Spirolactones from Dirhodium(II)-Catalyzed Diazo Decomposition with Regioselective Carbon–Hydrogen Insertion

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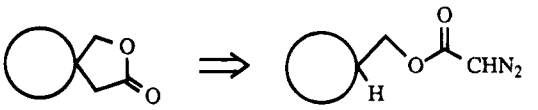
Dirhodium(II) caprolactamate, $Rh_2(cap)_4$, catalyzes diazo decomposition of cycloalkylmethyl diazoacetates which form spirolactones in moderate to high yield by insertion into a tertiary carbon–hydrogen bond. Similar results are obtained with diazoacetates derived from tetrahydropyran-2-methanol and tetrahydrofurfuryl alcohol but not from cyclopropylmethanol. With tetrahydrofuran-3-ylmethyl diazoacetate, $Rh_2(cap)_4$ catalysis promotes δ-lactone formation via insertion into the oxygen-activated secondary C–H bond instead of γ-lactone formation by carbene insertion into the unactivated tertiary C–H bond. However, when both 1,5- and 1,6-positions are activated for insertion by adjacent oxygen atoms, as in (2,2-dimethyl-1,3-dioxolan-4-yl)methyl diazoacetate, five-membered ring formation occurs exclusively in $Rh_2(cap)_4$-catalyzed reactions, whereas use of dirhodium(II) acetate leads to both insertion products.

Dirhodium(II) catalysts facilitate diazo decomposition of diazocarbonyl compounds and promote insertion into remote C–H bonds.[1–5] Extensive investigations by Taber,[6–8] Adams,[9–11] ourselves,[12–14] and others[15–17] have shown that, in the absence of overriding influences, five-membered ring formation is virtually the exclusive outcome of C–H insertion reactions, that oxygen and nitrogen can activate an adjacent C–H bond for insertion, and that the order of reactivity of carbon–hydrogen bonds in competitive processes is tertiary > secondary > primary. Exceptions, including those where insertion into primary C–H bonds[13] occurs preferentially as compared to insertion into secondary C–H bonds[13] or where six-membered or four-membered ring products are formed in competition with or instead of five-membered ring compounds,[17–22] have been observed in conformationally restricted systems or when activation of a C–H bond by an adjacent oxygen or nitrogen overrides the "normal" course of insertion. However, exceptions such as these rarely occur with diazo compounds in which hydrogen and a carbonyl group are bound to the diazo carbon (diazoacetate esters, diazoacetamides, and diazoketones). As a consequence, a general predictability appears to exist regarding the outcome of most targeted C–H insertion reactions.

We have undertaken an investigation of dirhodium(II)-catalyzed C–H insertion reactions of diazoacetate esters directed to the synthesis of spirolactones (**1**) for which few alternative methodologies are available.[23]



1 **2**

These transformations were anticipated to occur with high selectivity because of the availability of a reactive tertiary C–H bond positioned for γ-lactone formation and the expected absence of conformational restrictions on insertion into a tertiary C–H bond. We report the generality of this synthetic transformation, notable exceptions, and the selection of dirhodium(II) catalysts most suitable to its operation.

Results and Discussion

In the presence of a catalytic amount of dirhodium(II) caprolactamate, $Rh_2(cap)_4$ (**3**), in refluxing dichloromethane, cyclohexylmethyl diazoacetate formed spirolactone **5** as virtually the sole product from carbon–hydrogen insertion (eq 1). Although the δ-lactone product from C–H insertion into a secondary carbon–hydrogen

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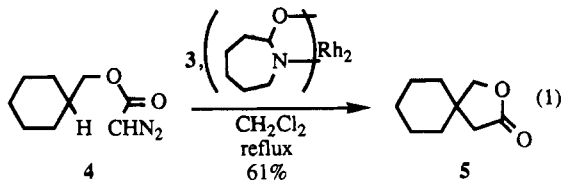
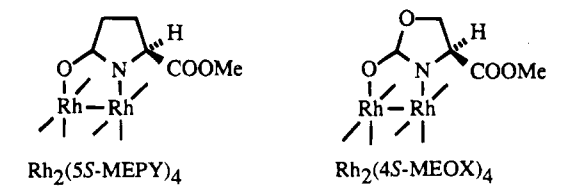
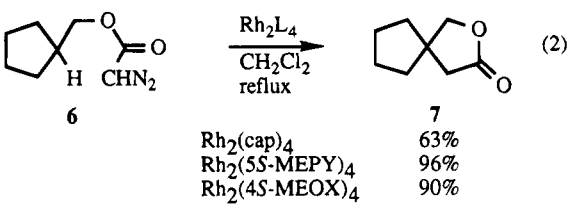


