Mechanistic Studies of the Rhodium-catalysed Cyclization of α,ω-Alkynoic Acids to Alkylidene Lactones. Crystal Structures of Two Iridium Model Catalytic Intermediates

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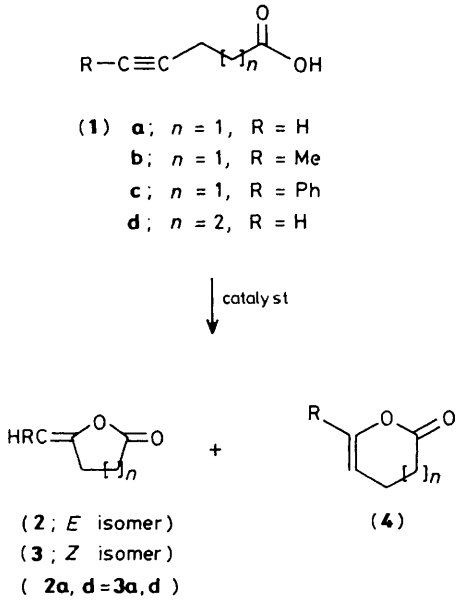
A mechanism for the Rh-catalysed cyclization of alkynoic acids to alkylidene lactones which accounts for the formation of *Z*-isomers only, is presented with the structures of Ir *cis*-hydrido-carboxylate and *cis*-hydrido-σ-vinyl model intermediates.

The Lewis acid-catalysed cyclization of alkynoic acids represents a useful method for the preparation of alkylidene lactones. The traditional catalysts such as Hg^{2+} (ref. 1,2) and Ag^{+} (ref. 3) compounds however, show poor regio- and stereoselectivity for substituted alkynoic acids (R ≠ H). Both *E*-and *Z*-isomers (**2**), (**3**) and larger ring lactones with internal double bonds (**4**) are produced (see Scheme 1). We have recently developed a series of Group VIII transition metal catalysts for the cyclization of alkynoic acids to the corresponding exocyclic enol lactones.[4,5] The most versatile of these catalysts, $[(Cy_2PCH_2CH_2PCy_2)RhCl]_2$ (**5**) (Cy = cyclohexyl) is active in CH_2Cl_2 at room temperature and offers very high regio- and stereoselectivities; only *Z*-isomers (**3**) are observed [no (**2**) is formed] and five membered ring products are strongly favoured (for $n = 1$).

It is critical that any proposed mechanism explain the exclusive formation of *Z* products (**3**) arising from rigorously *trans*-addition of the carboxylate OH to –C≡C–. Small amounts of the larger ring products (**4**) also derive from *trans*-addition. Utilizing very basic Ir^{I} complexes which show little or no catalytic activity at room temperature in tetrahydrofuran, we have isolated several complexes which serve as models for intermediates on the proposed catalytic pathway.



(**1**) **a**; $n = 1$, R = H
b; $n = 1$, R = Me
c; $n = 1$, R = Ph
d; $n = 2$, R = H

(**2**; *E* isomer)
(**3**; *Z* isomer)
(**2a, d** = **3a, d**)

(**4**)

Scheme 1

Proton n.m.r. spectra indicate the first step to be the protonation of the basic metal complex forming M^{III}-H. This species can exist either as the mono-($\mathbf{A_1}$) or bidentate carboxylate hydride ($\mathbf{A_2}$) or, perhaps as the ion pair $[M–H]^+[RC{\equiv}C(CH_2)_nCO_2]^-$ ($\mathbf{A^{\pm}}$) (Scheme 2). The stoicheiometric reaction of $[(PEt_3)_3IrCl]$[6] with $CH_3C{\equiv}C(CH_2)_2CO_2H$ (**1b**) yields the *cis* monodentate carboxylate hydride complex (**6a**);‡ the molecular structure§ is shown in Figure 1. A similar complex (**6b**) is formed in the analogous reaction using (**1c**). The M^{III}–H complexes should have Lewis acid properties, particularly in the ionic form (*cf.* $\mathbf{A^{\pm}}$), and co-ordination of C≡C to the M-H^+ centre (*cf.* **B**) should enhance nucleophilic attack of carboxylate on the

