Anomalous Products from Intramolecular C−H Insertion by a Rhodium Carbenoid. Possible Involvement of a Zwitterionic Mechanism

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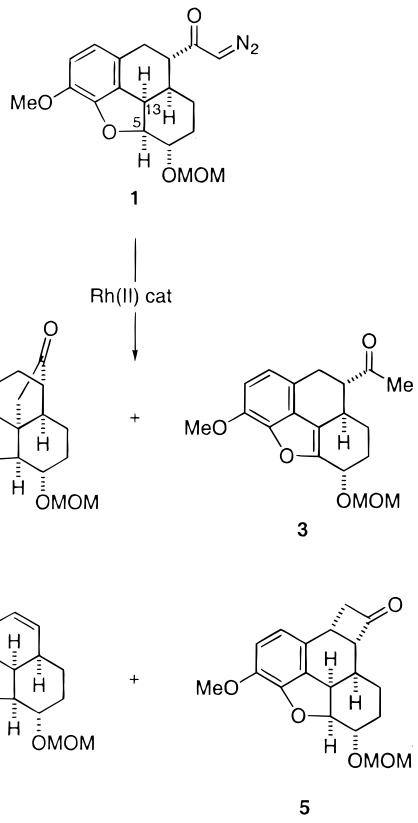
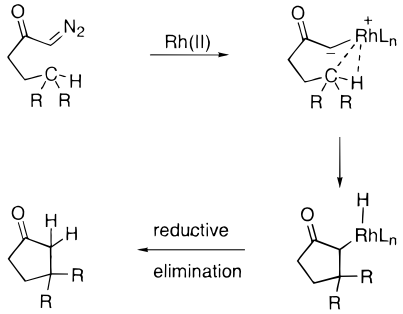
Metal-catalyzed decomposition of α-diazoketones to yield metal carbenoids is a technique for generating a reactive species that can undergo remarkably selective intramolecular C−H insertion.[1] The reaction has been widely applied in ring construction, particularly to the synthesis of cyclopentanones.[2] A mechanism has been put forward by Taber for carbenoid C−H insertion mediated by rhodium(II) in which the new C−C bond is formed directly via a four-centered transition state (Scheme 1).[3] This mechanism is also favored by Doyle who has buttressed the argument with calculations using an MM2 force field.[4] A central feature of the mechanism shown in Scheme 1 is that C−C bond formation is accompanied by simultaneous transfer of hydride from carbon to rhodium and is concluded by reductive elimination at the metal atom. Quite frequently, it is found that C−H insertion reactions of rhodium carbenoids give rise to anomalous products which cannot be easily explained by this "concerted" mechanism. Thus, Clark in a study of rhodium-catalyzed decomposition of α-diazo-α′-alkoxy ketones, observed products that are more readily accommodated by a zwitterionic intermediate.[5] In this scenario, hydride transfer takes place from carbon to rhodium, leading to a discrete intermediate A that precedes C−C bond formation (Scheme 2). This pathway would be favored in those cases where a stable carbocation is generated after hydride transfer.

A key reaction in our recently published synthesis of (+)-codeine involved rhodium(II)-catalyzed decomposition of diazoketone **1**.[6] In addition to the desired pentacyclic ketone **2**, three products were obtained: methyl ketone **3** containing a benzofuran nucleus, olefin **4** resulting from fragmentation, and the fused cyclobutanone **5**. The ratio of **2**, **3**, **4**, and **5** exhibited a marked dependence upon the rhodium catalyst employed in the decomposition of **1** (Table 1). The highest yield of **2** was obtained with dirhodium(II) tetrakis(acetamide) ($Rh_2(acam)_4$, **6**), a catalyst that Doyle has shown can lead to high selectivity for carbene insertion into electron-rich methine C−H bonds.[7] When dirhodium(II) tetra(trifluoroacetate) ($Rh_2(TFA)_4$, **7**)[8] was employed as catalyst, a significant quantity of **4** was obtained, and both **3** and **4** were produced in addition to **2** when $Rh_2(OAc)_4$ (**8**) was used. Benzofuran **3** was not formed with the sterically demanding dirhodium(II) tetra(triphenylacetate) ($Rh_2(TPA)_4$, **9**)[9] as catalyst.