4 5

bond could also be inferred, the molar ratio of **5** to this minor product was 98:2. Carbene dimer formation and intermolecular water insertion were the major competing processes, but even these were minimized when chiral dirhodium(II) carboxamide catalysts, specifically dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate], Rh_2(5*S*-MEPY)$_4$,[24] and dirhodium(II) tetrakis[methyl 1-oxo-2-oxazolidine-4(*S*)-carboxylate], Rh_2(4*S*-MEOX)$_4$,[25] replaced Rh_2(cap)$_4$ (86% and 81% isolated yield of **5**, respectively). Furthermore, with either Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$, the reaction mixture did not contain even a trace amount of the δ-lactone product. Dirhodium(II) acetate, the catalyst most commonly employed for C–H insertion reactions, was relatively ineffective, affording **5** in only 25% isolated yield. The cyclopentyl analog of **4** gave similar results (eq 2), with even higher isolated yields of **7** from reactions catalyzed by Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$ than by Rh_2(cap)$_4$.



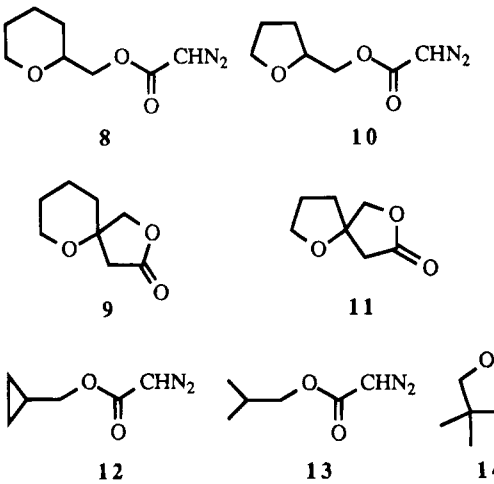


6 7

Rh_2(cap)$_4$	63%
Rh_2(5*S*-MEPY)$_4$	96%
Rh_2(4*S*-MEOX)$_4$	90%

In contrast, use of Rh_2(OAc)$_4$ resulted in multiple products, of which **7** was a minor constitutent. Trace amounts of a δ-lactone product (97:3) were observed from reactions catalyzed by Rh_2(cap)$_4$ but not by the chiral dirhodium(II) carboxamide catalysts.

In a similar fashion, Rh_2(cap)$_4$-catalyzed diazo decomposition of **8** and **10** formed spirolactones **9** and **11** in moderate to high isolated yields. Use of Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$ with **8** or **10** resulted in a diminished return of spirolactone products **9** and **11** and in the formation of several unidentified compounds. Enantioselectivities from the use of chiral dirhodium(II) carboxamides on **10** were low; for **11**, ee = 12% with Rh_2(5*S*-MEPY)$_4$ and ee = 24% with Rh_2(4*S*-MEOX)$_4$. Cyclopropylmethyl diazoacetate (**12**), an analog of **4** and **6**, did not undergo intramolecular C–H insertion; only carbene dimer formation occurred. However, with isobutyl diazoacetate (**13**), the ring-opened analog of **12**, formation of γ-lactone **14** occured cleanly with Rh_2(cap)$_4$ or Rh_2(4*S*-MEOX)$_4$ in comparable yields, suggesting that a cyclopropane C–H bond has a low reactivity for insertion.

