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INFLUENCE OF OLEFIN COORDINATION ON CYCLOPROPANATION SELECTIVITY

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Catalyst-dependent differences in regioselectivity for cyclopropanation result from the degree of charge development in the transition state rather than from intramolecular collapse of a coordinated olefin.

The first reference to differential selectivity in transition metal catalyzed carbenoid transformations of diazo compounds was reported by Salomon and Kochi.[1] Comparing relative reactivities for cyclopropanation of tetramethylethylene and 1-hexene, they found that copper complexes capable of olefin coordination (CuOTf, $CuBF_4$) favored reaction with 1-hexene whereas those not capable of olefin coordination ($Cu(acac)_2$, $CuCl\cdot P(OR)_3$, $CuSO_4$) favored tetramethylethylene, and analogous differences were obtained for regioselective cyclopropanation of 7-methyl-1,6-octadiene. These observations were attributed to the differential influences of olefin coordination with the transition metal, and CuOTf was inferred to form cyclopropane products by reaction of the coordinated olefin with the metal-associated carbene. Intramolecular collapse of the coordinated olefin onto the carbene has been offered as one of two fundamental mechanisms for olefin cyclopropanation,[2] and palladium catalysts have been reported to have exceptional selectivity for the cyclopropanation of terminal olefins, including limonene.[3] However, the coordinated olefin is activated towards nucleophilic attack[4] but the proposed collapse involves addition of an electrophilic metal carbene to the coordinated olefin.

The stable palladium(II) chloride complexes of 5-methylenebicyclo[2.2.1]hept-2-ene (1) and *endo*-5-vinylbicyclo[2.2.1]hept-2-ene (2)[5] were subjected to

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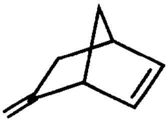

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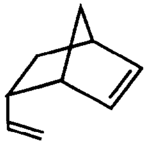


ethyl diazoacetate in chloroform. Neither underwent any observable reaction with this diazo compound and remained unchanged even when either $Rh_2(OAc)_4$ or $PdCl_2\cdot 2PhCN$ was added to the combination of ethyl diazoacetate and palladium complex. However, addition of excess diene to either of these palladium complexes, even in equivalent amounts, followed by ethyl diazoacetate resulted in rapid cyclopropanation. This data clearly excludes electrophilic carbene addition to a coordinated olefin as well as the alternate electrophilic addition of the coordinated olefin to the diazo compound, but cyclopropanation of an uncoordinated carbon-carbon double bond of a diene from an intramolecularly coordinated metal carbene remains a distinct mechanistic possibility.

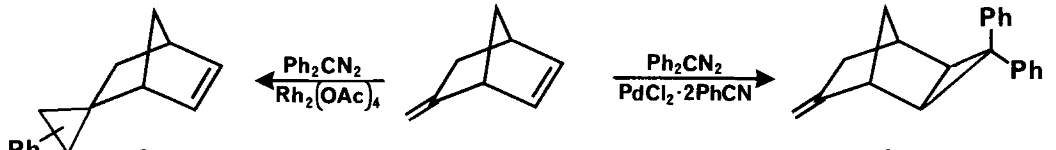
Catalysts with two available coordination sites were employed for cyclopropanation reactions with representative dienes, limonene and 5-methylenebicyclo[2.2.1]hept-2-ene, and $Rh_2(OAc)_4$, a catalyst that does not coordinate with alkenes, served as the reference. Treatment of excess olefin with ethyl diazoacetate (10:1) in the presence of $Rh_2(OAc)_4$, $Cu(OTf)_2$[6], or $PdCl_2 \cdot 2PhCN$ (1-2 mol %) gave the results described in Table I. Regio- and stereoselectivities obtained with $Rh_6(CO)_{16}$, Cu bronze, and $CuCl \cdot P(O\text{-}i\text{-}Pr)_3$ were nearly identical with those obtained with $Rh_2(OAc)_4$. Palladium catalysts, $Pd(OOCCF_3)_2$, $PdCl_2 \cdot 2PhCN$, **1**-$PdCl_2$, and **2**-$PdCl_2$ gave nearly identical regio- and stereoselectivities. For reactions with limonene, regioselectivities were relatively invarient with the catalyst, and cyclopropanation of the disubstituted double bond was favored over addition to the trisubstituted double bond. In constrast, $Rh_2(OAc)_4$-catalyzed reactions of ethyl diazoacetate with **1** resulted in the favored production of cyclopropane products from electrophilic attack at the exocyclic double bond, whereas $PdCl_2 \cdot 2PhCN$ effected highly selective cyclopropanation of the endocyclic double bond.[7]

Table I. Regioselectivities in Catalytic Cyclopropanation of Limonene and Bicyclo[2.2.1]hept-2-ene.