Scheme 1. "Concerted" Mechanism of Rhodium(II) Carbenoid C−H Insertion



Scheme 2. Zwitterionic Mechanism of Rhodium(II) Carbenoid C−H Insertion

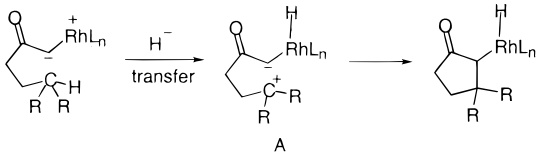


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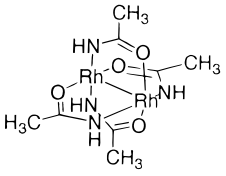
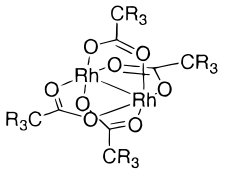
Table 1. Rhodium(II)-Catalyzed Decomposition of Diazoketone 1

	yield of product (%)			
catalyst	**2**	**3**	**4**	**5**
$Rh_2(acam)_4$ (**6**)	65	4	4	0
$Rh_2(TFA)_4$ (**7**)	<2	28	40	0
$Rh_2(OAc)_4$ (**8**)	51	17	15	5
$Rh_2(TPA)_4$ (**9**)	38	0	19	11

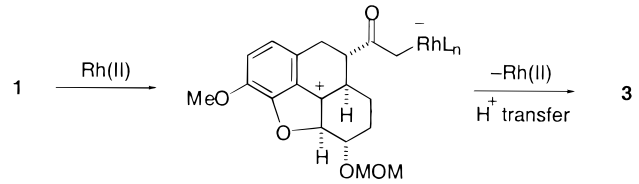


6, $Rh_2(acam)_4$



7, R = F: $Rh_2(TFA)_4$
8, R = H: $Rh_2(OAc)_4$
9, R = Ph: $Rh_2(TPA)_4$

Scheme 3



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While the results in Table 1 reflect the divergent electronic and steric properties of the rhodium catalysts employed, it is difficult to reconcile all of the products from **1** with the concerted mechanism shown in Scheme 1. Formation of the benzofuran **3** in particular seems anomalous, since it is clear that a hydrogen must migrate from C5 to the carbene to yield this methyl ketone. However, **3** can be accommodated by a mechanism in which zwitterion **10** is formed by hydride transfer from C13 to the carbenoid carbon followed by loss of a proton from C5 (Scheme 3). To investigate this possibility, rhodium(II)-catalyzed decomposition of diazoketone **11** was examined. It was expected that the presence of the C6 keto group in **11** should favor proton elimination so that an increased proportion of benzofuran analogous to **3** should result from this reaction.

Treatment of diazoketone **11** with $Rh_2(OAc)_4$ afforded diketone **12** as the major product, with olefin **13** and cyclobutanone **14** as minor products. *Surprisingly, no benzofuran analogous to **3** was seen in the reaction mixture.* Thus, the presence of a keto function at C6 of **11** apparently suppresses removal of the C5 hydrogen. While this result tends to cast doubt on the intermediacy of zwitterion **10**, other factors such as the subtle conformational change introduced in the conversion of C6 from sp^3 to sp^2 hybridization may be responsible for the absence of benzofuran.[10] A more definitive explanation of the decomposition products from **1** and **11** must await further study; however, it is noteworthy that cyclobutanones **5** and **14** could also be derived from a zwitterionic intermediate, in this case one whose cationic center is stabilized by benzylic resonance at C10.

In conclusion, we find that a concerted mechanism analogous to that presented in Scheme 1 cannot easily rationalize the formation of *all* products from rhodium-catalyzed decomposition of α-diazoketones **1** and **11**. The possibility of a stepwise process involving zwitterionic species is entertained as a competing pathway and may predominate where hydride transfer is favored by the formation of a particularly stable carbocation.

(10) A C6 keto function would provide little conjugative stabilization to this structure.

