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On the Mechanism of Pd(0) Catalyzed Formation of Oxazolidin-2-ones from Vinyl Epoxides

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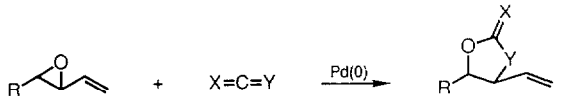
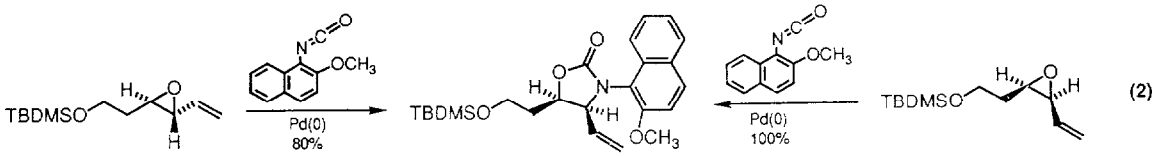
Summary. The reaction of vinyl epoxides with isocyanates proceeded with overall retention of configuration.

The reaction of vinyl epoxides with cumulative unsaturated electrophiles like carbon dioxide[1] and isocyanates[2] provides a facile entry to five membered ring heterocycles according to eq 1.[3] Whereas, the use of carbon dioxide as the reaction partner proceeded



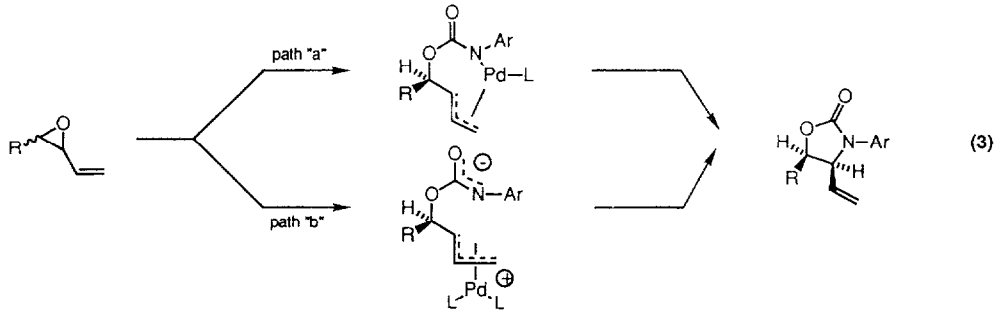
(1)

stereospecifically; the stereochemistry of the reaction with isocyanates depended upon the choice of isocyanate. Aryl isocyanates, especially 2-methoxynaphthyl-1-isocyanate, condense with vinyl epoxides to form the thermodynamically less stable *cis*-4,5-disubstituted-oxazolidin-2-ones regardless of the stereochemistry of the starting vinyl epoxide (eq 2). The possibility arises that the explanation may lie in a pathway in which



(2)

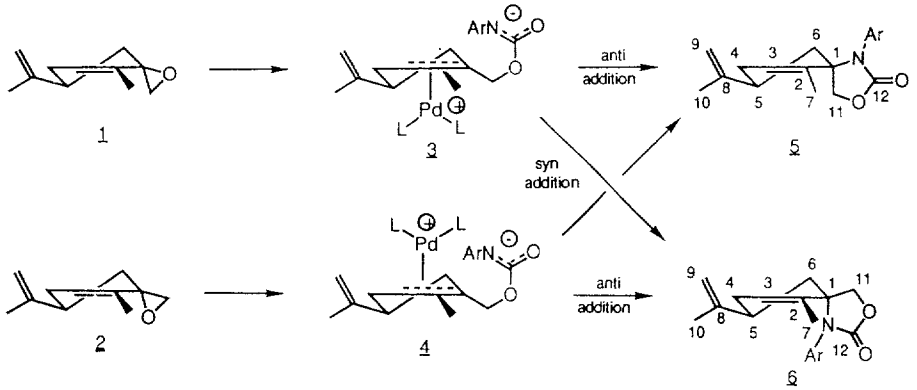
nitrogen initially coordinates to the palladium in the intermediate π-allyl complex, and this species then collapses to product (eq 3a).[4,5]



(3)

Establishing the stereochemistry of the nitrogen addition relative to the stereochemistry of the palladium in the intermediate π-allyl complex provides a test for such a pathway. The reaction of carvone epoxides 1 and 2 should test this question, as shown in the Scheme. Since palladium initiated ionization has been established to proceed

Scheme. **Carvone Epoxides as Mechanistic Test Substrates**



with inversion of configuration,[5] the diastereomeric epoxides 1 and 2 should generate the diastereomeric π-allylpalladium complexes 3 and 4, which cannot interconvert by the usual unimolecular isomerization processes. Attack *anti* to palladium creates the product of overall retention of configuration (*i.e.* 1 --> 5 and 2 --> 6); whereas, attack *syn* to palladium forms the product of overall inversion of configuration (*i.e.* 1 --> 6 and 2 --> 5).

The diastereomeric epoxides were prepared from R-(-) - carvone by three routes: (1) dimethylsulfoniummethylide addition (1:2, 9:1),[6] (2) addition of methylthiomethyllithium, methylation and base (1:2, 4:1),[7] and (3) addition of methylthiomethylcesium dichloride,[8] methylation, and base (1:2, 4:1).

