Ruthenium Hydride Catalyzed Direct Oxidation of Alcohols to Carboxylic Acids via Transfer Hydrogenation: Styrene Oxide as Oxygen Source

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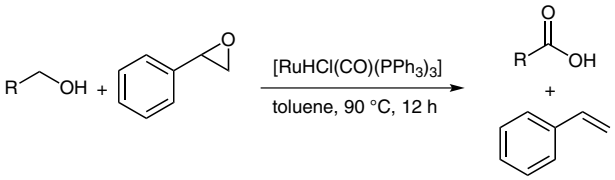
Abstract: Direct oxidation of alcohols to carboxylic acids using styrene epoxide as oxidant in the presence of [RuHCl(CO)(PPh_3)$_3$] complex as catalyst is reported. By this catalytic system, a variety of primary alcohols including substituted benzyl alcohols as well as linear ones were directly converted into carboxylic acids in good to excellent yields.

Key words: ruthenium hydride complex, alcohols, carboxylic acids, epoxides, oxidation

Transition-metal hydrides have recently attracted great attention due to their high efficiency and tolerance to functional-group transformation.[1] In particular, ruthenium hydride catalysts have played a large rule in these important reactions.[2] However, most of the examples are limited to the reduction of polar functional groups[3] and reductive carbon–carbon bond formations.[2,4]

Carboxylic acids are key building blocks for the synthesis of a variety of pharmaceutically important compounds[5] and also have specific industrial applications for production of several compounds.[6] Transition-metal-catalytic systems have been used for the oxidative dehydrogenation of alcohols to their corresponding carboxylic acids which represents one of the most fundamental transformations in organic chemistry.[7] Generally, the direct oxidation of alcohols to carboxylic acids is a two-step process; oxidation of the alcohol to the (potentially sensitive) aldehyde and oxidation of the resulting aldehyde to the desired carboxylic acid. Despite recent progress in the direct conversion of primary alcohols into carboxylic acids, the number of methods available is still limited, and often harsh reaction conditions with low functional-group compatibility have to be employed.[8] But to date, application of transition-metal hydrides for oxidation of alcohols to carboxylic acids have not been reported. Considering the importance of this reaction and relying pronounced ability of ruthenium hydride complex to influence the reactivity of organic compounds, we decided to explore the ability of [RuHCl(CO)(PPh_3)$_3$][9] catalyst in the direct oxidation of alcohols to carboxylic acids in the presence of styrene oxide as oxygen source (Scheme 1).



Scheme 1

First, the reaction parameters were optimized in the reaction of benzyl alcohol (**1a**) with styrene oxide (**2a**, Table 1). First, the effect of catalyst amount was studied in the model reaction and 5 mol% of catalyst was chosen as optimal catalyst amount (Table 1, entry 2). Increasing the amount of catalyst to 10 mol% did not affect the yield of product, but decreasing the catalyst amount to 3 mol%, the yield decreased to 53% (Table 1, entries 1–3). The effect of solvent was also checked in the model reaction. Among toluene, dichloromethane, dioxane, 1,2-dichloroethane, acetonitrile, and THF as solvents; toluene was chosen as reaction medium because the highest yield was obtained in this solvent (Table 1, entries 2 and 4–8). The ability of other ruthenium catalysts such as [RuH_2(CO)(PPh_3)$_3$],[10] [Ru(O_2CCF_3)$_2$(CO)(PPh_3)$_2$],[11] [RuHCl(PPh_3)$_3$],[12] [RuH_2(PPh_3)$_3$],[13] and [Ru(cod)(cot)][14] were also investigated, and no better results were obtained in comparison with [RuHCl(CO)(PPh_3)$_3$] (Table 1, entries 9–13). It seems that the ease of selective substitution of phosphine ligand *trans* to H^- in *cis*,*mer*-[RuHCl(CO)(PPh_3)$_3$] by alkoxy ligand (from epoxide) provide clear evidence for the kinetic *trans* effect of the strong σ-donor hydrido ligand.[15] The carbon monoxide, which acts as a weak σ-donor but a strong π-acceptor ligand, is ideal for tuning the electronic and steric properties of the Ru center in the reaction intermediates.[16] The presence of ligands, which increases the electron density on the Ru, reduces the catalytic activity. In the case of [Ru(cod)(cot)] both electronic and steric effects should be considered.[17] Finally, different epoxides were also applied as oxygen source. The results showed that the best oxygen source is styrene oxide (Table 1, entries 14–19). This can be attributed to increased stability of styrene (as one of the reaction products) relative to the other alkenes which were produced upon oxidation reaction. On the other hand, no progress was observed using H_2O_2 or *tert*-BuOOH as oxygen source. The scope and generality of this method was checked in the oxidation of a wide range of primary alcohols including benzylic and linear ones using styrene ox-

