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Efficient Alternative Catalysts and Methods for the Synthesis of Cyclopropanes from Olefins and Diazo Compounds

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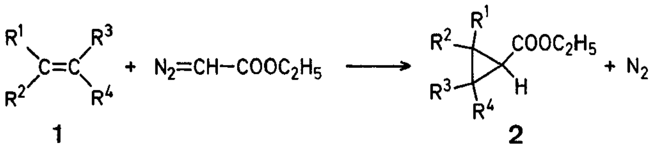
Rhodium(II) carboxylates have been reported to be highly effective catalysts for the cyclopropanation of olefins with diazo compounds[1,2], and we have recently described the surprising versatility of the hexarhodium carbonyl cluster, $Rh_6(CO)_{16}$, for these same transformations[3]. However, although superior conversions have been observed with these catalysts when a 5- to 10-fold excess of the olefinic component is employed, the effectiveness of rhodium(II) carboxylates and $Rh_6(CO)_{16}$ for reactions in which the olefin is the limiting reagent has not been indicated[4,5]. Catalysts other than well-defined copper compounds have not been utilized in synthetic schemes that employ cyclopropanation reactions despite the common occurrence of isomeric C—H insertion and rearrangement products in the copper-catalyzed processes[6,7].

Previous studies have indicated that the formation of cyclopropane compounds in rhodium-catalyzed reactions of ethyl diazoacetate is limited by competitive dimerization of the carbenoid equivalent of the diazo compound, even when more than a 5-fold excess of olefin is employed[1,2,3]. However, if competition between olefin and ethyl diazoacetate for the reactive intermediate, presumably a metal carbene, is the cause of limited cyclopropane production, then merely minimizing the available concentration of ethyl diazoacetate in the reaction medium should afford optimal yields of cyclopropane products. As a consequence, exact control of the rate of addition of the diazo compound to the reaction medium should afford superior cyclopropane yields even when only equivalent amounts of olefin (**1**) and ethyl diazoacetate are employed. Such procedural control should also offer economical limitations in the amount of catalyst required for effective cyclopropanations. These advantages have been realized (Table 1).



Equivalent amounts of ethyl diazoacetate and alkene (**1**), each dissolved in anhydrous solvent, were employed in order to determine the degree of approach of these catalytic transformations to the ideal stoichiometry. Product yields listed in Table 1 are based on ethyl diazoacetate. Since more than 60% of the alkene submitted to the reaction could be recovered, optimization of conditions through the use of excess ethyl diazoacetate can be expected to provide ethyl cyclopropanecarboxylates **2** in amounts that approach quantitative yield. Products isomeric with **2** are remarkably absent from reaction mixtures, and diethyl maleate, diethyl fumarate, and a residual non-volatile substance derived solely from ethyl diazoacetate generally account for the not incorporated ethyl diazoacetate.

Control of the rate of addition of ethyl diazoacetate [EDA] to the reaction medium provided remarkable control over the yield of **2**. Generally, ethyl diazoacetate was introduced through the second half of the addition at a rate which was one-half of that initially employed. The effect of this control on product yield is dramatically illustrated for reactions of 1-methoxycyclohexene with ethyl diazoacetate: at a [EDA]/[$Rh_2(OAc)_4$] ratio of 200 and an addition rate of 10, 5.0 mmol/h, **2d** was obtained in 80% yield. With a [EDA]/[$Rh_2(OAc)_4$] ratio of 2000 and an addition rate of 5.0, 2.5 mmol/h, the yield of **2d** was only 60%. However, by decreasing the rate of addition of ethyl diazoacetate to 0.5, 0.25 mmol/h, **2d** could again be isolated in 80% yield. Thus, extremely small amounts of these catalysts can be effectively employed if the rate of addition of diazo compound is decreased in proportion to the decrease in olefin and catalyst concentration.