‡ *Spectroscopic data* for (**6a**): i.r. [tetrahydrofuran (thf)] ν_{Ir-H} 2224m, ν_{CO} 1636s(CO) cm^{-1}; $^{31}P\{^1H\}$ n.m.r. (121.69 MHz, THF-d_8). –8.88 (d, $^2J_{P-P}$ 19 Hz), –20.04 p.p.m., (t, $^2J_{P-P}$ 19 Hz); $^{13}C\{^1H\}$ n.m.r. (75.59 MHz, THF-d_8): δ174.78 (d, $^3J_{P-C}$ 2.3 Hz, $-CO_2-$), 80.51, 74.60 (s, –C≡C–), 37.34 (d, J_{P-C} 5.5 Hz, $-CH_2-$), 20.53 (dt, J_{P-C} 36.0, $^3J_{P-C}$ 2.4 Hz, P–CH_2Me), 17.25 (vt, J_{P-C} 16.1 Hz, 2PCH_2Me), 16.93 (s, $-CH_2-$), 8.77 (s, 2PCH_2CH_3), 8.64 (d, $^2J_{P-C}$ 4.0 Hz, PCH_2CH_3); ^1H n.m.r. (360 MHz, THF-d_8), δ2.29 (s, 4H, $-CH_2-CH_2-$), 2.01–1.68 (m, 18H, 3PCH_2Me), 1.66 (s, 3H, C≡C–CH_3), 1.15 (m, 18H, 2PCH_2CH_3), 1.06 (m, 9H, PCH_2CH_3), –20.00 (dt, $^2J_{P-H}$ 19 and 12 Hz, 1H, Ir–H).

For (**7**): i.r. (nujol) ν_{Ir-H} 2193m, ν_{CO}1764s, 1729w(sh) (trace isomer), ($\nu_{C=C}$)1646m cm^{-1}; $^{31}P\{^1H\}$ n.m.r 121.69 MHz, CD_2Cl_2: –42.19 (d, $^2J_{P-P}$ 21 Hz), –50.33 p.p.m (t, $^2J_{P-P}$ 21 Hz); $^{13}C\{^1H\}$ n.m.r, (75.59 MHz, CD_2Cl_2: δ 177.13 (s, $-CO_2-$), 141.82 (overlapped dt, $^2J_{P-C}$ 10 and 5 Hz, $=C_\beta$–O), 109.84 (dt, $^2J_{P-C}$ 87, $^2J_{P-C}$ 14 Hz, Ir–Cα), 30.80 (s, $-CH_2-$), 29.93 (s, –Me), 22.37 (s, $-CH_2-$), 20.38 (dt, $^2J_{P-C}$ 30, $^3J_{P-C}$ 1 Hz, PMe_3), 17.94 (td, $^2J_{P-C}$ 19, $^3J_{P-C}$ 2 Hz, 2PMe_3); ^1H n.m.r, (360 MHz, CD_2Cl_2), δ 2.64 and 2.50 (m, $-CH_2-CH_2-$), 1.99 (m, –Me), 1.57 (d, $^2J_{P-H}$ 8 Hz, PMe_3), 1.50 (vt, $^2J_{P-H}$ 3 Hz, 2PMe_3), –23.53 (dt, $^2J_{P-H}$ 15 and 16 Hz, Ir–H).

§ *Crystal data* for (**6a**): $C_{24}H_{53}ClIO_2P_3$, orthorhombic, $Pca2_1$, (No. 29), a = 18.076(3), b = 10.774(2), c = 15.703(2)Å, T –75 °C, U = 3058.2 Å^3, Z = 4, μ(Mo) 46.09 cm^{-1}; Enraf–Nonius CAD4 diffractometer, Mo-K_α radiation, 3954 data collected using ω-scan method, 4.4°≤2θ≤55.0°, corrected for absorption (DIFABS), 2901 unique reflections with $I \geq 3.0\ \sigma(I)$ used in solution and refinement; solution by automated Patterson analysis, refinement by full-matrix least-squares, weights $\alpha[\sigma^2(I) + 0.0009I^2]^{-1/2}$, 281 parameters, all non-H atoms anisotropic, H atoms fixed [except for Ir–H(1) located on diff. map and refined]; 3 ethyl groups show disorder; R = 0.027, R_w = 0.029, largest residual density 0.76 eÅ^{-3} near Ir.

