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Regioselective Cyclopropanation via Unsymmetrical Oxatrimethylenemethane Palladium Intermediates

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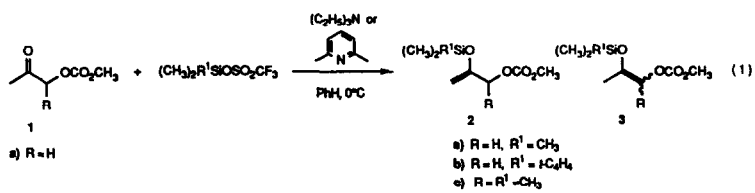
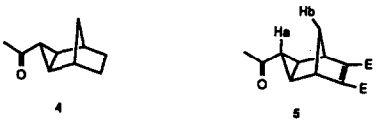
Summary. The mechanism of the unusual cyclopropanation of norbornenes via oxatrimethylenemethane palladium complexes is probed by regiochemical labels to establish the symmetry of the reactive intermediate.

The diverse reactivity observed in the palladium catalyzed [3+ 2] cycloadditions of 2-trimethylsilylmethylallyl carboxylates[1] and methylenecyclopropanes[2] constitutes an interesting mechanistic puzzle. While a trimethylenemethanepalladium complex has been invoked for both, the exact species clearly cannot be the same. The totally different type of behavior observed in the palladium catalyzed cycloadditions of 1-acetoxy-3-trimethylsilylpropan-2-one raises the question of the type of reactive intermediate.[3] Our postulate of an oxatrimethylenemethanepalladium complex[4] derived from parallelisms in the structural requirements for reaction between the all carbon and the mono-oxa substrates. The highly unusual reactivity led us to search for alternative probes of the structure of the reactive intermediate. Examining substituted analogues would provide insight into the symmetry of the reactive intermediate.

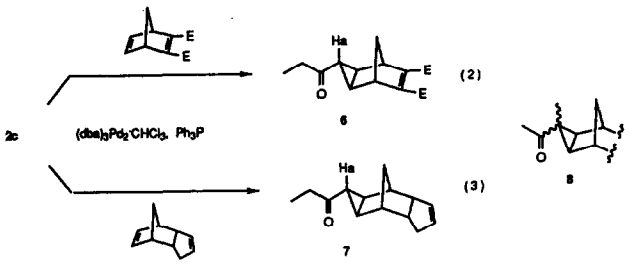
Since α-acyloxyketones are readily available in the substituted series, the use of their enol silyl ethers as cycloaddition donors appeared to be most attractive. To establish the protocol, the methyl carbonate of α-hydroxyacetone was converted to its enol silyl ethers 2a and 2b according to eq. 1. A 5:1 ratio of 2a : 3a[5] was obtained with trimethylsilyl triflate and a 2.6: 1 ratio of 2b : 3b[5] with t-butyldimethylsilyl triflate. Cycloaddition of 2a



(1.25 eq.) with norbornene (1 eq.) in the presence of 5 mol % $(dba)_3Pd_2CHCl_3$ and 20 mol % triphenylphosphine in refluxing THF gave a 67% yield of the cyclopropyl ketone 4.[3,6,7] 2,3-Dimethoxycarbonyl norbornadiene, which previously reacted only in poor yield, gave a 92% yield of the cycloadduct 5[5] using a 1.25: 1 ratio of 2a: acceptor and an 85% yield using a 1.08: 1 ratio of 2b: acceptor. The exo stereochemistry of the acetyl group of 5 derives from 1) analogy, 2) the 2.2 Hz vicinal coupling of Ha, and 3) the 14% NOE between H_a and H_b.

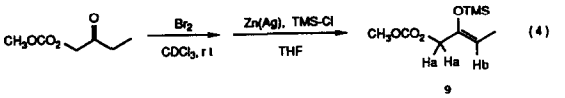


Having established the feasibility of the cycloaddition, we examined the ability to use substituted precursors. If carbene complexes were involved as reactive intermediates, unsaturated ketones arising from hydrogen migration might be expected to be the products. Gratifyingly, substrate 2c, prepared as a single regiosomer by the method of eq. 1, undergoes



palladium catalyzed cycloaddition with 2,3-di(methoxycarbonyl)norbornadiene in 64% yield (eq. 2) and with dicyclopentadiene in 61% yield (eq. 3). Both reactions showed extraordinary chemo-, regio-, and diastereoselectivity in that only a single adduct[7] resulted in each case, i.e., 6[5] and 7[5]. The selectivity is easily discerned from the nmr data for the cycloadducts.[8] No products derived from the alternative cyclopropanation to give products like 8 are seen.

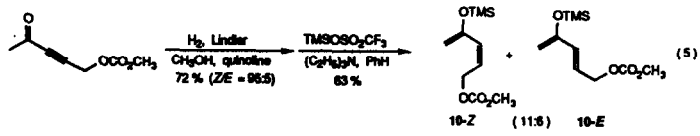
To test the dependence of the regioselectivity on the structure of the precursor, the regioisomeric substrate 9[5] was prepared as outlined in eq. 4 in 42% overall yield.[9] Interestingly, the enol silyl ether was produced as a single geometric isomer (>95:5).[10]

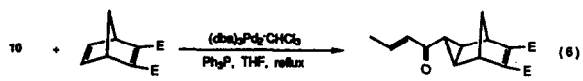


The Z-stereochemistry depicted stems from a 6-9% NOE between H_a and H_b. *Cycloaddition of 9 with 2,3-di(methoxycarbonyl)norbornadiene generated the same cyclopropane 6 as that from precursor 2c!* These results support the intermediacy of a species in which the positional identity of the leaving group is lost.