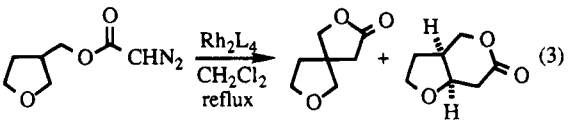


8 10

9 11

12 13 14

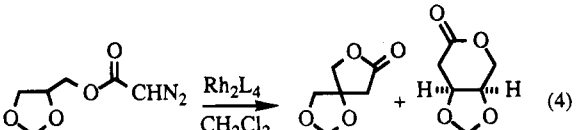
The design of **8** and **10** favors in three ways the exclusive formation of **9** and **11**: (1) five-membered ring formation, (2) activation for insertion of the C–H bond adjacent to oxygen, and (3) preferential insertion into a tertiary C–H bond. However, with tetrahydrofuran-3-ylmethyl diazoacetate (**15**), only two of these three conditions favor spirolactone formation and, as can be seen from the results in eq 3, oxygen activation of C–H insertion is the dominant factor in product selection. With



15

	16	17
Rh_2(cap)$_4$ (67% yield)	1	99
Rh_2(OAc)$_4$ (< 10% yield)	15	85

the diazoacetate derivative of solketal (**18**), five-membered ring spirolactone formation (eq 4) is the exclusive pathway for product formation with Rh_2(cap)$_4$ catalysis, even though oxygen activation of C–H bonds would have allowed both δ- and γ-lactone formation; however, both of these products are formed in reactions catalyzed by Rh_2(OAc)$_4$. The synthesis of enantiomerically pure (*S*)-



18

	19	20
Rh_2(cap)$_4$ (60% yield)	100	0
Rh_2(OAc)$_4$ (47% yield)	50	50

19 from (2,2-dimethyl-1,3-dioxolan-4(*S*)-ylmethyl diazoacetate, (*S*)-**18**, with Rh_2(cap)$_4$ catalysis (60% isolated yield) confirmed the synthetic potential of this conversion. These results are consistent with those of Adams and coworkers who initially reported with diazo ketones the dominant influence of ether activation resulting in the preferential formation of a six-membered ring and the "preference for five-membered ring when two ether oxygens were present to activate the C–H bonds leading to either the 5- or the 6-membered rings".[20] However,

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as suggested by comparative results with $Rh_2(cap)_4$ and $Rh_2(OAc)_4$, the catalyst ligand plays an important role in determining regioselection in C–H insertion reactions.[13,14,26] Increasing the stability of the intermediate metal carbene, which results from the replacement of carboxylate ligands by carboxamide ligands, increases its selectivity in C–H insertion.

As is evident from this data, $Rh_2(cap)_4$ is clearly superior to $Rh_2(OAc)_4$ for C–H insertion reactions of diazoacetates and, in many cases, $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$ provide further improvements in product selectivity and isolated yields. Yield and process improvements from the use of dirhodium carboxamidates with diazoacetates have been previously noted[27,28] but not with the universality reported here. The same effect does not appear to be operative with α-diazo-β-keto esters.[13]

Experimental Section

General. ^1H NMR spectra were obtained from a 300-MHz spectrometer, and ^{13}C NMR spectra were recorded at 75 MHz. Mass spectra were obtained from a quadruple instrument at an ionizing voltage of 70 eV. Infrared spectra were recorded on a FT instrument having a resolution of ±1 cm^{-1}. Microanalyses were performed at Texas Analytical Laboratories, Inc. Dirhodium(II) tetraacetate was obtained commercially or prepared from rhodium(III) chloride hydrate.[29] The preparation and properties of $Rh_2(cap)_4$,[13] $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$,[24] and $Rh_2(4S\text{-MEOX})_4$[25] have been previously reported. Dichloromethane and acetonitrile were distilled from calcium hydride prior to use.

