

REGIOSELECTIVITY IN CATALYTIC CYCLOPROPANATION REACTIONS

Michael P. Doyle*, Roberta L. Dorow, William H. Tamblin and William E. Buhro
Department of Chemistry, Hope College, Holland, Michigan 49423

Regioselectivities of cyclopropanation reactions with ethyl diazoacetate and monosubstituted dienes correlate linearly with the reaction catalyst and provide definition of the "metal carbene regioselectivity index".

Carbenoid entry into cyclopropanes through catalytic transformations of diazo compounds with olefins is generally acknowledged as occurring by the interaction of an electrophilic metal carbene with an olefin, but the specific details of that interaction remain unresolved.¹⁻⁶ A broad selection of catalysts suitable for cyclopropanation has been identified. However, the characteristics of these catalysts for cyclopropanation have invariably been defined by product yield and relative reactivity data from which mechanistic interpretations have been drawn. The inherent selectivity of transition metal catalyzed cyclopropanation reactions, although offering useful synthetic and critical mechanistic information, has received only scant attention.³⁻¹⁰ We have examined regioselectivity for cyclopropane formation in reactions of ethyl diazoacetate with a broad selection of monosubstituted conjugated dienes (eq 1) and wish to report the striking correlations that have been identified in this investigation.

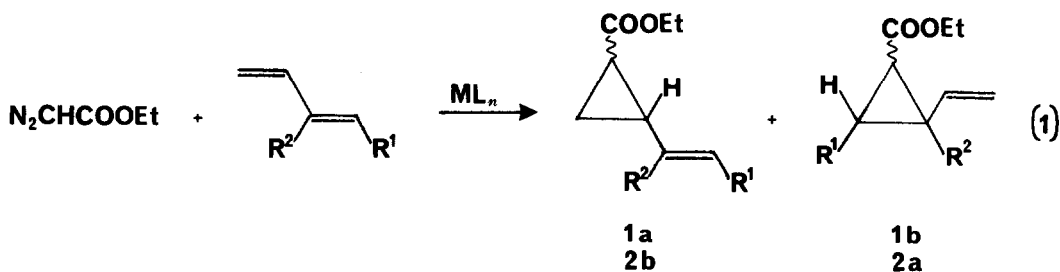


Table I reports the product yields and regioselectivities that are obtained in reactions of ethyl diazoacetate with monosubstituted conjugated dienes in the presence of representative effective transition metal cyclopro-

Table I. Cyclopropanation Regioselectivities from Reactions of Ethyl Diazoacetate with 1-Substituted (1) and 2-Substituted (2) Butadienes in the Presence of Transition Metal Catalysts.

Diene	R ¹	R ²	Rh ₂ (OAc) ₄		Rh ₆ (CO) ₁₆		CuCl·P(O- <i>i</i> -Pr) ₃		PdCl ₂ ·2PhCN	
			yield, %	a/b	yield, %	a/b	yield, %	a/b	yield, %	a/b
Isoprene	H	CH ₃	93	1.58	70	1.63	81	1.94	24	0.54
2-Phenylbutadiene	H	C ₆ H ₅	81	2.27	71	2.48	28	3.18	<10	0.9
2-Chlorobutadiene	H	Cl	76	3.8	80	4.1	33	5.1		
2-Methoxybutadiene	H	OCH ₃	88	>200	63	>200	38	>100	18	>100
Piperylene	CH ₃	H	61	7.5	72	8.2	23	10.1	31	3.4
1-Phenylbutadiene	C ₆ H ₅	H	84	50	40	54	56	65	13	24
1-Chlorobutadiene	Cl	H	73	>100	21	>100	17	>100		
1-Methoxybutadiene	OCH ₃	H	90	7.8	56	8.0	57	5.4	22	2.9