For (**7**)·CH_2Cl_2: $C_{16}H_{37}Cl_3IrO_2P_3$, monoclinic-b, $P2_1/c$ (No. 14), a = 9.248(1), b = 14.137(2), c = 18.262(2)Å, β = 91.27(1)°, T –100 °C, U = 2386 Å^3, Z = 4, μ(Mo) 60.02 cm^{-1}; Nicolet R3, Mo-K_α radiation, 5905 data collected using ω-scan method, 4.4° ≤ 2θ ≤ 55.0°, corrected for absorption (DIFABS), 4310 unique reflections with $I \geq 3.0\ \sigma(I)$ used in solution and refinement; solution by direct methods (MULTAN), refinement by full-matrix least-squares, weights $\alpha[\sigma^2(I) + 0.0009I^2]^{-1/2}$, 221 parameters, all non-H atoms anisotropic, H atoms fixed [except for Ir–H(1Ir) located on diff. map and refined]; the CH_2Cl_2 of crystallization was best modelled as being four fold disordered about the centre of symmetry (0.5, 0.5, 0.5); R = 0.024, R_w = 0.029. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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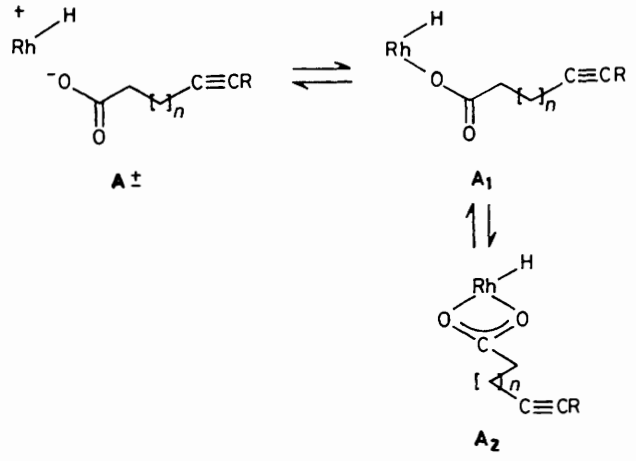
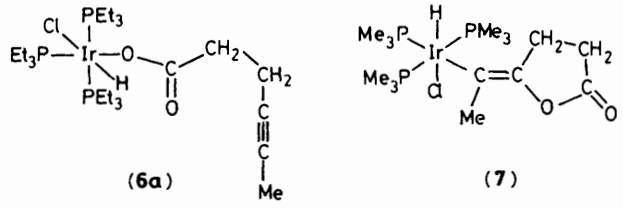
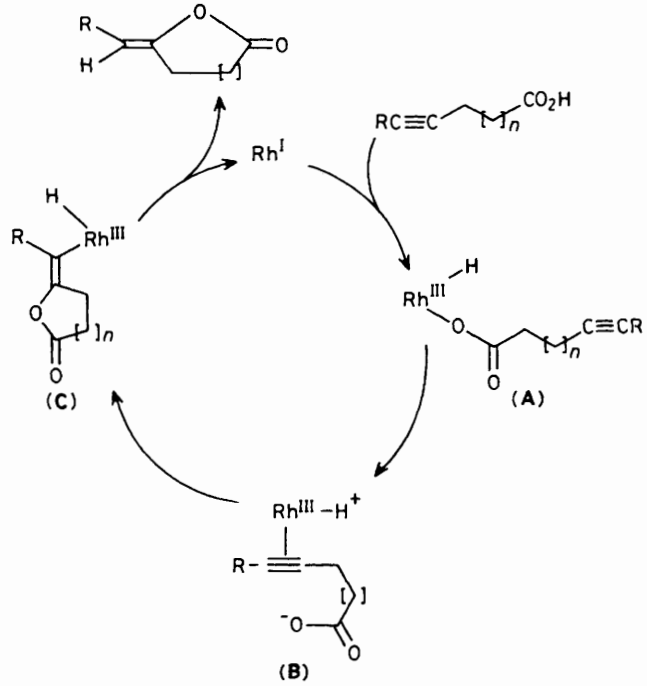