Preparation of Diazoacetates. General Procedure. A solution of alcohol (20.0 mmol) and freshly distilled (under reduced pressure) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (2.84 g, 20.0 mmol) in 50 mL of xylene was refluxed for 1 h according to the published procedure,[30] and then xylene was evaporated under reduced pressure. The residual acetoacetate was purified by Kugelrohr distillation which provided a product whose purity was greater than 90%. The purified acetoacetate (10.0 mmol) was dissolved in 100 mL of anhydrous acetonitrile containing triethylamine (1.30 g, 13.0 mmol), and methanesulfonyl azide[31] (1.46 g, 12.0 mmol) in 50 mL of acetonitrile was added dropwise over 20 min. The reaction mixture was stirred overnight at room temperature, after which $LiOH\cdot H_2O$ (1.37 g, 30 mmol) in 50 mL of water was added, and the resulting solution was stirred at room temperature for 6 h. After the addition of 200 mL of water, the reaction solution was extracted four times with 50-mL portions of ether. The combined ether solution was dried over anhydrous $MgSO_4$, and the ether was evaporated under reduced pressure to provide a yellow oil that was purified by column chromatography.

Cyclohexylmethyl Diazoacetate (4). Yellow oil, 78% yield from cyclohexylmethanol; purification on silica gel with 80:20 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.74 (s, 1H), 3.97 (d, J = 6.5 Hz, 2H), 1.80–1.60 (m, 6H), 1.34–1.10 (m, 3H), 1.05–0.85 (m, 2H). IR (film): 2114 (C=N_2), 1706 (C=O) cm^{-1}. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.27; H, 7.81; N, 15.33.

Cyclopentylmethyl Diazoacetate (6). Yellow oil, 64% yield from cyclopentylmethanol; purification on silica gel with 80:20 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.75 (s, 1H), 4.05 (d, J = 7.1 Hz, 2H), 2.21 (hept, J = 7.3 Hz, 1H), 1.79–1.67 (m, 2H), 1.67–1.49 (m, 4H), 1.31–1.20 (m, 2H). IR (film): 2109 (C=N_2), 1697 (C=O) cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66. Found: C, 57.03; H, 7.28; N, 16.73.

Tetrahydropyran-2-ylmethyl Diazoacetate (8). Yellow oil, 67% yield from tetrahydropyran-2-methanol; purification on silica gel with 70:30 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.84 (s, 1H), 4.17 (dd, J = 11.6, 3.5 Hz, 1H), 4.09 (dd, J = 11.6, 6.7 Hz, 1H), 4.05–3.98 (m, 1H), 3.60–3.51 (m, 1H), 3.49–3.39 (m, 1H), 1.95–1.80 (m, 1H), 1.65–1.40 (m, 4H), 1.40–1.25 (m, 1H). IR (film): 2127 (C=N_2), 1702 (C=O) cm^{-1}. Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.15; H, 6.63; N, 15.10.

Tetrahydrofuran-2-ylmethyl Diazoacetate (10). Yellow oil, 60% yield from tetrahydrofurfurol; purification on silica gel with 90:10 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.83 (s, 1H), 4.30–4.20 (m, 1H), 4.19–4.05 (m, 2H), 3.95–3.73 (m, 2H), 2.10–1.80 (m, 3H), 1.70–1.55 (m, 1H). IR (film): 2119 (C=N_2), 1702 (C=O) cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.45. Found: C, 49.21; H, 6.16; N, 16.31.

Cyclopropylmethyl Diazoacetate (12). Yellow oil, 50% yield from cyclopropylmethanol; purification on silica gel with 80:20 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.77 (s, 1H), 4.00 (d, J = 7.3 Hz, 2H), 1.19–1.07 (m, 1H), 0.61–0.54 (m, 2H), 0.32–0.26 (m, 2H). IR (film): 2125 (C=N_2), 1688 (C=O) cm^{-1}. Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.37; H, 5.65; N, 19.97.

2-Methyl-1-propyl Diazoacetate (13). Yellow oil, 49% yield from 2-methylpropan-1-ol; purification on silica gel with 80:20 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.74 (br s, 1H), 3.95 (d, J = 6.7 Hz, 2H), 1.94 (nontet, J = 6.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H). IR (film): 2109 (C=N_2), 1699 (C=O) cm^{-1}. Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.73; H, 7.13: N, 19.68.

