A Bimetallic System for the Catalytic Hydroxylation of Remote Primary C−H Bonds in Functionalized Organics Using Dioxygen

Chengyu Shen, Eduardo A. Garcia-Zayas, and Ayusman Sen*

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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Abstract: In a mixture of trifluoroacetic acid and water, the combination of metallic palladium and copper chloride catalyzes the hydroxylation of remote primary C−H bonds of a variety of acids, alcohols, and aliphatic halides, in the presence of carbon monoxide and dioxygen. Experiments suggest that the principal role of metallic palladium is to generate hydrogen peroxide in situ and that the species responsible for the remote hydroxylation of the substrate by hydrogen peroxide is copper chloride. The unusual preference for the catalytic hydroxylation of primary C−H bonds was also found in an experiment involving competition between ethane and either cumene or *p*-isopropylbenzoic acid: even though the solution concentration of ethane was significantly lower than the competing substrate, the vast majority of the oxidation product (ethanol) was derived from ethane. In the reactions studied, acetic acid and formic acid were formed through C−C cleavage steps. An examination of the site of C−C cleavage in propionic acid indicated that both C−C bonds were being broken.

Introduction

The catalytic functionalization of aliphatic C−H bonds is one of the most important problems in chemistry.[1] In particular, the selective oxidation of ***remote primary C−H bonds*** of organic substrates continues to be an intellectual and practical challenge despite past efforts by organic and organometallic chemists. To date, the only examples of metal-catalyzed functionalization (hydroxylation) of remote primary C−H bonds involve the combination of $PtCl_4^{2-}/PtCl_6^{2-}$ (the Shilov system).[1a,b,2] Despite its many attractive features, however, the Shilov system suffers from one crippling drawback: dioxygen cannot be used efficiently as the reoxidant.[3]

We had earlier reported that, in a mixture of trifluoroacetic acid and water, the combination of metallic palladium and copper chloride catalyzes the oxidation of alkanes in the presence of carbon monoxide.[1a,e,4] We now report that this system is also effective for the hydroxylation of remote primary C−H bonds of functional organics. Further experiments also confirm that the oxidations do not involve free alkyl radicals.

Experimental Section

Caution. *Appropriate precautions should be taken while working with gases under high pressures. Particular attention should be paid to flammability limits of gas mixtures.*

General. The following chemicals were used as received: 5% Pd/carbon (60 μmol surface Pd atoms/g catalyst, as determined by dihydrogen chemisorption studies) (Johnson Matthey); $CuCl_2$, CuCl, $CuBr_2$, $Cu(CF_3CO_2)_2$, 50% H_2O_2, propionic acid, butyric acid, *n*-propanol, ethanesulfonic acid sodium salt monohydrate, propanesulfonic acid sodium salt monohydrate, ethylphosphonic acid, *n*-propyl chloride, cumene, *p*-isopropyl benzoic acid, ethylbenzene, *p*-ethylbenzene sulfonic acid, trifluoroacetic acid, NaCl, and chlorine (Aldrich); ethane, dioxygen, dinitrogen, and carbon monoxide (Matheson); $C_2H_5{}^{13}COOH$; and CD_3CH_2COOH (Cambridge Isotopes). Reactions under pressure were carried out in 300 mL Parr general purpose stainless steel bombs with glass liners. Reaction products were identified by their ^1H and ^{13}C NMR spectra recorded on a Bruker AM 300 FT-NMR spectrometer using an external standard consisting of a capillary tube containing 1 μL of DMSO in 60 μL of D_2O for lock, reference, and as an integration standard. The identity of specific NMR resonances was confirmed by comparison to standard reference spectra and/or co-injection of standards.

Procedure. The substrate, anhydrous $CuCl_2$, and 5% Pd on carbon were added to a glass liner containing 1.5 mL of CF_3COOH and 0.5 mL of H_2O. The liner was then placed in a high-pressure reactor (bomb) which was then sealed. The reactor was purged and then pressurized to 200 psi with CO, to 1000 psi with N_2, and to 1100 psi with O_2. The contents were stirred at 70−90 °C for 18 h. The reactor was subsequently cooled and the gases slowly released. The reaction mixture was then directly analyzed by NMR spectroscopy.

