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The First Palladium Catalyzed Oxidative Kinetic Resolution Using Ambient Air as the Stoichiometric Oxidation Gas

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Material and Methods. Unless stated otherwise, reactions were performed in oven-dried glassware, under an atmosphere of oxygen, using freshly distilled solvents. Although we have never experienced an accident, all reactions must be performed with appropriate caution in a fume hood due to the flammable nature of mixtures of oxygen and organic solvents. Spectroscopic grade chloroform (Aldrich) or chloroform stabilized by amylenes was used without further purification. Chloroform stabilized by EtOH must be distilled prior to use. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed on a Chiralcel OJ, AS, AD, OB-H or OD-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 m) column. Analytical chiral GC was carried out using a Chiraldex B-DM column (30.0 m x 0.25 mm) purchased from Bodman Industries. Commercially available racemic alcohols in Tables 2 (entries A, B, C, E, F, I, and J) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Non-commercially available racemic alcohols used in Figure 1

(corresponding to entries D, G, H, K, and L) were prepared as previously described.[1] Commercially available samples of enantiopure alcohols for analytical comparison purposes (entries A, C, F, and J) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Non-commercially available enantiopure alcohols prepared by palladium-catalyzed oxidative kinetic resolution (Figure 1 entries E,[2] I,[3] and G[1,4]) were compared by optical rotation to known values. The previously unknown enantiopure alcohols (Figure 1, entries B, D, H, K, and L) were assigned absolute stereochemisty by analogy to assigned resolution products.

General Procedure for the Room Temperature Oxidative Kinetic Resolution of Secondary Alcohols Under O_2. An oven dried reaction tube (outer diameter 16 mm, length 120 mm) equipped with a magnetic stir bar was charged with oven dried powdered molecular sieves (MS3Å, 0.5 g). After cooling, Pd(nbd)Cl_2 complex (0.05 mmol, 0.05 equiv) was added followed by chloroform (2.0 mL), and (–)-sparteine (0.2 mmol, 0.20 equiv). The flask was cooled to -78 °C, then vacuum evacuated and filled with O_2 (3x, balloon) then stirred at room temperature for 15 min. Powdered anhydrous Cs_2CO_3 (0.4 mmol, 0.4 equiv.) and a chloroform solution (2.0 mL) of the alcohol (1.0 mmol, 1.0 equiv) was introduced and the reaction mixture was maintained at room temperature. The reaction was monitored by standard analytical techniques (TLC, GC, 1H-NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 4 h, 8 h, 12 h, 24 h, and 48 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (Et_2O eluent), evaporated and analyzed.[5]

General Procedure for the Room Temperature Oxidative Kinetic Resolution of Secondary Alcohols Under Ambient Air. An oven dried reaction tube (outer diameter 16 mm, length 120 mm) equipped with a magnetic stir bar was charged with oven dried powdered molecular sieves (MS3Å, 0.5 g). After cooling, Pd(nbd)Cl_2 complex (0.05 mmol, 0.05 equiv) was added followed by chloroform (2.0 mL), and (–)-sparteine (0.2 mmol, 0.20 equiv). The reaction flask was sealed with a septa and the contents were stirred at room temperature for 15 minutes before the consecutive addition of powdered anhydrous Cs_2CO_3 (0.4 mmol, 0.4 equiv.) and a chloroform solution (2.0 mL) of the alcohol (1.0 mmol, 1.0 equiv) The reaction was fitted with a short drying tube packed with drierite

(1.0 X 7.5 cm plug) and maintained at room temperature and was monitored by standard analytical techniques (TLC, GC, 1H-NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 4 h, 8 h, 12 h, 24 h, and 48 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (Et_2O eluent), evaporated and analyzed.[5]

General Procedure for the Oxygen Uptake Experiments for the Room Temperature Oxidative Kinetic Resolution of Secondary Alcohols Under Ambient Air and Pure Oxygen. An oven dried 25 ml round bottom flask equipped with a magnetic stir bar was charged with oven dried powdered molecular sieves (MS3Å, 1.5 g). After cooling, $Pd(nbd)Cl_2$ complex (0.15 mmol, 0.05 equiv) was added followed by chloroform (6.0 mL), and (–)-sparteine (0.6 mmol, 0.20 equiv). The contents were stirred at room temperature for 15 minutes before the consecutive addition of powdered anhydrous Cs_2CO_3 (1.2 mmol, 0.4 equiv.) and a chloroform solution (6.0 mL) of the alcohol (3.0 mmol, 1.0 equiv). The reaction vessel was fitted with a gas inlet tube attached consecutively to a short drying tube then a water filled burette tube (charged with either pure oxygen, or air, as appropriate). The water filled burette was equipped with a side reservoir to permit pressure equilibration to ensure accurate gas measurements. Aliquots were taken at 4 h, 8 h and 12 h, noting the gas consumption and measuring conversion by GC analysis.