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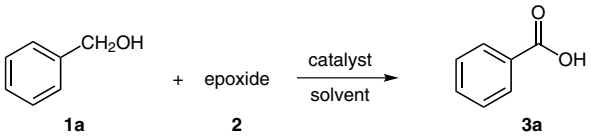
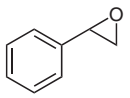
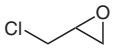
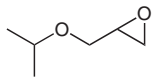
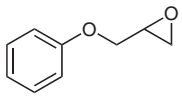
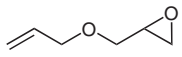
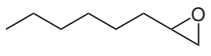
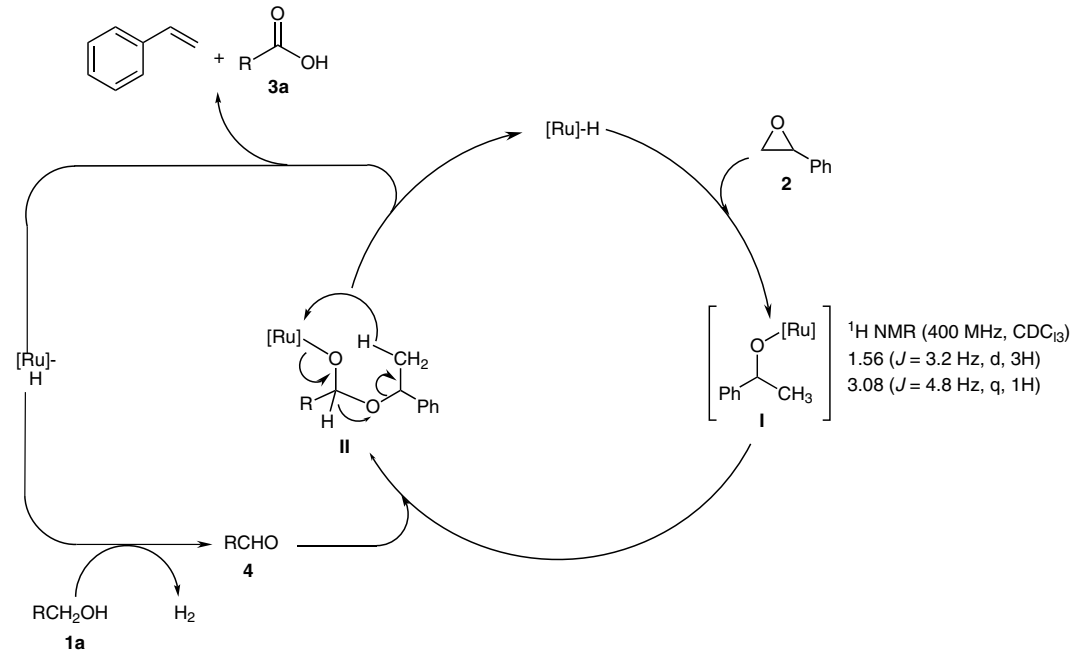
Table 1 Optimization of Conditions for the Reaction of **1a** with **2**[a]



