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DIASTEREOSELECTIVITY IN *UNCATALYZED* INTRAMOLECULAR C-H INSERTION BY AN ALKYLIDENE CARBENE

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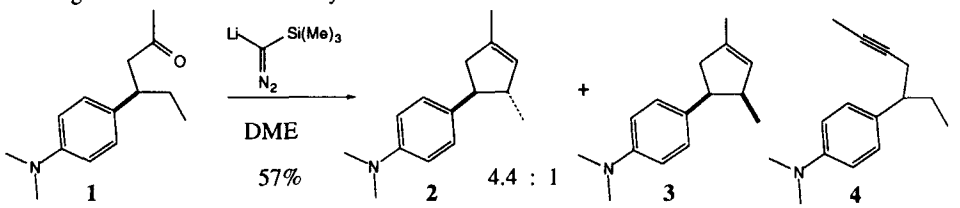
Abstract: Uncatalysed intramolecular C-H insertion by a transient alkylidene carbene derived from ketone **1** is reported to proceed with significant diastereoselectivity, providing cyclopentenes **2** and **3** in a ratio of 4.4 : 1. An improved procedure has been developed for addition of the anion of trimethylsilyldiazomethane to a ketone to generate the alkylidene carbene.

Intramolecular C-H insertion has recently been developed as a method for the construction of, *inter alia*, cyclopentenes[1] and cyclopentanones.[2] Although intramolecular Rh-mediated carbene insertion has been reported to proceed with substantial diastereoselectivity,[3] no such studies have been reported for uncatalyzed alkylidene carbenes. We now report that intramolecular C-H insertion by a transient alkylidene carbene can proceed with significant diastereoselectivity.



The competing side reaction to C-H insertion is 1, 2-rearrangement[4], to give the alkyne **4**. Ketone **1**[5] is a particularly challenging substrate for cyclization, as C-H insertion must take place into a methylene H (as opposed to a more reactive methine) that is not activated by an α-heteroatom. We first investigated alkylidene generation using diethyl diazomethyl phosphonate, as developed by Gilbert.[1a,b] In our hands, this reagent gave only low conversion of **1** to **2**, **3** and **4**.

We next turned to the Ohira[1c] modification of the Gilbert cyclization, adding the anion of trimethylsilyldiazomethane.[6] Although the published[1e] procedure specifies butyllithium as base with THF/hexane as the reaction solvent, we have found that under these conditions the cyclization proceeds in low yield. A more efficient protocol is presented here, using DME as solvent and employing *hexane free* trimethylsilyldiazomethane in combination with lithium bromide free methyllithium in *diethyl ether*[7].

The apparently modest yield yield in the transformation of **1** to **2** and **3** is tempered by the fact that this is a multi-step reaction, during which three carbon-carbon bonds and a ring are formed. In work still in progress,

we have found that this procedure cyclizes more active substrates (C-H insertion into a methine, especially an oxygenated methine) very efficiently. The work presented here establishes that the transition state for C-H insertion of an alkylidene carbene can be perturbed by the effect of a group adjacent to the site of insertion, resulting in the stereocontrolled formation of a new stereogenic center.

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5. Ketone **1** was prepared by base promoted condensation of 4-*N,N*-dimethylaminobenzaldehyde with acetone, followed by Cu-catalyzed conjugate addition of ethyl magnesium bromide (71% yield overall).
6. Trimethylsilyldiazomethane, purchased from Aldrich, showed 30% impurity, ^{1}H NMR = 2.63 δ. We separated the trimethylsilyldiazomethane from solvent hexane by spinning band distillation. This did not, however, remove the impurity.
7. Cyclization of **1** to **2** and **3**: Methyllithium (0.67 mL, 1.4 M in diethyl ether, 0.94 mmols) was added to a solution of trimethylsilyldiazomethane (153 mg, 0.94 mmol, 70% pure) in 4 mL of DME at -60° C. The solution was stirred for 3 min, then 0.100 g (0.45 mmol) of 4-(4-*N,N*-dimethylaminophenyl)-2-hexanone as a solution in 1 mL of DME was added. The reaction was stirred at -60°C for 2 h, then warmed slowly to rt over 2 hr and after workup (sat. aq. NH_4Cl) the combined organics were chromatographed (silica gel eluted with ethyl acetate/petroleum ether) to give 58 mg (0.27 mmol, 57% yield) of the desired 1,3-dimethyl-4-(4-*N,N*-dimethylaminophenyl)-cyclopentene isomers, 4.4 : 1 by integration of the methyl doublets in the ^{1}H NMR[8]. Individual diastereomers were isolated by HPLC (partisil, gradient eluted with ethyl acetate/petroleum ether). ANTI: ^{1}H NMR (δ): 7.16 (d, J=8.6 Hz, 2H), 6.71 (d, J=8.6 Hz, 2H), 5.2 (bs, 1H), 2.91 (s, 6H), 2.81-2.30 (m, 4 H), 1.74 (s, 3H), 1.01 (d, J=6.5 Hz, 3H). ^{13}C NMR (δ): 149.1, 138.3, 134.3, 128.9, 128.0, 112.9, 53.3, 49.0, 45.9, 40.9, 20.2, 16.7 SYN: ^{1}H NMR (δ): 7.08 (d, J=8.7 Hz, 2H), 6.70 (d, J=8.7 Hz, 2H), 5.33 (s, 1H), 3.51 (q, J=8.2 Hz, 1H), 2.91 (s, 6H), 3.0-2.90 (m, 1H), 2.62-2.39 (m, 2H), 1.79 (s, 3 H), 0.57 (d, J=7.1 Hz, 3H). ^{13}C NMR (δ): 130.5, 128.9, 112.6, 47.5, 43.9, 41.0, 40.9, 16.8
8. The syn diastereomer is assigned to the signal δ=0.57, the methyl doublet being shifted upfield by the ring current of the syn arene substituent (see references 3a and 3b).

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