Results and Discussion

Table 1 summarizes our results on remote oxidation of C−H bonds in aliphatic acids and alcohol. Since the reactions were carried out in the presence of CF_3COOH, a significant amount of the alcohol formed was converted to the ester. Thus, the yield of hydroxylated product was calculated as the sum of the alcohol plus the corresponding ester. Table 1 shows that the $Pd/CuCl_2$ system is effective as a remote functionalization agent for a

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Table 1. Remote Oxidation of Substrates by the Pd−C/$CuCl_2$ System[a]

substrate (mmol)	5% Pd−C/$CuCl_2$ (mg/mg)	time (h)	convn[b] (%)	products	yield[b] (%)
C_2H_5COOH (1.34)	3/10	18	40	3-hydroxypropionic acid	22
n-C_3H_7COOH (1.09)	3/15	18	59	4-hydroxybutyric acid	22
				3-hydroxybutyric acid	24
$C_2H_5SO_3Na$ (0.67)	3/15	18	36	2-hydroxyethanesulfonic acid	10
n-$C_3H_7SO_3Na$ (0.61)	3/15	18	38	3-hydroxypropanesulfonic acid	13
				2-hydroxypropanesulfonic acid	10
$C_2H_5PO_3H$ (0.90)	3/15	18	17	2-hydroxyethanephosphonic acid	7
n-C_3H_7OH (1.34)	3/15	18	46	1,3-propanediol	15
				1,2-propanediol	10

[a] Reaction conditions: $CO/N_2/O_2$, 200 psi/800 psi/100 psi; CF_3COOH/H_2O, 1.5 mL/0.5 mL, 75 °C. [b] Relative to substrate.

Table 2. The Effect of Varying the Amount of $CuCl_2$ on the Oxidation of Propionic Acid[a]

$CuCl_2$ (mg)	C_2H_5COOH (final mmol)	3-hydroxypropionic acid (mmol)	CH_3COOH (mmol)	HCOOH (mmol)
0	1.30	0	0.07	tr.
3.5	0.55	0.23	0.20	0.71
15	0.81	0.22	0.19	0.44
25	1.10	0.16	0.07	0.17

[a] Reaction conditions: 1.34 mmol of C_2H_5COOH, 3 mg of 5% Pd−C, 1.5 mL of CF_3COOH, 0.5 mL of H_2O, 800 psi N_2, 200 psi CO, 100 psi O_2, 75 °C, 18 h.

broad spectrum of substrates, including a variety of acids, alcohol, and aliphatic halide (cf., Table 4). In all reactions, carbon monoxide and water are necessary since little or no oxidation occurred in their absence. We believe the same mechanism operates here as was proposed for the oxidation of alkanes.[1a,e,4,5] This mechanism involves a metal-catalyzed water gas shift reaction and the subsequent formation of hydrogen peroxide.[6]

The system is clearly catalytic with turnovers of 1666 and 4 relative to surface Pd atoms and $CuCl_2$, respectively, for the formation of 3-hydroxypropionic acid. Both Pd on carbon and $CuCl_2$ are required for the reaction. We had earlier demonstrated that a critical function of Pd is to generate hydrogen peroxide. In the absence of $CuCl_2$, however, very little oxidation and no remote hydroxylation was observed with propionic acid (Table 2). Increasing the amount of Pd on carbon results in an increase in the conversion of the substrate. For example, in CF_3COOH/D_2O in 18 h, the conversion of 1.34 mmol of propionic acid increased from 8% to 28% and the yield of 3-hydroxypropionic acid increased from 0.10 to 0.26 mmol as the amount of Pd on carbon was increased from 1 to 11 mg in the presence of 25 mg of $CuCl_2$. An interesting issue is whether the active form of Pd is the metal itself or the Pd^{2+} ion present in the solution phase. When the oxidation of propionic acid was repeated in the presence of 2 drops of metallic Hg, no significant formation of ***any*** of the oxidation products was observed. This suggests (but does not prove, since Hg could be acting as a reductant for Pd^{2+}) that metallic Pd is the active ingredient since Hg would deactivate the surface atoms through amalgamation.[7]

Table 3. Oxidation of *n*-Propanol by Hydrogen Peroxide[a]

5% Pd−C (mg)	$CuCl_2$ (mg)	propane-1,3-diol (mmol)	propane-1,2-diol (mmol)	CH_3COOH (mmol)	HCOOH (mmol)
0	0	0	0	0.1	0.1
25	0	0	0	2.3	1.4
0	25	0.40	0.35	1.1	3.1

[a] Reaction conditions: 6.5 mmol of *n*-propanol, 7.5 mL of CF_3COOH, 2.5 mL of 50% H_2O_2 (added by syringe pump), 90 °C, 18 h.