1a **2** **3a**

Entry	Catalyst	Catalyst amount (mol%)	Epoxide	Solvent	Yield (%)[b]
1	$RuHCl(CO)(PPh_3)_3$	10	 **2a**	toluene	85
2	$RuHCl(CO)(PPh_3)_3$	5	**2a**	toluene	83
3	$RuHCl(CO)(PPh_3)_3$	3	**2a**	toluene	53
4	$RuHCl(CO)(PPh_3)_3$	5	**2a**	CH_2Cl_2	30
5	$RuHCl(CO)(PPh_3)_3$	5	**2a**	dioxane	45
6	$RuHCl(CO)(PPh_3)_3$	5	**2a**	DCE	38
7	$RuHCl(CO)(PPh_3)_3$	5	**2a**	MeCN	25
8	$RuHCl(CO)(PPh_3)_3$	5	**2a**	THF	5
9	$RuH_2(CO)(PPh_3)_3$	5	**2a**	toluene	55
10	$Ru(O_2CCF_3)_2(CO)(PPh_3)_2$	5	**2a**	toluene	35
11	$RuHCl(PPh_3)_3$	5	**2a**	toluene	19
12	$RuH_2(PPh_3)_4$	5	**2a**	toluene	29
13	Ru(cod)(cot)	5	**2a**	toluene	33
14	$RuHCl(CO)(PPh_3)_3$	5	 **2c**	toluene	47
15	$RuHCl(CO)(PPh_3)_3$	5	 **2d**	toluene	30
16	$RuHCl(CO)(PPh_3)_3$	5	 **2e**	toluene	15
17	$RuHCl(CO)(PPh_3)_3$	5	 **2f**	toluene	28
18	$RuHCl(CO)(PPh_3)_3$	5	 **2g**	toluene	17
19	$RuHCl(CO)(PPh_3)_3$	5	 **2h**	toluene	60

[a] All reactions were performed using **1a** (1 mmol), **2** (1.3 mmol), catalyst, and solvent (2 mL) for 12 h in a screw capped test tube at 90 °C.
[b] The yields refer to pure isolated products.



Scheme 2

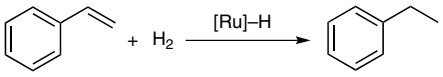
ide as oxygen source (Table 2). Different benzyl alcohols bearing electron-withdrawing and electron-donating substituents were efficiently converted into their corresponding substituted benzoic acids (Table 2, entries 1–5, 12, and 13). It seems that the nature of the substituents has no significant effect on the product yield. Surprisingly, upon oxidation of 4-methoxybenzyl alcohol (**1l**), the 4-hydroxybenzoic acid (**3l**) was obtained as product, and the methyl ether was deprotected to its corresponding hydroxy compound (Table 2, entry 13).

A series of substituted *N*-(2-hydroxyethyl)benzamides were also oxidized to their corresponding carboxylic acids in high to excellent yields with styrene oxide in the presence of [$RuHCl(CO)(PPh_3)_3$] (Table 2, entries 7–10). Cinnamyl alcohol as a linear alcohol was also oxidized successfully to cinnamic acid in high yield (Table 2, entry 11).

Despite the ability of this catalyst in the catalyzing the Tishchenko reaction,[2l] no Tishchenko products were observed in the presence of styrene oxide (even for compound **1f**).

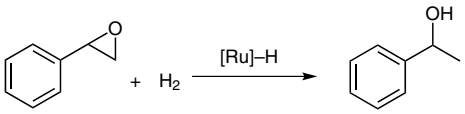
The plausible mechanism for this reaction is as following: First, the [$RuHCl(CO)(PPh_3)_3$] reacts with styrene oxide **2**, and a hydroruthenation reaction gives the ruthenium complex **I**. The structure of complex **I** was confirmed by ^1H NMR and ^{13}C NMR spectroscopy. As mentioned previously, the alcohol **1** can be converted into aldehyde **4** by [$RuHCl(CO)(PPh_3)_3$] and releases H_2 gas.[2k] The resulting complex **I** would undergo a nucleophilic reaction with aldehyde **4** to give the ruthenium complex **II**, which in turns converts into styrene and carboxylic acid **3**, the [$RuHCl(CO)(PPh_3)_3$] releases, and the catalytic cycle will continue (Scheme 2).

Further investigations showed that, in addition to styrene, ethylbenzene is also present in the reaction mixture. This can be attributed to the fact that the produced styrene acts as a hydrogen accepter (Scheme 3).[18]



Scheme 3

On the other hand, excess styrene oxide was not detected in the reaction mixture, but a small amount of 1-phenylethanol was. It seems that the styrene oxide can also act as hydrogen acceptor (Scheme 4).



Scheme 4

To stress this point, the oxidation of benzaldehyde with styrene oxide was also investigated in the presence of [$RuHCl(CO)(PPh_3)_3$]. The results showed that the benzoic acid was obtained in 80% after eight hours, and styrene was produced as byproduct. These observations show that benzyl alcohol should be converted firstly into benzaldehyde and then converted into benzoic acid. All these observations showed that the proposed mechanism is reasonable.