The relative effectiveness of rhodium catalysts is indicated by the comparative results obtained with $CuCl \cdot P(O—C_3H_7\text{-}i)_3$[8] for reactions of ethyl diazoacetate with 2-methoxypropene (**1b**) and cyclohexene (**1e**). The Moser catalyst $CuCl \cdot P(O—C_3H_7\text{-}i)_3$ was chosen for this comparison because, in our evaluation of this catalyst against copper(II) acetylacetonate and copper bronze in reactions of ethyl diazoacetate with a 10-fold molar excess of alkenes **1b–1f**, this catalyst promoted 10–30% higher yields of isolated cyclopropane compounds. Copper triflate[9] was not employed because of its capacity to cause polymerization of vinyl ethers[1]. The results described in Table 1 show that even with an addition rate of 0.25 mmol/h and a [EDA]/[$CuCl \cdot P(O—C_3H_7\text{-}i)_3$] molar ratio of 200, the yields of isolated cyclopropane products are significantly lower than those obtained using rhodium catalysts. Similar results are observed in catalyst comparisons with reactions performed with a 10-fold excess of alkenes **1b–1f** and indicate that rhodium catalysts are the most suitable general-purpose cyclopropanation catalysts currently available.

Cyclopropanation selectivities in reactions of dienes with equimolar amounts of diazo compounds have not been previously described, although results from intermolecular competition studies have represented rhodium(II) catalysts as poorly discriminating in cyclopropanation reactions[1]. With conjugated dienes, monocyclopropanation modifies both the electronic and steric identity of the unreacted C=C double bond and could be expected to inhibit bis-cyclopropanation. The results obtained for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene (**1f**) with ethyl diazoacetate are in accord with this expectation. Bis-cyclopropanation of **1f** is not competitive with mono-cyclopropanation under the reaction conditions described by us (Table 1) although, when ethyl diazoacetate is employed in a 3-fold molar excess relative to the diene, the bis-cyclopropane compound is the major product.

The variability of cyclopropane yields and the requirement for use of excess alkene for cyclopropanations of simple alkenes with ethyl diazoacetate that have been attributed to copper ca-

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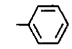
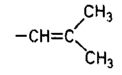
Table 1. Ethyl Cyclopropanecarboxylates (**2**) from Catalytic Cyclopropanation of Alkenes (**1**) with Ethyl Diazoacetate

	Alkene[a] **1**	Catalyst	Ratio $\frac{[EDA]}{[catalyst]}$	Addition rate [mmol/h][b]	Product **2** R^1	R^2	R^3	R^4	Yield [%][c]	Isomer ratio[d]
a	1-methoxystyrene	$Rh_2(OAc)_4$	100	7.5, 3.8	OCH_3		H	H	94	1.0
b	2-methoxypropene	$Rh_2(OAc)_4$	200	10, 5.0	OCH_3	CH_3	H	H	65	2.3
		$Rh_6(CO)_{16}$	500	5.0, 2.0					63	2.0
		$CuCl \cdot P(O{-}C_3H_7\text{-}i)_3$	200	0.25					40	2.5
c	ethyl vinyl ether	$Rh_2(OAc)_4$	300	6.7, 3.5	OC_2H_5	H	H	H	75	1.6
d	1-methoxycyclohexene	$Rh_2(OAc)_4$	2000	0.5, 0.25	OCH_3	$-(CH_2)_4-$		H	80	2.4
e	cyclohexene	$Rh_2(OAc)_4$	200	10, 5.0	H	$-(CH_2)_4-$		H	80	4.5
		$Rh_6(CO)_{16}$[e]	1000	5.0, 2.0					43	3.0
		$CuCl \cdot P(O{-}C_3H_7\text{-}i)_3$	200	0.25					40	12
f	2,5-dimethyl-2,4-hexadiene	$Rh_2(OAc)_4$[f]	1100	0.60	CH_3	CH_3	H	 $-CH{=}C(CH_3)_2$	58	2.2
		$Rh_6(CO)_{16}$[g]	200	0.33					50	2.3

[a] Equivalent amounts of alkene and ethyl diazoacetate were employed. Unless specified otherwise, reactions were performed at 25 °C in anhydrous diethyl ether.

[b] Rate of addition of the ethyl diazoacetate solution. Two equal portions of the ethyl diazoacetate solution were added at the two specified rates. The second portion was added at the slower rate.

[c] Yield of isolated product based on ethyl diazoacetate.

[d] (*E/Z*)-isomer ratio except for **2d, e** *(anti/syn)* determined by G.L.C. and ^{1}H-N.M.R. analyses. The (*E/Z*)-notation (*E*: *trans* relationship for groups of higher priority) is employed to avoid confusion in assignment, particularly for **2a, b**.