Scheme 2





Scheme 3

alkyne yielding *cis* alkenyl hydride species (*cf.* **C**) *i.e.* alkenyl and hydride ligands in mutually *cis* positions. Nucleophilic attack on co-ordinated alkynes is known[7] to yield *trans*-alkenyl species as primary reaction products (*i.e.* the nucleophile and metal are *trans* with respect to the C=C double bond). We have isolated such a species (**7**)‡ from the reaction of $[(PMe_3)_3(\eta^2\text{-}C_8H_{14})IrCl]$[8] with (**1b**); the molecular structure§ is shown in Figure 2. Complex (**7**) is also related to

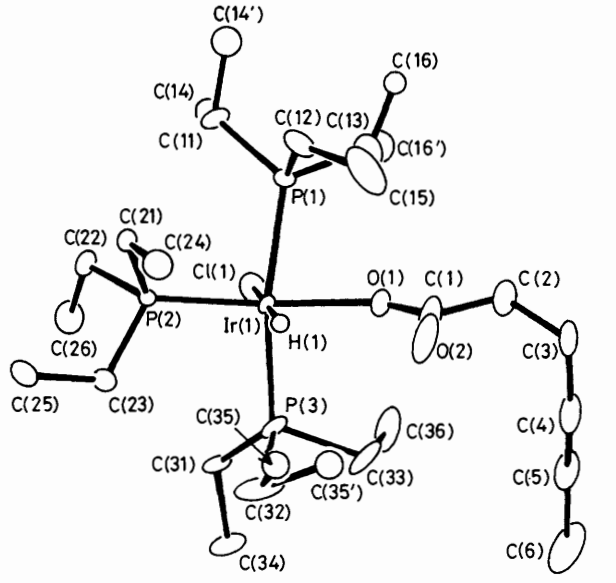


Figure 1. ORTEP drawing of a molecule of (**6a**). Selected bond distances (Å) and angles (degrees): Ir(1)–H(1) 1.58(9), Ir(1)–P(1) 2.354(2), Ir(1)–P(2) 2.256(2), Ir(1)–P(3) 2.350(2), Ir(1)–C(11) 2.497(2), O(1)–C(1) 1.270(11), O(2)–C(1) 1.223(14); C(11)–Ir(1)–H(1) 173(3); C(11)–Ir(1)–O(1) 86.0(2), P(1)–Ir(1)–O(1) 82.4(2), O(1)–Ir(1)–H(1) 91(3), Ir(1)–O(1)–C(1) 127.3(6).

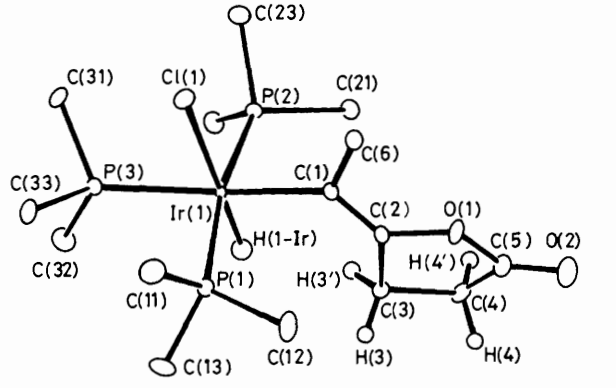


Figure 2. ORTEP drawing of a molecule of (**7**). Selected bond distances (Å): Ir(1)–H(1) 1.64(5), Ir(1)–C(11) 2.510(1), Ir(1)–P(1) 2.315(1), Ir(1)–P(2) 2.315(1), Ir(1)–P(3) 2.338(1), Ir(1)–C(1) 2.113(4), C(1)–C(6) 1.511(6), C(1)–C(2) 1.328(6); O(1)–C(2) 1.458(5), C(2)–C(3) 1.500(7), C(3)–C(4) 1.537(6); C(4)–C(5) 1.493(8).

the Pd–vinyl intermediate proposed in ref. 5. Reductive elimination of C–H from a five-co-ordinate[9] analogue of (**7**) should proceed with retention of configuration at the α-carbon giving the alkylidene lactone resulting from overall *trans*-addition of OH to C≡C, as observed in our catalytic systems.[4] Thus, both regio- and stereochemistry of the product lactones are determined by the nucleophilic attack of carboxylate on the alkyne when bound to a Lewis acidic M^{III}–H^+ centre.