Table 4. Comparison of CO/O_2 versus Cl_2 as Oxidants for $ClCH_2CH_2CH_3$[a]

oxidant	$ClCH_2CH_2CH_2X$ (mmol)	$ClCH_2CH(X)CH_3$ (mmol)	CH_3COOH (mmol)	HCOOH (mmol)
CO/O_2	0.12 (X = OH)	0.14 (X = OH)	0.06	0.37
Cl_2	0	0.35 (X = Cl)	0	0

[a] Reaction conditions: 1.14 mmol of ClC_3H_7, 3 mg of 5% Pd−C, 10 mg of $CuCl_2$, 1.5 mL of CF_3COOH, 0.5 mL of H_2O, 800 psi N_2, 100 psi O_2, 200 psi CO or 90 psi Cl_2, 75 °C, 18 h.

Given the observation that little substrate oxidation occurs in the absence of added $CuCl_2$, the possibility arises that the principal role of metallic Pd is to generate hydrogen peroxide in situ and that the species responsible for the oxidation of substrate by hydrogen peroxide is $CuCl_2$. To test this hypothesis, the oxidation of *n*-propanol by hydrogen peroxide was attempted in the presence of Pd on carbon or $CuCl_2$. To minimize the parallel metal-catalyzed decomposition of hydrogen peroxide, the oxidant was added slowly through a syringe pump. Although the reaction conditions were inevitably different from those in Table 1, it is clear from Table 3 that remote hydroxylation of *n*-propanol is observed ***only*** in the presence of $CuCl_2$! Additionally, the ratio of 1,3- and 1,2-diols formed is similar to that observed with the bimetallic system (Table 1). Thus, at least to a first approximation, in the bimetallic system metallic Pd is responsible for the generation of hydrogen peroxide and $CuCl_2$ is responsible for the remote hydroxylation step.

In the bimetallic system, the $CuCl_2$ also appears to suppress the formation of products due to overoxidation and C−C cleavage, and this is illustrated in Table 2. However, as shown in Table 2, the use of excess $CuCl_2$ also results in decreased conversion of the substrate. Clearly, the best yield (conversion × selectivity) of the remote hydroxylation product is obtained with a moderate amount of $CuCl_2$. Both copper(II) and halide ions are essential for the formation of the desired product. In the presence of ***either*** $Cu(O_2CCF_3)_2$ ***or*** NaCl (but not both), and palladium on carbon, little oxidation and no remote hydroxylation was observed with propionic acid. However, a 1:2 molar ratio of $Cu(O_2CCF_3)_2$ and NaCl was found to be similar to $CuCl_2$. Finally, the effectiveness of halide ion in combination with copper(II) was found to decrease in the order $Cl^- > Br^- > I^-$.

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Table 5. Competition between Ethane and Either Cumene or *p*-Isopropylbenzoic Acid[a]

substrate (initial mmol)	substrate (final mmol)	C_2H_5OH (mmol)	CH_3COCH_3 (mmol)	CH_3COPhX (mmol)	CH_3COOH (mmol)
i-C_3H_7Ph (0.72)	*i*-C_3H_7Ph (0.47)	0.44	0.26	0.01 (X = H)	0.20
i-$C_3H_7PhCOOH$ (0.31)	*i*-$C_3H_7PhCOOH$ (0.26)	0.24	0.04	0.06 (X = COOH)	0.03

[a] Reaction conditions: 3 mg of 5% Pd−C, 10 mg of $CuCl_2$, 1.5 mL of CF_3COOH, 0.5 mL of H_2O, 200 psi CO, 100 psi O_2, 550 psi (*i*-C_3H_7Ph) or 500 psi (*i*-$C_3H_7PhCOOH$) C_2H_6, 300 psi (*i*-C_3H_7Ph) or 500 psi (*i*-$C_3H_7PhCOOH$) N_2, 75 °C, 18 h. Solubility of C_2H_6 in water: 0.03 M (0.06 mmol/2 mL) at 550 psi.

