Are Heterogeneous Catalysts Precursors to Homogeneous Catalysts ?

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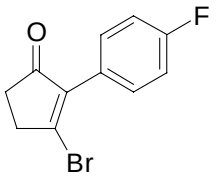
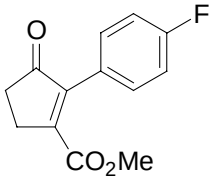


1

A 5 L round bottom flask was charged sequentially with palladium acetate (2.30g, 0.01 mol), 2-(di-*t*-butylphosphine)biphenyl (6.70 g, 0.02 mol), 1,3-cyclopentane-dione (50.0 g, 0.51 mol), potassium phosphate (207.7 g, 0.98 mol), 1,4-dioxane (1.02 L), and 1-chloro-4-fluorobenzene (79.8 g, 0.61 mol).[1] The reaction mixture was heated to reflux for 18 h, cooled to ambient temperature, and diluted with water. The resulting mixture was acidified with conc. HCl and the product isolated by filtration as an off-white solid (83.4 g, 85 %) which was used directly in the bromination step. To a solution of diketone (83.4 g, 0.43 mol) in acetonitrile (0.85 L) was added $POBr_3$ (124 g, 0.43 mol) at ambient temperature and the mixture was heated to 45 °C for 15 hr. The acetonitrile was removed under reduced pressure to afford a brown oil which was diluted with tert-butylmethyl ether (MTBE). The organics were washed with sat. Na_2CO_3 and brine, and then concentrated under reduced pressure to a brown solid which was then recrystallized with MTBE/heptane to afford **1** (84.9 g, 78 %). as an off-white solid. Anal. Calcd. For $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73. Found: C, 66.47; H, 4.92. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (m, 2H), 2.94 (m, 2H), 3.77 (s, 3H), 7.09 (t, 2H, *J* = 8.9 Hz), 7.35 (2H, dd, *J* = 8.9 and 5.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.8, 36.3, 114.4 (d, *J* = 21 Hz), 126.0, 131.0 (d, *J* = 12 Hz), 142.1, 156.0, 162.9 (d, *J* = 248 Hz), 202.2. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -112.7. LC-MS 254.9, 255.9 (M+H).

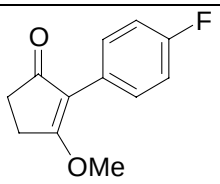
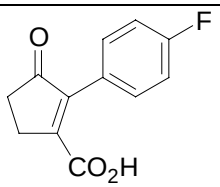


2

A conditioned autoclave (316 stainless steel) equipped with stirrer, temperature probe, nitrogen inlet, was charged bromide **1** (253 g, 1.00 mol), 5 wt % Pd/C (21.25 g, 0.01 mol), methanol (0.20 L), dimethylacetamide (1.00 L), and tributylamine (0.48 L). The autoclave reactor was purged with nitrogen (x 5) then with CO (x 5). The CO pressure was set at 80 psig and the reactor was heated to 60°C and aged for 8 hours. After complete reaction (HPLC > 99 % assay yield) the catalyst is filtered

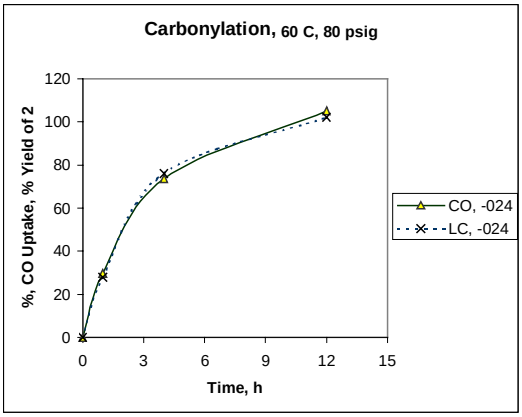
[1] Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald , S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

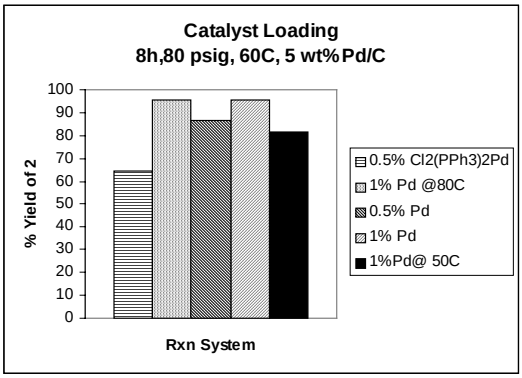
on a pad of solka floc (filter aid) and the excess methanol is removed by distillation.[2] 1N HCl (1.5 L) is added the and the solid is isolated by filtration and dried to give **2** as a light brown solid (211 g, 90 %, 99.5 wt % by HPLC) : Anal. Calcd. For $C_{13}H_{11}FO_3$: C, 66.66; H, 4.73 Found: C, 66.47; H, 4.92. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.64 – 2.72 (m, 2H), 2.90 – 2.98 (m, 2H), 3.77 (s, 3H), 7.09 (t, 2H, *J* = 9 Hz), 7.35 (dd, 2H, *J* = 9, 6 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.0, 34.5, 52.5, 115.0 (d, *J* = 21 Hz), 126.0 (d, *J* = 2 Hz), 131.0 (d, *J* = 8 Hz), 145.4, 156.3, 163.0 (d, *J* = 249 Hz), 166.0, 207.1. ^{19}F-NMR ($CDCl_3$, 376.5 MHz) δ -112.4. LC-MS 235.0 (M+H). Two low levels impurities (**A** and **B**) are observed at < 0.5 A% by HPLC in the reaction stream.

