann, J. *Bull. Soc. Chim. Fr.* **1971**, 4138.

(14) Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326.

(15) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

(16) After submission of the manuscript, an alternative vinylation procedure appeared in the literature: Chang, T. C. T.; Rosenblum, M.; Samuels, S. B. *J. Am. Chem. Soc.* **1980**, *102*, 5930.

(17) At the suggestion of one referee, *l*-dihydrocarvone, **i**, was submitted to our vinylation procedure; ketone **ii** was obtained in 65% yield after purification, using method A without the lithium aluminum hydride reduction step.