	Limonene		5-Methylenebicyclo[2.2.1]hept-2-ene		
catalyst	yield,%	A/B[a]	yield,%	A/B[b]	exo/endo[c]
$Rh_2(OAc)_4$	98	3.4	93	2.3	2.6
$Cu(OTf)_2$	59	3.9	53	1.0	1.3
$PdCl_2 \cdot 2PhCN$	32	3.6	82	0.16	1.2

[a] Cyclopropanation of disubstituted (A) and trisubstituted (B) double bond. [b] Exocyclic (A)/endocyclic (B) double bond. [c] Stereoisomer ratio for cyclopropanation of the endocyclic double bond.

If a metal carbene coordinated with the exocyclic double bond of **1** were to undergo intramolecular cyclopropanation of the endocyclic double bond, cyclopropanation would occur exclusively from the endo side. However, comparative results using ethyl diazoacetate from $Rh_2(OAc)_4$-catalyzed cyclopropanation of this diene (*exo:endo* = 72:28) and of bicyclo[2.2.1]hept-2-ene (exo:endo = 70:30) with those from $PdCl_2 \cdot 2PhCN$ (exo:endo = 54:46 and 56:44, respectively) are incompatable with intramolecular cyclopropanation. Furthermore, results obtained with the use of diphenyldiazomethane (eq 1), in which 3 was formed exclusively (>100:1) with $Rh_2(OAc)_4$ catalysis and 4 was produced



3 4 (1)

exclusively as the exo isomer in similar high selectivity (>50:1) with $PdCl_2 \cdot 2PhCN$, are in accord with this conclusion.

Competitive catalytic cyclopropanations of the two model compounds, bicyclo[2.2.1]hept-2-ene and 2-methylenebicyclo[2.2.1]heptane, were performed according to the previously described procedure.[8]. The relative reactivity for cyclopropanation of the exocyclic double bond of 2-methylenebicyclo[2.2.1]-heptane was only 0.22 in $PdCl_2 \cdot 2PhCN$-catalyzed reactions of ethyl diazoacetate but was 2.5 with $Rh_2(OAc)_4$. Thus the relative reactivities of the two model compounds reflect the regioselectivities in cyclopropanation of 5-methylenebicyclo[2.2.1]hept-2-ene by ethyl diazoacetate with these same catalysts (Table I). Based on the composite results, the observed selectivity differences can be attributed to electronic influences on the transition state for cyclopropanation. A transition state with little charge development at the olefinic carbons favors cyclopropanation at the endocyclic double bond (5),[9,10] where the low out-of-plane deformation energy in the "early" transition state of a concerted *syn* addition controls regioselectivity,[11] whereas a transition state with considerable charge development (6) favors cyclopropanation at the exocyclic double bond.[12] In addition, since the relative reactivities for the model compounds are nearly identical with the regioselectivities for cyclopropanation of 1 with ethyl diazoacetate, there is no compelling evidence for homoallylic stabilization in either 5 or 6.

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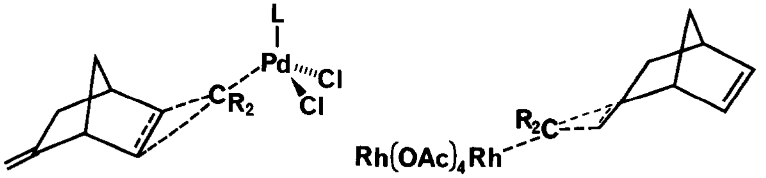

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Electrophilic metal carbenes are the reactive intermediates in these catalytic cyclopropanation reactions,[8,13] and their relative reactivities towards addition to carbon-carbon double bonds reflect the degree of bond making and bond breaking in the transition state for cyclopropane formation. Olefin coordination at the metal center of a metal carbene, if present in these catalytic reactions, does not influence cyclopropanation reactivity or selectivity.

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