Interestingly, copper(I) chloride was not effective in suppressing the formation of unwanted products. However, a 1:1 molar mixture of CuCl and NaCl gave similar product distribution as $CuCl_2$. For example, in CF_3COOH/D_2O in 18 h, the sum of acetic acid and formic acid formed from 1.34 mmol of propionic acid increased from 0.73 to 0.91 mmol when CuCl was increased from 2 to 20 mg in the presence of 3.5 mg of Pd on carbon. On the other hand, 15 mg of CuCl and 6 mg of NaCl in combination reduced that yield to 0.22 mmol.

In the case of butyric acid, propanesulfonic acid, and *n*-propanol (Table 1) and *n*-propyl chloride (Table 4) hydroxylation occurred at both ω-methyl and ω-1-methylene carbons (the relative preference on a per C−H bond basis was 0.6, 0.9, 1, and 0.6, respectively). The significant degree of attack at a stronger, primary, C−H bond in the presence of secondary C−H bonds is clearly inconsistent with a mechanism involving the formation of radicals through H-atom abstraction. This is further highlighted by a direct comparison of functionalization regioselectivity between the present system and chlorination in the presence of Pd/$CuCl_2$. As shown in Table 4, (radical) chlorination under similar conditions occurred ***exclusively*** at the secondary C−H bond. To further confirm the very unusual preference of the present system for the catalytic hydroxylation of primary C−H bonds, experiments involving competition between ethane and either cumene or *p*-isopropylbenzoic acid were run. As shown in Table 5, even though the solution concentration of ethane was significantly lower than the competing substrate, the vast majority of the oxidation product (ethanol) was derived from ethane. This is despite the very weak tertiary (and benzylic) C−H bond that is present in the competing substrate. An identical trend was also found in competitions involving ethane and either ethylbenzene or *p*-ethylbenzene sulfonic acid.

In each of the reactions examined, significant amounts of acetic acid and formic acid were formed through C−C cleavage steps. One possible mechanism for C−C cleavage would involve the loss of CO_2 from a carboxyl radical. An examination of the site of C−C cleavage in propionic acid indicated that the situation was more complex. Significant H/D exchange was not observed in the unreacted starting material when the oxidation of propionic acid-H_6 was carried out in CF_3COOH/D_2O. When CD_3CH_2COOH was employed, ^1H NMR silent CD_3COOH was expected for cleavage of the C1−C2 bond and ^1H NMR active CH_3COOH for cleavage of the C2−C3 bond. In fact, CH_3COOH was observed indicating the occurrence of C2−C3 bond cleavage (this does not rule out C1−C2 bond cleavage occurring in parallel). In another experiment $CH_3CH_2{}^{13}COOH$ was employed and a ^1H NMR spectrum was obtained at the end of the reaction. The presence of ^{13}C uncoupled CH_3COOH would be indicative of C1−C2 bond cleavage while ^{13}C coupled CH_3-COOH would be evidence for C2−C3 bond cleavage. However, a mixture of ^{13}C coupled ***and*** uncoupled CH_3COOH was obtained due to cleavage occurring at both sites. Finally, the formation of formic acid from sulfonic acids and phosphonic acid also shows the C2−C3 bond can be cleaved under the reaction conditions.

Conclusion

We have discovered the first catalytic system that uses dioxygen for the hydroxylation of remote primary C−H bonds of functional organics. There appears to be an interesting synergism between the two metals with metallic Pd activating and converting dioxygen to hydrogen peroxide and $CuCl_2$ using the hydrogen peroxide to carry out the hydroxylation of the substrate. The system exhibits several interesting features. First, the reactions are very specific with respect to the degree of oxidation: only hydroxylation is observed and further oxidation to the corresponding aldehyde and carboxylic acid functionality does not occur. Second, the C−C cleavage and overoxidation can be minimized under suitable conditions. While the system represents a significant advance over the currently known procedures,[1] further improvement in regioselectivity (e.g., ω versus ω-1) is clearly needed before the procedure can become practical.

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