A vinylogue of the above types of precursors was synthesized according to eq. 5. *This*

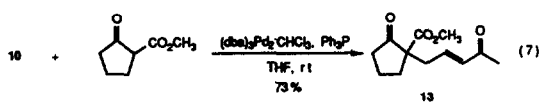
precursor behaves analogous to the α-acyloxyketones giving only cyclopropanation with high



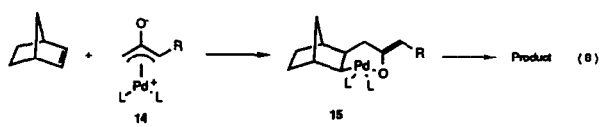


chemo-, regio-, and diastereoselectivity (eq. 6, 50% yield). This result suggests that the initially formed π-allylpalladium intermediate 11 equilibrates with the isomer 12 responsible for cyclopropanation.

Verification of the formation of 11 derives from reaction of 10 with a pro-nucleophile, 2-methoxycarbonylcyclopentanone which gives the single alkylated product 13 in the presence of a palladium (0) catalyst at room temperature (eq. 7).[11]



Regardless of the nature or the position of the substituent in the precursor, cyclopropanation always occurs at the terminal methylene carbon. This fact, combined with the required symmetry property of the reactive intermediate as established herein and the great



facility of desilylation of O-silyl ethers under these conditions, provides strong support for invoking the intermediacy of the oxatrimethylenemethane palladium complex 14. Steric factors dictate insertion of the olefin at the less substituted carbon terminus of 14 to adduct 15 which then must tautomerize before collapsing to cyclopropane. The failure of 15 to collapse

to cyclopentanones before tautomerization remains puzzling. Further mechanistic work to more firmly establish the sequence of events in the cyclopropanation and the nature of the reactive intermediates is required to extend this potentially very useful cyclopropanation sequence due to the ready availability of the precursors, their safety compared to diazocarbonyl compounds, the mildness of the reaction conditions, and the high selectivity.

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1. For a review, see Trost, B. M. *Angew. Chem. Internal. Ed. Engl.* **1986**, *25*, 1; Trost, B. M.; Miller, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

2. For a review, see Binger, P.; Buch, H. M. *Topics Curr. Chem.* **1987**, *135*, 77.

3. Trost, B. M.; Schneider, S. *J. Am. Chem. Soc.* **1989**, *111*, 4430.

4. Cf Kemmitt, R.D.W.; McKenne, P.; Russell, B. R.; Sherry, L.J.S. *J. Chem. Soc. Dalton Trans.* **1985**, *259*. Yanase, N.; Nakamura, Y.; Kawaguchi, S. *Inorg. Chem.* **1980**, *19*, 1575.

5. Satisfactory spectral data has been obtained for this compound.

6. Sauers, R. R.; Schlosberg, S.B.; Pfeffer, P.E. *J. Org. Chem.* **1968**, *33*, 2175.

7. Both endo and exo cyclopropyl methyl ketones arise from α-diazocarbonyl substrates with norbornadiene. See Kirmse, W.; Olbricht, T. *Chem. Ber.* **1975**, *108*, 2629; Creary, X. *J. Org. Chem.* **1975**, *40*, 3326. Palladium chloride catalysis is claimed to give a syn-anti mixture of only the exo isomers: Kirmse, W.; Olbricht, T. Synthesis **1975**, 173. For α-diazoacetate and norbornene to produce exo attack see Sauers, R. R.; Sonnet, P. E. Tetrahedron **1964**, *20*, 1029; Lam, J.; Johnson, B. L. *Aust. J. Chem.* **1972**, *25*, 2269.

8. 6. IR (neat): 1740, 1640 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 400 MHz): δ 3.79 (s, 6H), 3.37 (s, 2H), 2.95 (bs, 1H), 2.54 (q, J=7Hz, 2H), 1.96 (bs, 2H), 1.31 (s, 2H), 1.05 (t, J=7Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.3 (C), 165.2 (C), 149.8 (C), 52.0 (CH_3), 45.7 (CH), 38.8 (CH_2), 38.3 (CH_2), 36.3 (CH), 32.6 (CH), 7.5 (CH_3). Anal. Calc'd for $C_{15}H_{18}O_5$: C, 64.73, H, 6.52. Found: C, 64.71; H, 6.53.

   7. IR (neat): 1705, 1690 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 400 MHz): 5.73 (dd, J=5.6, 2Hz, 1H), 5.63 (dd, J=5.6, 2.4Hz, 1H), 3.11 (m, 1H), 2.56 (m, 1H), 2.50 (q, J=7Hz, 2H), 2.43 (m, 1H), 2.35 (m, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.94 (t, J=2.4Hz, 1H), 1.50 (bd, J=7Hz, 1H), 1.20 (bd, J=7H, 1H), 1.09 (d, J=10Hz, 1H), 1.03 (t, J=7Hz, 3H), 0.93 (d, J=10Hz, 1H). ^{13}C NMR ($CDCl_3$): 211.6 (C), 133.0 (CH), 130.3 (CH), 54.5 (CH), 42.8 (CH), 39.5 (CH), 38.3 (CH_2), 36.7 (CH_2), 31.5 (CH_2), 31.3 (CH), 26.3(CH), 23.3 (CH), 23.0 (CH), 7.8 (CH_3).

9. Cf Itoh, A.; Oshirna, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2050.

10. The use of such compounds in aldol type condensations should prove interesting and useful.

11. Cf Trost, B. M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.

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