Reactions were performed at 25°C under an inert atmosphere of nitrogen or argon by the addition of ethyl diazoacetate over a 6 to 8 h period to a 10-fold molar excess of the diene in the presence of 0.5-1.0 mole % (based on ethyl diazoacetate) of the transition metal catalyst. Cyclopropane products were isolated individually by GC collection and identified by spectral methods. Regioselectivities were determined by GC analyses in combination with NMR spectral confirmation. Stereospecificity is observed in cyclopropane formation from 1-substituted dienes (E-isomers), and Z-isomers of 1-phenylbutadiene and 1-chlorobutadiene exhibit no difference in regioselectivity and little difference in relative reactivity (< 5) when compared to their corresponding E-isomers. A minimum of two reactions was employed for each determination, and reported regioselectivities are averaged values (normally ± 5% of the values listed in this table). Monocyclopropanation products of 1-methoxy- and 2-methoxybutadiene were isolated in 51% and 62% yields, respectively, from reactions with equivalent amounts of ethyl diazoacetate and the use of 0.1 mol % of Rh₂(OAc)₄ by the procedure outlined in reference 7.

panation catalysts. Clearly $\text{Rh}_2(\text{OAc})_4$ is the most suitable of the catalysts examined for cyclopropanation under the mild reaction conditions that are employed. More striking, however, is the observed dependence of regioselectivity on the reaction catalyst and the internal consistency that is observed for regioselectivity in these reactions. Using values obtained for $\text{Rh}_2(\text{OAc})_4$ as reference points, regioselectivities observed for $\text{Rh}_6(\text{CO})_{16}$ and $\text{CuCl}\cdot\text{P}(\text{O}-i\text{-Pr})_3$ are consistently higher than those for $\text{Rh}_2(\text{OAc})_4$, and the regioselectivities of $\text{PdCl}_2\cdot 2\text{PhCN}$ catalyzed reactions are consistently lower. Since the regioselectivity ratio is a direct measure of the relative rates for reactions at the substituted and unsubstituted double bond of the reactant diene, a plot of the regioselectivity ratios observed in these catalytic transformations versus those of a reference catalyst, $\text{Rh}_2(\text{OAc})_4$ in this study, provides an index of metal carbene selectivity (Figure 1). Values for the slope of the lines in Figure 1, which we define as the "metal carbene regioselectivity index"¹¹ are 1.44 for $\text{CuCl}\cdot\text{P}(\text{O}-i\text{-Pr})_3$, 1.10 for $\text{Rh}_6(\text{CO})_{16}$, and 0.48 for $\text{PdCl}_2\cdot 2\text{PhCN}$. These indices provide a characteristic identity to each catalyst and identify, for the first time, a specific correlation with which cyclopropanation catalysts can be evaluated.

The regioselectivities observed for catalytic cyclopropanation reactions with ethyl diazoacetate are in accord with electrophilic interaction of catalytically generated metal carbenes with the reactant dienes. Variation of the

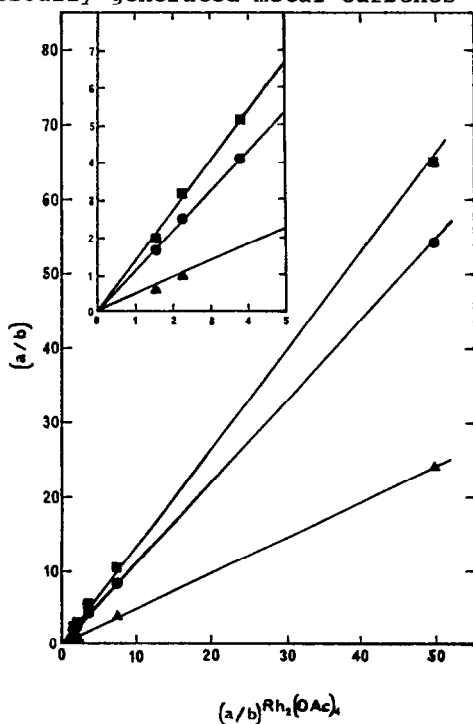


Figure 1.