[e] Reaction performed in refluxing cyclohexane.

[f] Reaction performed without solvent; the bis-cyclopropane compound was formed in 1% yield.

[g] Reaction performed at 60 °C in toluene; the bis-cyclopropane compound was not observed (<0.1%).

Table 2. Characterization of New Cyclopropane Compounds **2a-d**

2	b.p./torr [°C]	Molecular formula[a]	I.R. (neat) $\nu_{C=O}$ [cm^{-1}][b]	Isomer	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
a	90-105°/0.5	$C_{13}H_{16}O_3$ (220.3)	1733	*E*[d]	7.5-7.2 (m, C_6H_5); 3.88 (q, $J = 7.1$ Hz, CH_2O); 3.14 (s, OCH_3); 2.32 (dd, $J_3 = 6.7$ Hz, $J_4 = 9.4$ Hz, $C\underline{H}COOC_2H_5$); 1.81 (dd, $J_3 = 6.7$ Hz, $J_{3,4} = 5.6$ Hz, H_3); 1.49 (dd, $J_4 = 9.4$ Hz, $J_{4,3} = 5.6$ Hz, H_4); 0.97 (t, $J = 7.1$ Hz, $\underline{H}_3C{-}CH_2O$).
				Z[e]	7.5-7.2 (m, C_6H_5); 4.22 (q, $J = 7.2$ Hz, CH_2O); 3.22 (s, OCH_3); 2.06 (dd, $J_3 = 7.0$ Hz, $J_4 = 8.5$ Hz, $C\underline{H}COOC_2H_5$); 1.52 (dd, $J_3 = 7.0$ Hz, $J_{3,4} = 5.4$ Hz, H_3); 1.41 (dd, $J_4 = 8.5$ Hz, $J_{4,3} = 5.4$ Hz, H_4); 1.29 (t, $J = 7.2$ Hz, $\underline{H}_3C{-}CH_2O$).
b	71-76°/18	$C_8H_{14}O_3$ (158.2)	1729	*E*	4.14 (q, $J = 7.1$ Hz, CH_2O); 3.29 (s, OCH_3); 1.86 (dd, $J_3 = 7.2$ Hz, $J_4 = 8.9$ Hz, $C\underline{H}COOC_2H_5$); 1.5-1.1 (m, 2H); 1.49 (s, CH_3); 1.26 (t, $J = 7.1$ Hz, $\underline{H}_3C{-}CH_2O$).
				Z	4.16 (q, $J = 7.2$ Hz, CH_2O); 3.27 (s, OCH_3); 1.7-1.5 (m, 1H); 1.44 (s, CH_3); 1.5-1.2 (m, 1H); 1.27 (t, $J = 7.2$ Hz, $\underline{H}_3C{-}CH_2O$); 0.95 (dd, $J = 7.2$, 10.1 Hz, 1H).
c	80-94°/18	$C_7H_{12}O_3$ (144.2)	1725	*E*	4.12 (q, $J = 7.1$ Hz, CH_2O); 3.60 (q, $J = 7.0$ Hz, CH_2O); 3.7-3.5 (m, $C\underline{H}OC_2H_5$); 1.76 (ddd, $J = 2.2$, 6.4, 8.9 Hz, $C\underline{H}COOC_2H_5$); 1.3-1.1 (m, 2H); 1.25 (t, $J = 7.1$ Hz, $\underline{H}_3C{-}CH_2O$); 1.19 (t, $J = 7.0$ Hz, $\underline{H}_3C{-}CH_2O$).
				Z	4.16 (q, $J = 7.1$ Hz, CH_2O); 3.54 (q, $J = 7.1$ Hz, CH_2O); 3.7-3.4 (m, $C\underline{H}OC_2H_5$); 1.8-1.4 (m, 2H); 1.26 (t, $J = 7.1$ Hz, $\underline{H}_3C{-}CH_2O$); 1.18 (t, $J = 7.1$ Hz, $\underline{H}_3C{-}CH_2O$); 1.1-0.9 (m, 1H).
d	68-78°/0.5	$C_{11}H_{18}O_3$ (198.3)	1742	*anti* (*Z*)	4.10 (q, CH_2O); 3.24 (s, OCH_3); 2.5-2.2 (m, $C\underline{H}COOC_2H_5$); 2.2-0.7 (m, 9H); 1.27 (t, $\underline{H}_3C{-}CH_2O$).
				syn (*E*)	4.14 (q, CH_2O); 3.28 (s, OCH_3); 2.2-1.2 (m, 10H); 1.27 (t, $\underline{H}_3C{-}CH_2O$).