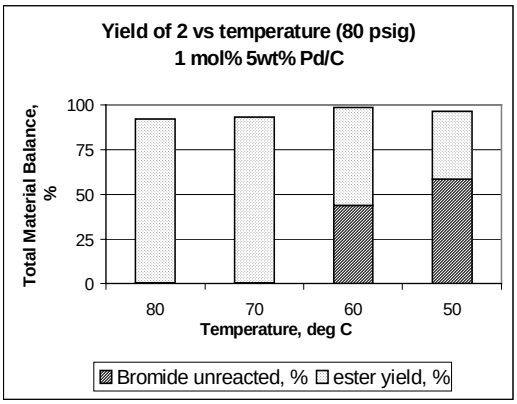
 **A**	Anal. Calcd. For $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.77; H, 5.46. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 – 2.62 (m, 2H), 2.78 – 2.85 (m, 2H), 4.02 (s, 3H), 7.05 (t, 2 H, *J* = 9 Hz), 7.75 (dd, 2H, *J* = 9 and 5 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.4, 33.6, 56.8, 114.7 (d, *J* = 20 Hz), 117.5, 126.7 (d, *J* = 2 Hz), 129.7 (d, *J* = 8 Hz), 161.0 (d, *J* = 247 Hz), 184.6, 202.8. ^{19}F-NMR ($CDCl_3$, 376.5 MHz) δ -115.2. LC-MS 207.0 (M+H).
 **B**	^{1}H-NMR (DMSO-d^6, 400 MHz) δ 2.52 – 2.58 (2H, m), 2.70 – 2.78 (2H, m), 7.16 (2H, t, J = 9), 7.32 (2H, dd, J = 9, 6). ^{13}C-NMR (DMSO-d^6, 100 MHz) δ 27.5, 34.6, 115.2 (d, *J* = 21 Hz), 127.5, (d, *J* = 2 Hz), 131.5 (d, *J* = 8 Hz), 142.7, 159.8, 162.5 (d, *J* = 248 Hz), 167.6, 207.6. ^{19}F-NMR (DMSO-d^6, 376.5 MHz) δ –113.7. LC-MS 221.0 (M+H).

Calculation of turnover number and frequency: A mixture of bromide **1** (25 mg, 0.1 mmol), dimethylacetamide (2.5 mL), tributyl amine (1.2 mL), methanol (0.5 mL) and 5 wt % Pd/C (50 mg, 0.024 mmol) was aged under nitrogen at 60 °C for 1 hr. The mixture was cooled and filtered through a frit followed by a 0.1 μm filter washing with dimethylacetamide (0.25 mL). Bromide **1** (250 mg, 1 mmol) was charged and the mixture was aged under CO, 60 °C, 60 psig for 3.5 hr. The mixture was diluted to 50 mL and analyzed by ICP-AES and HPLC. ICP-AES showed 1.3 ppm Pd (65 μg, 0.0006 mmol). HPLC assay of **2** was 122 mg (0.52 mmol). Assuming all of the palladium present was catalytically active the turnover number is 866, turnover frequency is 247/hr.

[2] On a small scale the DMA may be diluted with water and extracted with ethylacetate. Concentration and chromatography gives a 97 % isolated yield of ester **2**.


Carbonylation, 60 C, 80 psig
%, CO Uptake, % Yield of 2
120
100
80
60
40
20
0
0
3
6
9
12
15
Time, h
CO, -024
LC, -024


Catalyst Loading
8h,80 psig, 60C, 5 wt% Pd/C
% Yield of 2
100
90
80
70
60
50
40
30
20
10
0
Rxn System
0.5% Cl2(PPh3)2Pd
1% Pd @80C
0.5% Pd
1% Pd
1%Pd@ 50C


Yield of 2 vs temperature (80 psig)
1 mol% 5wt% Pd/C
Total Material Balance, %
100
75
50
25
0
80
70
60
50
Temperature, deg C
Bromide unreacted, %
ester yield, %