Reaction of either epoxide 1 or 2 with *p*-toluenesulfonylisocyanate proceeds even in the absence of palladium to give a 1:1 mixture of oxazolidin-2-ones 5 and 6 (Ar=$SO_2C_7H_7$-p). On the other hand, the less electrophilic isocyanates do not react in the absence of a palladium(0) catalyst. In a typical procedure, equimolar amounts of the carvone epoxide and the arylisocyanate in THF (1M) containing 1-2 mol% $(dba)_3Pd_2 \cdot CHCl_3$ and 12-24 mol% of triisopropyl phosphite are stirred at room temperature for 1-3 days. Dilution of the reaction with ethyl acetate or methylene chloride and filtration through a pad of silica gel gives the product, which is directly analyzed by vpc and/or ^1H nmr to determine isomer ratios. Purification for identification involves flash chromatography on silica gel.[9] In spite of the pseudoequatorial nature of the C-O bond of epoxide 1 and the requirement that this bond must become parallel to the π system during Pd initiated ionization, reaction proceeds very smoothly with diastereomer 1, as well as 2.

Assignment of stereochemistry involves detailed analysis of the ^1H nmr spectra, including NOE and solvent induced shift studies. Table 1 records the ^1H and ^{13}C shifts for two pairs of oxazolidin-2-ones. All of the trends observed are consistent with the "a" series corresponding to the adducts of type 5, and the "b" series to those of type 6. Particularly dramatic are the very large differences seen for the isopropenyl group as a

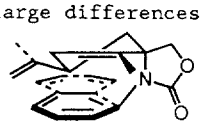


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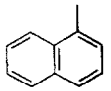
Table 1. ^{1}H and ^{13}C NMR Shifts for Diastereomeric Oxazolidin-2-ones[a]

	R = Ph				R = 			
	5[b]		6[c]		5[d]		6[e]	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1.	---[f]	66.1	---[f]	64.2	---[f]	67.4	---[f]	65.2
2.	---[f]	135.8	---[f]	133.3	---[f]	135.3	---[f]	132.7
3.	5.76(b)	128.4	5.80(b)	129.8	5.80(b)	129.2	5.83(b)	129.8
4.	NA[g]	30.7	NA[g]	30.1	1.75(dd)	30.9	1.77(m)	29.9
					2.10(d)			
5.	NA[g]	39.0	NA[g]	37.0	2.10(m)	39.4	0.99(m)	36.5
6.	NA[g]	37.6	NA[g]	41.0	1.48(t)	38.7	1.46(t)	40.9
			2.23(d)		1.90(d)		2.24(d)	
7.	1.86(s)	17.9	1.96(s)	17.7	2.11(s)	18.2	2.09(s)	17.8
8.	---[f]	137.3	---[f]	136.7	---[f]	135.9	---[f]	135.2
9.	4.66(s)	110.4	4.44(s)	110.4	4.46(s)	110.3	4.00(s)	109.8
	4.74(s)		4.64(s)		4.61(s)		4.38(s)	
10.	1.69(s)	20.8	1.50(s)	20.8	1.55(s)	20.8	0.93(s)	20.3
11.	4.22(d)	74.5	4.08(d)	73.9	4.48(d)	76.7	4.30(d)	73.9
	4.27(d)		4.37(d)		4.52(d)		4.53(d)	
12.	---[f]	157.1	---[f]	157.7	---[f]	157.4	---[f]	157.7

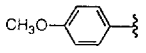
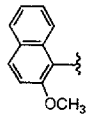
(a) All shifts in ppm downfield from internal TMS in $CDCl_3$. Abbreviations are standard. (b) Oil; (c) Mp 106-8°; (d) Mp 190-2°; (e) Mp 140°; (f) No signal; (g) Not assigned.

function of oxazolidin-2-one stereochemistry. Models show that the aryl group for diastereomers 6 are forced to adopt a conformation depicted in 7 in which the isopropenyl group lies in the shielding region of the aryl rings (cf shifts for positions 9 and 10 in each pair). The extended shielding region of the naphthalene nucleus compared to the phenyl nucleus leads to even larger shielding. NOE studies reinforce these assignments. Eu(+3) induced solvent shifts for 5 (Ar=1-naphthyl) demonstrate that the absorption for the equatorial proton at position 6 shifts more rapidly than that for the axial proton at this same position - an observation also in agreement with the assignments made. Similar chemical shift trends are observed for all of the oxazolidin-2-ones and thus the same assignments are made.

Table 2 summarizes the analysis of the product mixtures starting from three different isomeric ratios of carvone epoxide - 1:2 being 80:20,[10a] 89:11,[10b] and 0:100.[10c] Within experimental error, the product ratios reflect the ratios of the diastereomeric starting materials. *The overall stereochemical result is net retention of configuration.* Thus, the mechanism of the oxazolidine-2-one formation is the double inversion as depicted in 1 -->3 -->5 and 2 --> 4 --> 6 in the Scheme.

This result requires that the selectivity for *cis*-oxazolidin-2-ones in acyclic cases must arise via path "b" of eq 3 and that equilibration of the diastereomeric π-allylpalladium complexes to the one depicted in eq 3b must be faster than cyclization. The source for the kinetic selectivity to be opposite that of the thermodynamic stability of the products remains yet to be established.

Table 2. Oxazolidin-2-one Ratios (5:6) as Function of Isocyanate[a]

Aryl isocyanate/Epoxide Ratio 1:2	4:1	8.6:1	0:100
Ph	3.5:1	10:1	N.D.[b]
	3.0:1	12:1	0:100
	4.0:1	7:1	N.D.[b]
	2.5:1	N.D.[b]	N.D.[b]
	2.6:1	8.6:1	0:100

(a) Determined by nmr spectroscopy. (b) N.D.=not determined.

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9. All new compounds have been fully characterized spectroscopically and elemental composition established by combustion analysis and/or high resolution mass spectroscopy.
10. (a) Obtained by method 2 in text.
(b) Obtained by method 1 in text.
(c) Obtained by chromatographic separation of the hydroxysulfides prepared in method 2 followed by methylation and base.

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