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.13; H, ±0.11. M^+ peak observed in mass spectra.

[b] Measured with a PE 621 instrument.

[c] Determined with the Varian FT-80A instrument at 80 MHz on G.C.-separated samples.

[d] b.p. 90 °C/0.5 torr.

[e] b.p. 105 °C/0.5 torr.

talysts[10] do not characterize reactions performed in the presence of rhodium catalysts. In addition, the suitability of these catalysts and methods for cyclopropanations of vinyl ethers provides a convenient entry into the broad group of oxycyclopropanes which have shown significant potential in organic syntheses[5].

Catalytic Cyclopropanation; General Procedure:

A solution of ethyl diazoacetate (10.41 g, 0.100 mol) in anhydrous diethyl ether (30 ml) is slowly added (Sage Model 352 syringe pump) to a stirred solution of the catalyst (≤ 1.0 mmol) and the alkene (0.100 mol) in ether (50 ml). Reactions are generally performed at 25 °C in air (reactions performed under nitrogen did not noticeably result in improved yields). The needle of the addition syringe is placed just below the surface of the reaction solution, and nitrogen evolution commences with each fractional addition of diazo compound. After addition of the first 15 ml of ethyl diazoacetate solution, the rate of addition is slowed to ~ 1/2 of the initial rate. When addition is complete, the mixture is filtered through active, neutral aluminum oxide. The aluminum oxide is washed with ether (200 ml), and the ether in the combined filtrate is evaporated to a residual oil which is distilled under reduced pressure (sample purity ≥97%).

The only detectable impurities (≤3%) in distilled **2a–f** from rhodium-catalyzed reactions were the carbenic dimers diethyl fumarate and diethyl maleate; the isolated product mixtures from $CuCl \cdot P(O—C_3H_7\text{-}i)_3$-catalyzed reactions contained 5–15% of the fumarate and maleate esters. Analytically pure samples were obtained by a subsequent distillation or by G.L.C. collection. Isomer separations were achieved by G.L.C. on Carbowax 20M columns. Compound **2e** was obtained at b.p. 104–109 °C/18 torr (Ref.[11], b.p. 109–110 °C/18 torr). Compound **2f** was obtained at b.p. 52–53 °C/0.3 torr (Ref.[12], b.p. 60 °C/0.5 torr).

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[1] A. J. Anciaux et al., *J. Org. Chem.* **45**, 695 (1980).

[2] A. J. Hubert, A. F. Noels, A. J. Anciaux, P. Teyssié, *Synthesis* **1976**, 600.

[3] M. P. Doyle, W. H. Tamblyn, *Abstracts of Papers, 180th National Meeting of the American Chem. Soc., Las Vegas, Nevada, Aug. 25–29, 1980;* ORGN-269.
M. P. Doyle, W. H. Tamblyn, W. E. Buhro, R. L. Dorow, *Tetrahedron Lett.* **22**, 1783 (1981).

[4] S. D. Burke, P. A. Grieco, *Org. React.* **26**, 361 (1979).

[5] E. Wenkert, *Acc. Chem. Res.* **13**, 27 (1980).

[6] M. E. Alonso, M. Gomez, *Tetrahedron Lett.* **1979**, 2763.

[7] D. S. Wulfman, G. Linstrumelle, C. F. Cooper, in: *The Chemistry of Diazonium and Diazo Groups*, S. Patai, Ed., John Wiley & Sons, New York, 1978, Chapter 18.

[8] W. R. Moser, *J. Am. Chem. Soc.* **91**, 1135 (1969).

[9] R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **95**, 3300 (1973).

[10] V. Dave, E. W. Warnhoff, *Org. React.* **18**, 217 (1970).

[11] F. Ebel, R. Brunner, P. Mangelli, *Helv. Chim. Acta* **12**, 19 (1929).

[12] T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1975**, 1707.

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