We believe that Scheme 3 illustrates the general features of the transition metal-catalysed pathway. The proposed mechanism accounts for the observed *trans*-stereochemistry of the addition of the carboxylate OH group to C≡C. In contrast, mechanisms based on migratory insertion of C≡C into either Rh–H[10] or Rh–O–C(O)– would be expected to yield *cis*-

addition products as was found[11] for the insertion of C≡C into Pd–C(O)–O– in the related Pd catalysed carbonylation of ω-alkynyl alcohols to α-alkylidene lactones. Preliminary kinetic evidence, in conjunction with other observations[10] of the reaction of Lewis acids with monodentate carboxylates, suggests that a second equivalent of acid assists the transformation **A**→**B**. Whereas reductive elimination of the alkenyl C–H bond (**C** → product) is no doubt a concerted reaction, the initial 'oxidative addition' of the carboxylic acid OH group need not be concerted (*vide supra*). Recent evidence [9] indicates that reductive elimination from d^6ML_6 complexes is preceded by ligand dissociation. The lack of facile phosphine dissociation from the tris-phosphine iridium complexes made possible the isolation of the model catalytic intermediates (**6a**) and (**7**), whereas the absence of a third phosphine ligand in (**5**) allows for rapid reductive elimination of alkylidene lactones and excellent catalytic activity.

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References

1 R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.*, 1978, **43**, 560.

2 M. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 582; A. Jellal, J. Grimaldi, and M. Santelli, *Tetrahedron Lett.*, 1984, 3179.

3 J. Castaner and J. Pascual, *J. Chem. Soc.*, 1958, 3962; P. G. Williard, J. T. Jong, and J. P. Porowoll, *J. Org. Chem.*, 1984, **49**, 736.

4 T. B. Marder, D. M. T. Chan, W. C. Fultz, and D. Milstein, 12th International Conference on Organometallic Chemistry (ICOMC), Vienna, Austria, September 1985, Abstract no. 163; D. M. T. Chan, T. B. Marder, N. J. Taylor, and D. Milstein, *J. Am. Chem. Soc.*, 1987, **109**, 6385.

5 While this work was in progress, a $Pd^{(II)}$–Et_3N catalyst system was described: C. Lambert, K. Utimoto, and H. Nozaki, *Tetrahedron Lett.*, 1984, 5323; N. Yanagihara, C. Lambert, K. Iritani, K. Utimoto, and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 2753. No mechanistic studies were reported.

6 T. Herskovitz, unpublished results.

7 See, for example: D. L. Reger and P. J. McElliott, *J. Am. Chem. Soc.*, 1980, **102**, 5923; D. L. Reger, K. A. Belmore, E. Mintz, and P. J. McElliott, *Organometallics*, 1984, **3**, 134; D. L. Reger and K. A. Belmore, *ibid.*, 1985, **4**, 305.

8 J. C. Calabrese, T. Herskovitz, T. B. Marder, D. Milstein, and T. Tulip, in preparation.

9 D. Milstein, *Acc. Chem. Res.*, 1984, **17**, 221; *J. Am. Chem. Soc.*, 1982, **104**, 5227; *Organometallics*, 1982, **1**, 1549; J. W. Suggs, M. J. Wovkulich, and S. D. Cox, *ibid.*, 1985, **4**, 1101; D. C. Wink and P. C. Ford, *J. Am. Chem. Soc.*, 1985, **107**, 5566; M. Basato, F. Morandini, B. Longato, and O. S. Bresadola, *Inorg. Chem.*, 1984 **23**, 649.

10 T. B. Marder, D. M. T. Chan, W. C. Fultz, and D. Milstein, *Organometallics*, in the press.

11 T. F. Murray, E. G. Samsel, V. Varma, and J. R. Norton, *J. Am. Chem. Soc.*, 1981, **103**, 7520; E. G. Samsel, and J. R. Norton, *ibid.*, 1984, **106**, 5505.

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