Tetrahydrofuran-3-ylmethyl Diazoacetate (15). Yellow oil, 68% yield from tetrahydrofuran-3-methanol; purification on silica gel with 90:10 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.79 (s, 1H), 4.18 (dd, J = 10.8, 6.6 Hz, 1H), 4.06 (dd, J = 10.8, 7.9 Hz, 1H), 3.89–3.71 (m, 3H), 3.57 (dd, J = 8.8, 5.4 Hz, 1H), 2.66–2.53 (m, 1H), 2.12–1.98 (m, 1H), 1.69–1.58 (m, 1H). IR (film): 2119 (C=N_2), 1694 (C=O) cm^{-1}. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.45. Found: C, 49.34; H, 6.01; N, 16.35.

2,2-Dimethyl-1,3-dioxalane-4-methyl Diazoacetate (18). Yellow oil, 77% yield from solketal; purification on silica gel with 90:10 hexanes:ethyl acetate. ^1H NMR ($CDCl_3$): δ 4.81 (s, 1H), 4.36–4.25 (m, 1H), 4.25 (dd, J = 11.3, 4.5 Hz, 1H), 4.17 (dd, J = 11.3, 5.8 Hz, 1H), 4.07 (dd, J = 8.5, 6.4 Hz, 1H), 3.74 (dd, J = 8.5, 6.1 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H). IR (film): 2112 (C=N_2), 1695 (C=O) cm^{-1}. For ***S*-18**, $[\alpha]^{23}_D$ +3.8° (*c* 0.56, MeOH). Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 14.00. Found: C, 47.83; H, 6.18; N, 13.76.

Diazo Decomposition of Diazoacetates. General Procedure. A solution of diazo ester (1.00 mmol) in 5.0 mL of anhydrous dichloromethane was added through a syringe pump over 10 h to a refluxing dichloromethane solution (20 mL) containing the dirhodium(II) catalyst (1.0 mol %). After addition was complete, the solvent was evaporated under reduced pressure, and the residue was purified by bulb-to-bulb distillation (90 °C at 0.3 Torr) to afford the lactone product in greater than 90% purity. Analytically pure lactones were obtained by column chromatography on silica using a gradient of 100% hexanes to 100% ethyl acetate, the fractions from which were monitored by GC. The physical and spectral characteristics of **14**[32,33] and **20**[34] were identical with those previously reported.

2-Oxaspiro[4.5]decan-3-one (5). Isolated in 61% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.04 (s, 2H), 2.37 (s, 2H), 1.60–1.38 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 177.3, 78.5, 41.4,

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40.7, 36.4, 25.7, 23.1. IR (film): 1780 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 154 (M, 12), 97 (12), 96 (100), 95 (62), 82 (89), 81 (100), 79 (22), 68 (70), 67 (96), 55 (63), 54 (70), 53 (36). Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.96; H, 9.18.

2-Oxaspiro[4.4]nonan-3-one (7). Isolated in 63% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.10 (s, 2H), 2.44 (s, 2H), 1.75–1.63 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 177.1, 78.5, 47.5, 41.3, 36.7, 24.2. IR (film): 1780 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 140 (M, 14), 95 (8), 83 (14), 82 (100) 81 (100), 79 (28), 68 (94), 67 (100), 55 (82), 54 (97), 53 (58). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.54; H, 8.51.

2,6-Dioxaspiro[4.5]decan-3-one (9). Isolated in 81% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.37 (d, J = 9.8 Hz, 1H), 4.08 (d, J = 9.8 Hz, 1H), 3.75 (dt, J = 12.0, 7.6 Hz, 1H), 3.64 (dt, J = 12.0, 6.0 Hz, 1H), 2.79 (d, J = 17.4 Hz, 1H), 2.47 (d, J = 17.4 Hz, 1H), 1.76–1.52 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 175.3, 78.0, 76.6, 63.4, 38.8, 32.5, 25.2, 20.2. IR (film): 1780 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 156 (M, 22), 124 (15), 111 (38), 99 (21), 98 (100), 97 (15), 83 (53), 70 (32), 69 (36), 56 (56), 55 (84). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.38; H, 7.85.