Table 2 Ruthenium Hydride Catalyzed Direct Oxidation of Alcohols to Carboxylic Acids with Styrene Oxide[a]

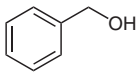
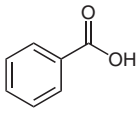
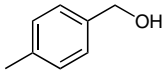
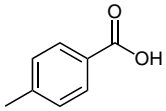
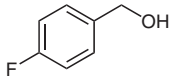
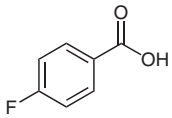
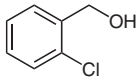
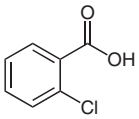
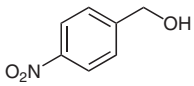
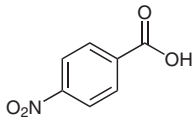
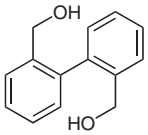
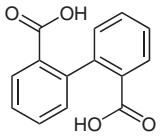
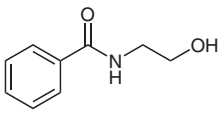
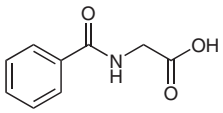
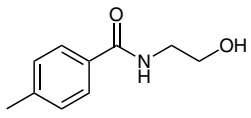
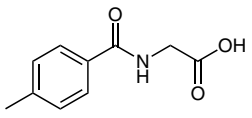
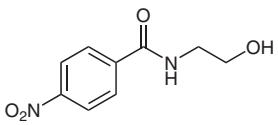
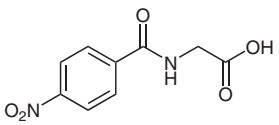
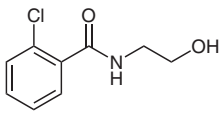
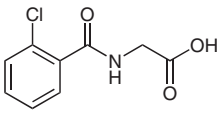
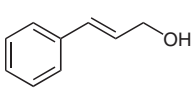
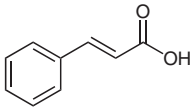
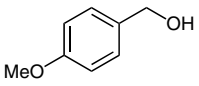
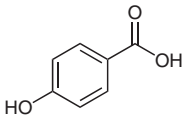
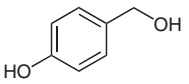
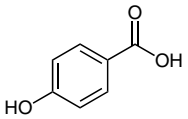
Entry	Alcohol **1**	Carboxylic acid **3**	Yield (%)[b]
1	 **1a**	 **3a**	83
2	 **1b**	 **3b**	80
3	 **1c**	 **3c**	90
4	 **1d**	 **3d**	86
5	 **1e**	 **3e**	93
6	 **1f**	 **3f**	71
7	 **1g**	 **3g**	80
8	 **1h**	 **3h**	80
9	 **1i**	 **3i**	83
10	 **1j**	 **3j**	85

Table 2 Ruthenium Hydride Catalyzed Direct Oxidation of Alcohols to Carboxylic Acids with Styrene Oxide[a] (continued)

Entry	Alcohol **1**	Carboxylic acid **3**	Yield (%)[b]
11	 **1k**	 **3k**	79
12	 **1l**	 **3l**	83
13	 **1m**	 **3l**	86

[a] All reactions were performed using alcohol (1 mmol), styrene epoxide (1.3 mmol), and catalyst (5 mol%) in toluene (2 mL) at 90 °C for 12 h.
[b] The yields refer to pure isolated products.

In conclusion, in the present work an efficient and new method for direct oxidation of alcohols to carboxylic acids is reported. In the presence of [RuHCl(CO)(PPh_3)$_3$] complex as catalyst different primary alcohols including substituted benzyl alcohols and also linear ones were directly converted into carboxylic acids in good to excellent yields.

Typical Procedure for the Ruthenium Hydride Catalyzed Oxidation of Benzyl Alcohol to Benzoic Acid

Benzyl alcohol (**1a**, 108.1 mg, 1.0 mmol), styrene epoxide (**2**, 156.2 mg, 1.3 mmol), [RuHCl(CO)(PPh_3)$_3$] (50.9 mg, 0.052 mmol), and toluene (2 mL) were mixed in a screw-capped test tube and purged with argon and sealed. The mixture was stirred at 90 °C for 12 h. After the reaction was completed, the solvent was removed under reduce pressure. The residue was purified by chromatography on silica gel plate (PE–EtOAc, 6:1), and the pure compound **3a** was obtained as a white crystal after recrystallization from H_2O–MeOH (101.4 mg, 83%).