Experimental Section

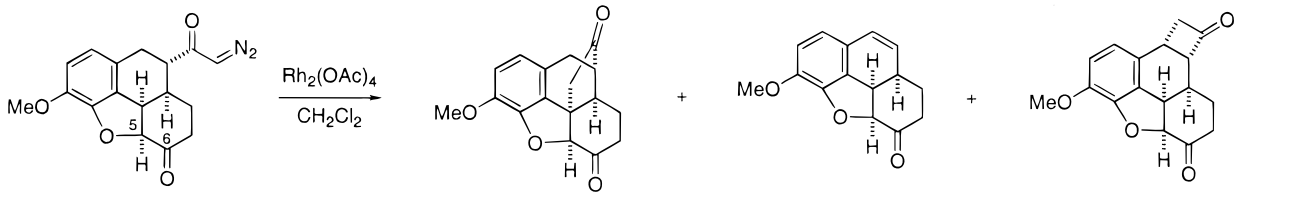
Decomposition of Diazoketone 1. To a solution of **1** (47 mg, 0.13 mmol) in CH_2Cl_2 (50 mL) under Ar was added $Rh_2(OAc)_4$ (1 mg). The mixture was stirred for 1 h at ambient temperature and was concentrated under reduced pressure. The residue was chromatographed on silica (10 g, EtOAc−hexane, 1:2) to afford 22 mg (51%) of **2** as a colorless oil: $[\alpha]^{23}_D$ +12.0 (*c* 0.44, $CHCl_3$); IR (neat) 2941, 1755, 1509, 1447, 1283, 1262, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21−1.31 (m, 1H), 1.34−1.57 (m, 1H), 1.73−1.83 (m, 1H), 1.86−1.95 (m, 1H), 2.47−2.55 (m, 1H), 2.49 (s, 2H), 2.72−2.76 (m, 1H), 2.85−2.93 (m, 2H), 3.40 (s, 3H), 3.57−3.64 (m, 1H), 3.87 (s, 3H), 4.72 (d, J = 7 Hz, 1H), 4.75 (d, J = 6 Hz, 1H), 4.79 (d, J = 7 Hz, 1H), 6.58 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 27.5, 28.4, 42.2, 49.1, 50.1, 53.9, 55.5, 57.0, 77.9, 90.9, 95.9, 115.3, 120.7, 122.4, 133.1, 144.0, 144.2, 217.9; MS *m*/*z* 330 (M^+), 285, 257, 243, 199, 113, 83, 69, 55, 49, 45; HRMS *m*/*z* 330.1469 (calcd for $C_{19}H_{22}O_5$, 330.1467).

Also obtained was 7.5 mg (17%) of **3**: IR (neat) 2930, 1719, 1513, 1279, 1259, 1162, 1103, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17−1.30 (m, 1H), 2.00−2.16 (m, 1H), 2.17−2.22 (m, 1H), 2.28 (s, 3H), 2.42−2.54 (m, 2H), 2.98−3.01 (m, 2H), 3.20−3.50 (m, 1H), 3.50 (s, 3H), 4.05 (s, 3H), 4.86 (d, J = 7 Hz, 1H), 4.39−4.84 (m, 1H), 5.07 (d, J = 7 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 6.91 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 30.3, 30.9, 32.1, 33.2, 55.8, 56.8, 57.1, 70.3, 96.2, 102.6, 120.9, 121.2, 122.4, 128.5, 142.7, 144.2, 151.3, 210.2; MS *m*/*z* 330 (M^+), 288, 243, 225, 199, 187, 183, 115; HRMS *m*/*z* 330.1468 (calcd for $C_{19}H_{22}O_5$, 330.1467).

In addition, 5.6 mg (15%) of **4** was obtained: IR (neat) 2931, 1723, 1639, 1505, 1460, 1440, 1280, 1157, 1107, 1037, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00−1.28 (m, 2H), 1.70−1.86 (m, 2H), 2.52−2.63 (m, 1H), 3.41 (s, 3H), 3.50−3.59 (m, 1H), 3.74 (t, J = 9 Hz, 1H), 3.90 (s, 3H), 4.74 (d, J = 7 Hz, 1H), 4.83 (d, J = 7 Hz, 1H), 4.91 (dd, J = 8, 9 Hz, 1H), 5.68 (dd, J = 6, 10, 1H), 6.42 (d, J = 10 Hz, 1H), 6.64 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.3, 33.9, 39.6, 55.4, 56.9, 91.7, 95.7, 113.6, 117.5, 124.1, 124.2, 125.7, 130.5, 145.0, 145.2; MS *m*/*z* 288 (M^+), 258, 243, 227, 211, 199, 187, 171, 149, 128, 115; HRMS *m*/*z* 288.1363 (calcd for $C_{17}H_{20}O_4$, 288.1362).

