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Improved Chemoselectivity in Intramolecular Alkylidene Carbene C-H Insertion

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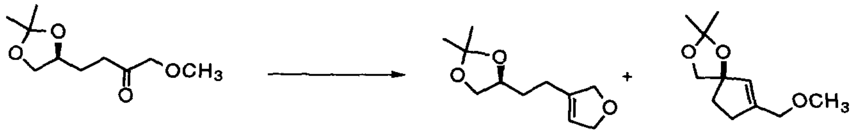
Abstract: The alkylidene carbene generated by chloromethylenation / α–elimination of **1** proceeds with a high degree of selectivity for methoxy C-H insertion over methine insertion, to give **2**. The carbene generated with trimethylsilyldiazomethane results in an approximately 1:1 mixture of **2** and **3**. © 1997 Elsevier Science Ltd.

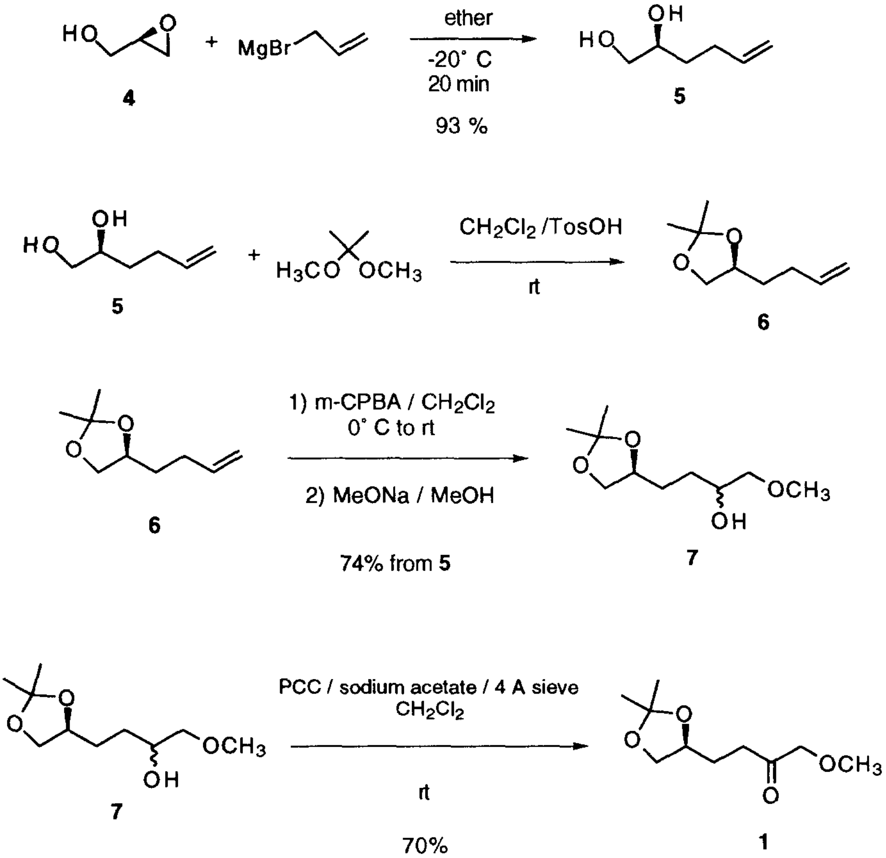
Intramolecular alkylidene carbene C-H insertions[1] have been widely used to prepare cyclopentene derivatives. We and others have used these product cyclopentenes as intermediates in the synthesis of natural products.[2] Alkylidene carbenes have been generated in a variety of ways.[1] The relative rates of insertion have consistently been reported to be methine > methylene > methyl.[1d] It has also been reported that a heteroatom adjacent to the carbon where the insertion occurs increases the rate of C-H insertion.[1e] With these considerations in mind, we cyclized **1**, expecting **3** to be the predominant product. In fact, cyclization using trimethylsilyldiazomethane with methyl lithium as base showed a small preference for **2**, while α-elimination produced **2** as the predominant cyclization product.[3]



1 **2** **3**

Method	Ratio	Yield
$TMSCH=N_2$ / MeLi	55:45	60%
a)$(Ph)_3P=CHCl$ b) KHMDS / rt	91:9	93%

SCHEME 1



To prepare methoxy ketone **1** (**Scheme 1**) we first added allyl Grignard to glycidol **4**, to give diol **5**, which was protected as the acetonide **6**. Epoxidation and methoxide ring opening then gave the methoxy alcohol **7**. PCC oxidation provided methoxy ketone **1**.

As summarized above, the method of carbene generation can significantly affect the selectivity of C-H insertion. It is well documented that carbenes generated via α-elimination are carbenoid in nature, and that their reactivity is dependent on the coordinating metal salts.[4a-e] We suggest that the alkylidene carbene generated by α-elimination is in fact a carbenoid,[5] and that it is more selective in insertion than the free alkylidene carbene generated by Peterson olefination (trimethlsilyldiazomethane / methyl lithium) followed by the loss of N_2.

It is striking that in this case insertion into the methyl C-H, to form **2**, is favored over methine C-H insertion, to form **3**. This suggests that the *endo* oxygen in the transition state leading to C-H insertion to form **2** is more efficiently activating than the *exo* oxygen in the transition state leading to C-H insertion to form **3**. A similar result has been reported for Rh-mediated intramolecular C-H insertion.[6] As the cyclization of **1** is an extreme example, with the usually *least* reactive methyl C-H competing effectively with the usually very reactive oxygenated methine C-H, the selective alkylidene insertion reported here may likely offer a general entry to substituted dihydrofurans.

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(3) The alkylidene carbene generation protocols that we used have been previously described (see references 11 and 2d). The characterization data for compounds **2** and **3** are:

2 TLC R*f* (30% EtOAc/hexane) = 0.45 ^{1}H NMR (δ) 5.50 (s, 1H), 4.62 (m, 2H), 4.55 (m, 2H), 4.1 (m, 2H), 3.7 (t, 1H,*J* = 7.0 Hz), 2.2 (m, 2H), 1.9-1.62 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (δ): C, 140.0, 109.0, CH, 119.5, 75.5, CH_2, 77.0, 76.5, 69.3, 31.9, 23.5, CH_3, 27.6, 25.9; IR (neat, cm^{-1}) 3342, 2986, 2936, 2866, 1660; HRMS: calcd for $C_{11}H_{18}O_3$ 199.133420, found 199.133069.

3 TLC R*f* (30% EtOAc/hexane) = 0.50 ^{1}H NMR (δ) 5.6 (s, 1H), 3.9 (2H, ab quart. *J* =1.2, 5.4 Hz), 3.89 (2H, ab quart.*J* = 8.6, 2.0 Hz), 3.39 (s, 3H), 2.42 (m, 1H), 2.3 (m, 1H), 2.15 (m, 2H), 1.42 (s, 3H), 1.2 (s, 3H); ^{13}C NMR (δ): C, 146.0, 109.0, CH, 130.0, 128.5, 120.6, 115.3, CH_2, 73.1, 71.2, 36.4, 30.9, CH_3, 58.4, 26.8 ; IR (neat, cm^{-1}) 3362, 2984, 2934, 2854, 1594, 1472; HRMS: calcd for $C_{11}H_{18}O_3$ 199.133420, found 199.133032.

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