Spectral Data

1-Benzoic Acid (3a)

Colorless crystals; yield 101.4 mg, 83%, mp 121–123 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.51 (t, 2 H, J = 16 Hz), 7.63 (t, 1 H, J = 8 Hz), 7.95 (d, 2 H, J = 4 Hz), 12.99 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 128.55, 129.23, 130.69, 132.58, 167.30.

4-Methylbenzoic Acid (3b)

White solid; yield 109.5 mg, 80%; mp 178–179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 1 H), 7.31 (d, 2 H, J = 8 Hz), 7.84 (d, 2 H, J = 8 Hz), 12.82 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.10, 127.96, 129.10, 129.30, 143.01, 167.29.

4-Fluorobenzoic Acid (3c)

White solid; yield 126.1, 90%; mp 182–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.33 (t, 2 H, J = 8 Hz), 7.99–8.03 (m, 2 H), 13.07 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.72, 127.26, 132.13, 163.61, 166.11.

2-Chlorobenzoic Acid (3d)

White solid; yield 134.6 mg, 86%; mp 137–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.42–7.55 (m, 3 H), 7.79 (d, 2 H, J = 8 Hz), 13.44 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 127.21, 130.58, 130.76, 131.50, 132.56, 166.28.

4-Nitrobenzoic Acid (3e)

White solid; yield 155.4 mg, 93%; mp 237–239 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27 (d, 2 H, J = 8 Hz), 8.38 (d, 2 H, J = 8 Hz), 12.92 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.4, 151.6, 133.9, 130.4, 124.7.

2,2′-Biphenyldicarboxylic Acid (3f)

White solid; yield 172.0 mg, 71%; mp 224–226 °C. IR (KBr): 3064, 2994, 2885, 2818, 2645, 2567, 1686, 1597, 1577, 1453, 1407, 1297, 1273, 1136, 1049, 1105, 1049, 1003, 921, 796, 754, 703 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.94–8.16 (m, 8 H), 12.47 (br s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 126.9, 129.4, 130.3, 131.0, 142.9, 167.9. MS (EI): *m/z* (%) = 242 (19) [M$^+$], 197 (100), 181 (28), 152 (46), 139 (13), 115 (18), 98 (6), 89 (3), 76 (11). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16; N, 5.78. Found: C, 69.23; H, 4.06; N, 5.68.

2-Benzamidoacetic Acid (3g)

White solid; yield 143.3 mg, 80%; mp 185–188 °C. IR (KBr): 3343, 3075, 2938, 1742, 1602, 1556, 1490, 1416, 1395, 1336, 1317, 1305, 1257, 1181, 1078, 999, 943, 849, 806, 723 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.95 (d, 2 H, J = 4 Hz), 7.49 (t, 2 H, J = 8 Hz), 7.55 (t, 2 H, J = 4 Hz), 7.89 (d, 1 H, J = 8 Hz), 8.87 (t, 1 H, J = 6 Hz), 12.64 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.2, 127.2, 128.2, 128.3, 131.4, 133.7, 166.4, 171.3. MS (EI): *m/z* (%) = 179 (10) [M$^+$], 135 (82), 104 (100), 83 (67), 77 (95), 69 (74), 57 (82), 51 (87), 45 (82), 43 (81), 41 (74). Anal. Calcd for $C_9H_9NO_3$: C, 60.34; H, 5.06; N, 7.82. Found: C, 60.22; H, 4.96; N, 7.69.

2-(4-Methylbenzamido)acetic Acid (3h)

White solid; yield 154.5 mg, 80%; mp 153–155 °C. IR (KBr): 3354, 2986, 1746, 1680, 1613, 1556, 1506, 1416, 1325, 1260, 1214, 1121, 1000, 833, 755 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3 H), 3.91 (d, 2 H, J = 8 Hz), 7.29 (d, 2 H, J = 8 Hz), 7.78 (d, 2 H, J = 8 Hz), 8.77 (t, 1 H, J = 4 Hz), 12.63 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.93, 41.33, 127.2, 128.8, 131.0, 141.3, 166.3, 171.4. MS (EI): *m/z* (%) = 193 (1) [M$^+$], 149 (37), 119 (100),

91 (80), 65 (38). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.63; N, 7.05.