The final fraction yielded 1.9 mg (5%) of **5**: IR (neat) 2936, 1784, 1511, 1444, 1282, 1158, 1100, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95−1.11 (m, 1H), 1.21−1.35 (m, 1H), 1.82−1.90 (m, 1H), 2.60−2.68 (m, 2H), 3.34−3.42 (m, 1H), 3.39 (s, 3H), 3.51−3.69 (m, 4H), 3.74−3.79 (m, 1H), 3.84 (s, 3H), 4.50 (d, J = 7 Hz, 1H), 4.77 (d, J = 7 Hz, 1H), 4.80 (dd, J = 7, 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 6.78 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.1, 28.3, 31.2, 39.3, 53.2, 55.4, 57.1, 65.1, 76.5, 90.4, 95.6, 115.0, 120.5, 126.3, 127.9, 144.3, 145.9, 210.6; MS (CI) *m*/*z* 330 (M^+ + 1), 288, 258, 243, 225, 211, 199, 187, 128, 115, 101, 86, 77, 69; HRMS (CI) *m*/*z* 330.1468 (calcd for $C_{19}H_{22}O_5$, 330.1467).

Decomposition of Diazoketone 11. To a stirred solution of **11** (0.19 g, 0.605 mmol) in dry CH_2Cl_2 (200 mL) under Ar was added $Rh_2(OAc)_4$ (2 mg), and the mixture was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica (30 g, EtOAc−hexane, 1:2) to afford 91 mg (53%) of **12** as a colorless oil: IR (neat) 2941, 2839, 1740, 1721, 1503, 1442, 1283, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48−1.63 (m, 1H), 2.03−2.11 (m, 1H), 2.39−2.50 (m, 1H), 2.55−2.64 (m, 2H), 2.72 (d, J = 17 Hz, 1H), 2.84−2.92 (m, 4H), 3.90 (s, 3H), 4.92 (s, 1H), 6.62 (d, J = 8 Hz, 1H), 6.72 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 27.5, 40.7, 42.6, 49.9, 52.0, 53.3, 56.9, 88.2, 115.5, 121.7, 121.9, 129.9, 143.5, 145.1, 207.3, 216.6; MS *m*/*z* 284 (M^+), 256, 242, 227, 213, 199, 185, 181, 128, 121, 115; HRMS *m*/*z* 284.1047 (calcd for $C_{17}H_{16}O_4$, 284.1048).



11 **12** (54%) **13** (17%) **14** (5%)

Also obtained was 25 mg (17%) of **13**: IR (neat) 3032, 2939, 1728, 1508, 1450, 1435, 1279, 1098, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34−1.49 (m, 1H), 1.98−2.07 (m, 1H), 2.33−2.41 (m, 2H), 2.91−3.02 (m, 1H), 3.92 (s, 3H), 4.19 (t, J = 9 Hz, 1H), 5.20 (d, J = 9 Hz, 1H), 5.88 (dd, J = 6, 10 Hz, 1H), 6.46 (d, J = 10 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 33.8, 38.6, 43.4, 56.7, 87.8, 113.8, 118.3, 122.9, 123.7, 125.1, 129.1, 144.7, 146.1, 208.0; MS m/z 242 (M^+), 211, 201, 199, 184, 171, 161, 143, 115, 86, 84; HRMS m/z 242.0944 (calcd for $C_{15}H_{14}O_3$, 242.0943).

In addition, 8.6 mg (5%) of **14** was obtained: IR (neat) 2931, 1776, 1729, 1503, 1447, 1283, 1103 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30−1.40 (m, 1H), 1.80−1.87 (m, 1H), 2.37−2.42 (m, 2H), 2.65−2.71 (m, 1H), 3.02−3.10 (m, 1H), 3.54−3.70 (m, 2H), 3.81−3.87 (m, 1H), 3.93 (s, 3H), 3.98−4.03 (m, 1H), 5.07 (d, J = 8 Hz, 1H), 6.66−6.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 27.1, 31.4, 39.6, 42.5, 53.3, 57.0, 64.5, 86.5, 115.2, 120.6, 121.3, 123.3, 127.5, 143.7, 207.4, 209.9; MS m/z 284 (M^+), 242, 199, 185, 174, 88, 86, 84; HRMS m/z 284.1047 (calcd for $C_{17}H_{16}O_4$, 284.1049).

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