General Procedure for the Preparation of Mixed Gas Systems. A glass stem equipped centrally with a Teflon stopcock is fitted at opposite ends with a securely fitted balloon and a fresh rubber septa. The ends are thoroughly taped with electrical tape to minimize leaks. Three such apparatus are constructed. One is charged with dry, oxygen (99.9% UHP from Aldrich), while the other is charged with nitrogen (99.9% UHP from Aldrich). Using a 100 ml Teflon lined syringe, the required gas volumes are syringed out of the charged balloons and into the remaining evacuated balloon until an appropriate volume of the desired percentage of O_2 has been attained. Once charged, the end of the septa is suspended in water to check for leaks. In the absence of leaks, the stopcock is closed and the septa is removed. See, "General Procedure for the Room Temperature Oxidative Kinetic Resolution of Secondary Alcohols Under O_2" for the remaining experimental details.

Table SM 1. Methods utilized for the determination of enantiomeric excess.

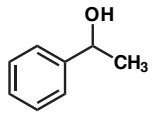
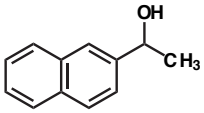
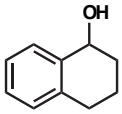
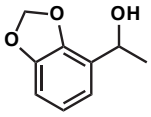
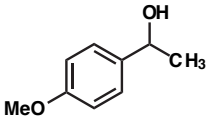
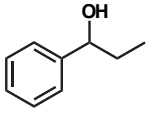
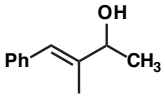
entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
A.		HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	10.69	13.37
B.		HPLC Chiralcel OJ	4% 2-propanol/hexane 1.0 mL/min	38.69	31.32
C.		HPLC Chiralcel AS	2% EtOH/hexane 1.0 mL/min	15.55	12.68
D.		HPLC Chiralcel OBH	2% IPA/hexane 1.0 mL/min	18.65	32.20
E.		HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	14.60	16.52
F.		HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	11.15	13.23
G.		HPLC Chiralcel OD-H	4% 2-propanol/hexane 1.0 mL/min	13.44	15.44

Table SM 1 (continued).

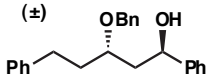
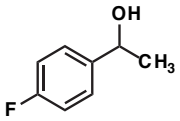
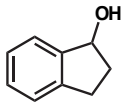
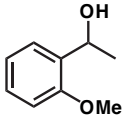
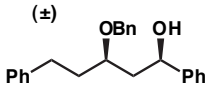
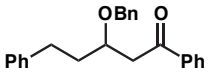
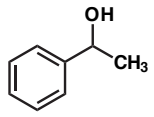
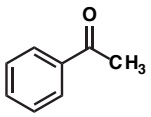
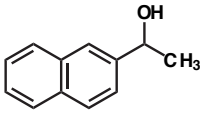
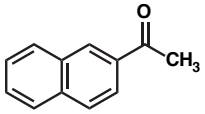
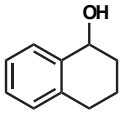
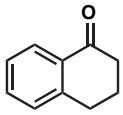
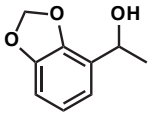
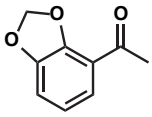
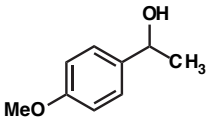
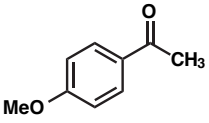
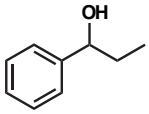
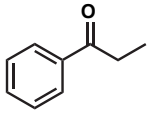
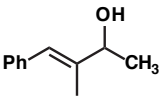
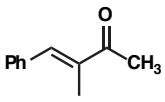
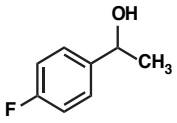
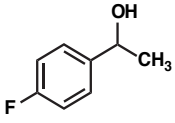
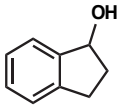
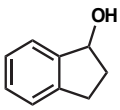
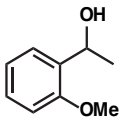
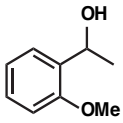
entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
H.		HPLC Chiracel AD	4% IPA/hexane 1.0 ml/min	25.90	30.61
I.		HPLC Chiracel AS	2% EtOH/hexane 1.0 ml/min	15.10	17.35
J.		HPLC Chiralcel OJ	3% EtOH/hexane 1.0 mL/min	17.35	14.76
K.		HPLC Chiralcel OBH	4% IPA/hexane 1.0 mL/min	8.67	9.67
L.		HPLC Chiracel OJ	10% EtOH/hexane 1.0 ml/min	19.54	25.18
Product H and L[6]		HPLC Chiracel OJ	4% IPA/hexane 1.0 ml/min	47.98	57.82