Plot of observed regioselectivities from $\text{CuCl}\cdot\text{P}(\text{O}-i\text{-Pr})_3$ (■), $\text{Rh}_6(\text{CO})_{16}$ (●), and $\text{PdCl}_2\cdot 2\text{PhCN}$ (▲) catalyzed reactions of ethyl diazoacetate with monosubstituted dienes versus regioselectivities from $\text{Rh}_2(\text{OAc})_4$ catalyzed cyclopropanation reactions. Data taken from Table I.

metal carbene regioselectivity index is thus related to changes in the electrophilicities of the reactant metal carbenes. That cyclopropane formation occurs stereospecifically suggests that the initial interaction between the metal carbene and the diene is that of a π -complex and that carbonium ion intermediates are not involved in this transformation. Subsequent steps proceeding from this initial diene-metal carbene interaction are less evident, but clearly they do not correspond to those between a "free" carbene such as dichlorocarbene and these dienes from which regioselectivities opposite to those reported in Table I are obtained.¹²

Acknowledgment. The support of the National Science Foundation for this research is gratefully acknowledged. We thank K.N. Houk for his helpful comments and the NSF-URP program for their support of R.L.D. during the summer of 1981.

REFERENCES AND NOTES

1. (a) Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F. In "The Chemistry of Diazonium and Diazo Groups", Patai, S., Ed.; Wiley: New York, 1978, Chapter 18. (b) Yanavskaya, L.A.; Dombroosku, V.A. *Russ. Chem. Rev.* 1975, 44, 154. (c) Jones, M.; Moss, R.A. "Carbenes", Vol. 1; Wiley: New York, 1973. (d) Kirmse, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971.
2. Tambllyn, W.H.; Hoffmann, S.R.; Doyle, M.P. *J. Organometal. Chem.* 1981, 216, C64.
3. Anciaux, A.J.; Hubert, A.J.; Noels, A.F.; Petiniot, N.; Teyssié, Ph. *J. Org. Chem.*, 1980, 45, 695.
4. (a) Nakamura, A.; Konishi, A.; Tsujitani, R.; Kudo, M.; Otsuka, S. *J. Am. Chem. Soc.* 1978, 100, 3449. (b) Nakamura, A.; Koyama, T.; Otsuka, S. *Bull. Chem. Soc. Jpn.* 1978, 51, 593.
5. Salomon, R.G.; Kochi, J.K. *J. Am. Chem. Soc.* 1973, 95, 3300.
6. Moser, W.R. *J. Am. Chem. Soc.* 1969, 91, 1135, 1141.
7. Doyle, M.P.; van Leusen, D.; Tambllyn, W.H. *Synthesis*, 1981, 787.
8. (a) ApSimon, J.W.; Sequin, R.P. *Tetrahedron* 1979, 35, 2797. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* 1975, 1707.
9. Callot, H.J.; Piechocki, C. *Tetrahedron Lett.* 1980, 21, 3489.
10. Wenkert, E.; Goodwin, T.E.; Ranu, B.C. *J. Org. Chem.* 1977, 42, 2137.
11. To differentiate from the recently defined "carbene selectivity index": R.A. Moss, *Acc. Chem. Res.* 1980, 13, 58.
12. Regioselectivities in reactions of dichlorocarbene with isoprene (49) and piperylene (0.72) have been reported: Skattebøl, L. *J. Org. Chem.* 1964, 29, 2951. Those for reactions with 2-phenylbutadiene (>100) and *trans*-1-phenylbutadiene (16) were obtained by the same procedure and correspond to values that were previously reported: (a) Kostikov, R.R.; Bepalov, A. Ya. *Zh. Org. Khim.* 1970, 6, 629. (b) D'yakanov, I.A.; Kostikov, R.R.; Aksenov, V.S. *ibid.* 1970, 6, 1965.

(Received in USA 31 December 1981)