2,6-Dioxaspiro[4.4]nonan-3-one (11). Isolated in 76% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.31 (d, J = 9.8 Hz, 1H), 4.17 (d, J = 9.8 Hz, 1H), 3.96–3.82 (m, 2H), 2.70 (d, J = 17.6 Hz, 1H), 2.55 (d, J = 17.6 Hz, 1H), 2.09–1.91 (m, 4H). IR (film): 1787 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 142 (M, 75), 101 (27), 100 (100), 82 (17), 81 (16), 71 (48), 69 (23), 58 (100), 57 (42). Enantiomer separation was achieved on a 30-m Chiraldex G-TA column operated at 150 °C with retention times of 38.4 and 42.1 min. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.12.

Dihydro-3,3-dimethyl-2(3*H*)-furanone (14).[32,33] Isolated in 65% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 3.99 (s, 2H), 2.34 (s, 2H), 1.20 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 177.1, 43.1, 36.1, 25.9. IR (film): 1783 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 114 (M, 16), 71 (10), 70 (44), 57 (23), 56 (100), 53 (12).

2,7-Dioxaspiro[4.4]nonan-3-one (16). Isolated from reaction performed with $Rh_2(4S\text{-}MEOX)_4$. ^1H NMR ($CDCl_3$): δ 4.26 (d, J = 9.1 Hz, 1H), 4.19 (d, J = 9.1 Hz, 1H), 3.93 (td, J = 7.0, 1.0 Hz, 2H), 3.78 (d, J = 8.8 Hz, 1H), 3.67 (d, J = 8.8 Hz, 1H), 2.59 (s, 2H), 2.05 (t, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 175.6, 76.3, 76.0, 67.5, 47.3, 38.2, 36.6. IR (film): 1788 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 142 (M, 12), 113 (7), 112 (61), 110 (15), 86 (15), 84 (55), 83 (42), 82 (35), 70 (25), 69 (33), 68 (58), 67 (76), 56 (40), 55 (96), 54 (100), 53 (59). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.14.

3,7-Dioxabicyclo[4.3.0]nonan-2-one (17). Isolated in 67% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.39 (ddd, J = 8.6, 4.6, 4.2 Hz, 1H), 4.28 (dd, J = 11.8, 4.2 Hz, 1H), 4.17 (dd, J = 11.8, 4.6 Hz, 1H), 3.98 (ddd, J = 7.3, 6.3, 3.2 Hz, 1H), 3.60 (ddd, J = 9.1, 9.1, 6.3 Hz, 1H), 2.78 (dd, J = 15.7, 4.2 Hz, 1H), 2.73 (dd, J = 15.7, 5.0 Hz, 1H), 2.72–2.64 (m, 1H), 2.18 (dddd, J = 12.6, 9.1, 6.3, 3.2 Hz, 1H), 1.85 (dddd, J = 12.6, 9.1, 7.3, 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 171.0, 74.2, 68.6, 67.3, 36.6, 35.3, 29.4. IR (film): 1758 cm^{-1}. Mass spectrum, *m/e* (relative abundance): 142 (M, 1), 114 (10), 84 (13), 83 (100), 71 (13), 70 (30), 69 (13), 55 (49), 54 (17), 53 (14). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.02; H, 7.18.

7,7-Dimethyl-2,6,8-trioxaspiro[4.4]nonan-3-one (19). Isolated in 60% yield after chromatography on silica gel from reaction performed with $Rh_2(cap)_4$. ^1H NMR ($CDCl_3$): δ 4.35 (d, J = 9.8 Hz, 1H), 4.28 (d, J = 9.8 Hz, 1H), 4.03 (s, 2H), 2.83 (d, J = 17.9 Hz, 1H), 2.66 (d, J = 17.9 Hz, 1H), 1.41 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 174.0, 111.0, 82.2, 76.4, 71.6, 38.9, 26.6, 26.1. IR (film): 1783 cm^{-1}. From **(*S*)-18**, $[\alpha]^{26}_D$ −46.0° (*c* 0.60, MeOH). Enantiomer separation was achieved on a 30-m Chiraldex G-TA column, operated initially at 80 °C for 2 min and then programmed at 1 deg/min to 150 °C, with retention times of 56.7 and 57.7 min. Anal. Calcd for $C_8H_{12}O_4$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.14.

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