Table SM 2. GC methods utilized for the determination of conversion.

entry	Substrate	Ketone	GC Conditions[a]	Retention Time of alcohol (min)	Retention Time of ketone (min)
A.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	28.60	25.53
B.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	42.00	38.85
C.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	32.95	34.47
D.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	36.32	35.04
E.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.44	33.50
F.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.66	26.97
G.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.22	32.54

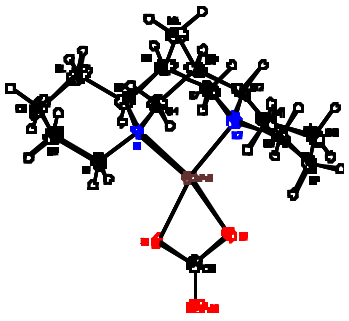
[a] All assays performed on Agilent DB-WAX column.

Table SM 2 (continued).

entry	Substrate	Ketone	GC Conditions[a]	Retention Time of alcohol (min)	Retention Time of Ketone (min
I.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.42	25.46
J.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	32.70	31.76
K.			70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	32.46	31.11

[a] All assays performed on Agilent DB-WAX column. Conversion for entries H and L determined from enantiomeric excess of resolved starting alcohol and product.[6]

Preparation of Pd(sparteine)CO_3: To a room temperature solution of Pd(sparteine)Cl_2 (500 mg, 1.21 mmol) in chloroform (240 mL) is added finely milled anhydrous cesium carbonate (3.734 g, 9.68 mmol) and deionized water (10 μL, 0.56 mmol). The solution is stirred at room temperature for 10 h, then celite (3.0 g) is added to the mixture and the resulting is slurry filtered, then washed with portions of chlolroform (2 x 20 mL). The resulting yellow liquor is concentrated to 8 mL, then triturated with ether. The solid is collected by vacuum filtration and dried under vacuum to provide Pd(sparteine)CO_3 (396 mg, 81%) of a light yellow powder, which was analytically pure. A sample for single crystal X-ray diffraction was prepared by recrystallization from a mixture of CH_2Cl_2/Et_2O. The structure has been deposited in the CCDC under the number 218105.



^{1}HNMR (300 MHz, CCl_2D_2)δ 1.31-1.71 (m, 8H), 2.13-2.36 (m, 2H), 2.62 (dd, 1H, J=2.7, 13.1 Hz), 2.90-3.05 (m, 3H), 3.05-3.33 (m, 2H), 3.90-4.05 (m, 1H) 4.05-4.21 (m, 1H); ^{13}C (300 MHz, CCl_2D_2)δ 20.2, 23.6, 23.8, 23.9, 25.4, 27.5, 30.2, 34.8, 44.3, 49.2, 60.9, 62.8, 65.7, 66.1, 68.6, 166.7.

References:

[1] a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492. b) J. C. Ruble, J. Tweddell, G. C. Fu, J. Org. Chem. **1998**, *63*, 2794.

[2] K. Nakamura, Y. Inoue, T. Matsuda, I. J. Misawa, *Chem. Soc., Perkin. Trans. 1* **1999**, 2397.

[3] T. R. Nieduzak, A. L. Margolin, *Tetrahedron: Asymmetry* **1991**, *2*, 113.

[4] C. L. Argus, L. A. Cort, T. J. Howard, L. B. Loc, *J. Chem. Soc.* **1960**, 1195.

[5] Percent conversions were measured by GC integration of the alcohol and the ketone peaks, correcting for response factors (for conditions see SM Figure 1).

[6] Conversion is calculated from the ee of product and starting alcohol according to equation: ee/ee' = C/(1 - C) where ee is the enantiomeric excess of the starting alcohol, and ee' is the enantiomeric excess of the product. For a derivation of this equation see: H. B. Kagan, J. C. Fiaud in Topics in Stereochemistry; E. L. Eliel, Ed.; Wiley & Sons: New York, **1988**; Vol. 18, pp 249-330.