2-(4-Nitrobenzamido)acetic Acid (3i)
Light brown solid; yield 186.1 mg, 83%; mp 152–154 °C. IR (KBr): 3316, 3110, 1706, 1641, 1601, 1541, 1425, 1351, 1297, 1231, 1108, 1013, 930, 874, 831, 801, 786, 716 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.97 (d, 2 H, *J* = 8 Hz), 8.11 (d, 2 H, *J* = 8 Hz), 8.33 (d, 2 H, *J* = 8 Hz), 9.28 (t, 1 H, *J* = 5 Hz), 13.14 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.3, 123.6, 128.8, 139.3, 149.1, 164.8, 170.9. MS (EI): *m/z* (%) = 224 (2) [M^+], (179, 29), 150 (100), 120 (24), 104 (91), 92 (62), 50 (83). Anal. Calcd for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.12; H, 3.47; N, 12.27.

2-(2-Chlorobenzamido)acetic Acid (3j)
White solid; yield 181.6 mg, 85%; mp 158–162 °C. IR (KBr): 3289, 3082, 1721, 1626, 1597, 1596, 1553, 1469, 1437, 1402, 1350, 1321, 1259, 1230, 1173, 1052, 999, 947, 842, 760 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.92 (d, 2 H, *J* = 8 Hz), 7.40–7.49 (m, 3 H), 7.51 (t, 1 H, *J* = 4 Hz), 8.79 (t, 1 H, *J* = 4 Hz), 12.71 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.9, 127.0, 129.0, 129.9, 130.8, 132.6, 136.2, 166.6, 170.9. MS (EI): *m/z* (%) = 213 (1) [M^+], 168 (34), 139 (100), 111 (47), 75 (38), 50 (17). Anal. Calcd for $C_9H_8NO_3Cl$: C, 50.60; H, 3.77; N, 6.56. Found: C, 50.45; H, 3.60; N, 6.46.

Cinnamic Acid (3k)
White solid; yield 117.5 mg, 79%; mp 129–132 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.56 (d, 1 H, *J* = 8 Hz), 7.43–7.73 (m, 5 H), 7.90 (d, 1 H, *J* = 8 Hz), 11.61 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.9, 147.16, 135.1, 130.9, 128.9, 128.3, 118.4.

4-Hydroxybenzoic Acid (3l)
White solid; yield 114.6 mg, 83%; mp 210–214 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.93 (d, 2 H, *J* = 8.4 Hz), 7.77 (d, 2 H, *J* = 8.4 Hz), 9.79 (s, 1 H), 10.63 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.8, 128.4, 132.1, 163.3, 191.0.

Formation of Ruthenium Complex I: {Ru[OCH(CH$_3$)Ph]Cl(CO)(PPh$_3$)$_2$}
$RuHCl(CO)(PPh_3)_3$ (0.05 mmol) and $CDCl_3$ (1 mL) were placed in an NMR tube. The tube was purged with N_2, capped with a rubber septum, and heated at 90 °C for 10 min. After cooling to r.t., styrene oxide (**2a**, 0.05 mmol) was added. The resulting mixture was heated at 90 °C for 30 min. The formation of complex **I** was confirmed by ^1H NMR and ^{13}C NMR measurements. Recrystallization from $CHCl_3$ and hexane gave the ruthenium complex **I**.

White solid. IR (KBr): ν_{CO} = 1920 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, 3 H, *J* = 3.2 Hz), 3.08 (q, 1 H, *J* = 4.8 Hz), 7.38–7.42 (m, 17 H), 7.51–7.55 (m, 6 H), 7.59–7.64 (m, 6 H), 7.73–7.76 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.27, 51.09, 125.34, 127.71, 128.10, 129.97 [d, ^3J(C–P) = 7 Hz], 130.42 [d, ^4J(C–P) = 2 Hz], 131.84 [d, ^2J(C–P) = 14 Hz], 134.42 [d, ^1J(C–P) = 43 Hz], 207.17 (t, *J* = 9.5 Hz). ^{31}P NMR (160 MHz, $CDCl_3$): δ = 35.95, 38.96. Anal. Calcd for $C_{45}H_{39}ClO_2P_2Ru$: C, 66.70; H, 4.85. Found: C, 66.47; H, 4.83.

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