Organometallics **2000,** *19,* 4435−4436

Regiospecific and Quantitative Oxidation of Palladium−Carbon Bonds by Hydrogen Peroxide

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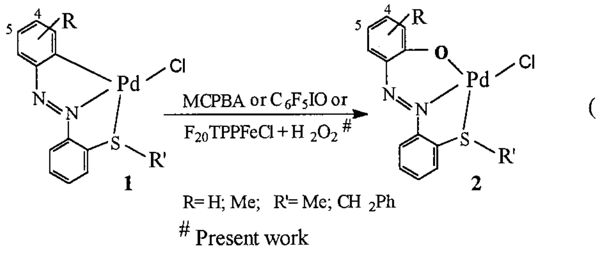
Received June 23, 2000

Summary: Regiospecific oxygenation of a palladium−carbon bond by hydrogen peroxide has been achieved in quantitative yields by using an electronegatively substituted iron(III) porphyrin catalyst.

Activation of C−H bonds that is catalyzed by transition metals has been an important area of intensive investigation for several decades.[1−3] The transformation of a C−H to a C−M bond, selective oxidation of a C−M to a C−OM bond, and then reductive demetalation of this O−M bond finally leads to the functionalization of the C−H to a C−OH bond. In this three-step process, the reaction involving the oxidation of the C−M bond is very important, because it requires a specific reagent and reaction conditions so that other sites susceptible to oxidation remain unaffected. This latter reaction becomes industrially important if such an oxidation is achieved in high yields and by using an environmentally friendly oxidant such as H_2O_2.[3b−d]

Regiospecific oxygenation of a series of C−Pd-bonded azo compounds of type **1** has been achieved by oxidants such as MCPBA and C_6F_5IO (eq 1).[4,5] Selective oxidation of the thioether fragment of **1** has, however, been achieved by an oxoiron(IV) porphyrin cation radical.[6] To achieve wider application of the selective C−Pd bond oxidation, especially toward the industrial and pharmaceutical samples containing multiple functionalities, we were looking for a method where a bio-friendly and cheaper oxidant such as hydrogen peroxide may be used. However, this search has remained unsuccessful for several years in our hands. Herein we wish to present results of our *first success* in achieving the selective and quantitative oxygenation of C−Pd bonds of **1** by H_2O_2 where an iron(III) porphyrin compound has been used as a catalyst.



(1)

R= H; Me; R'= Me; CH 2Ph

Present work

1a : R= 4-Me, R'= Me
1b : R= H R'= Me

2a : R= 4-Me, R'= Me
2b : R= H R'= Me

Hydrogen peroxide alone does not show any observable reactivity with compounds **1** up to 48 h in solvents such as CH_2Cl_2 and CH_3CN; however, in the presence of a suitable iron(III) porphyrin catalyst **1** has been selectively oxidized to **2** under specific reaction conditions. Three catalysts of varying electronegativity, namely *meso*-tetrakis(pentafluorophenyl)porphyrinatoiron(III) chloride (F_{20}TPPFeCl), *meso*-tetrakis(2,6-dichlorophenyl)porphyrinatoiron(III) chloride (Cl_8TPPFeCl), and *meso*-tetrakis(2,4,6-trimethylphenyl)porphyrinatoiron(III) chloride (TMPFeCl), have been used in this study, where compound **1a** has been used for method standardization. All three catalysts were prepared by literature methods.[7]

In this oxidizing system the solvent plays a very important role. Among the various solvent systems studied, 33% methanol in dichloromethane has been found to be the most suitable one where $F_{20}TPPFe^{III}Cl$ was the catalyst.[8] Thus, 99 ± 2% of **2a** was produced from a reaction mixture of **1a** (18.4 mg, 32 mM), H_2O_2 (1 μL, 28.5%, 5.58 mM), and $F_{20}TPPFe^{III}Cl$ (15.6 μM) only when the solvent was $CH_3OH-CH_2Cl_2$ (1:2).[9,10] At the end of this reaction almost 90% of the catalyst was still active. At lower concentrations of **1a** the yields of **2a** were lower and the catalyst decay was also higher. In pure dichloromethane there was no observable reaction, and in solvents of any other composition of CH_3OH in CH_2Cl_2 the yields of **2a** were always lower than that observed from 33% CH_3OH in CH_2Cl_2. In the same solvent system compound **1b** has also been selectively oxidized to **2b** by this oxidizing system. These results are summarized in Table 1.

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(8) The choice of the solvent was guided by the nature of the catalyst. These results will be published elsewhere.

(9) All the yields reported in this study are with respect to the total H_2O_2.

10.1021/om000538d CCC: $19.00

Table 1. $F_{20}TPPFe^{III}Cl$ Catalyzed Oxidation of Compound 1 by H_2O_2

entry	compd (concn (mM))	concn of H_2O_2 (mM)	concn of catalyst (μM)	product (yield (%))[a]	catalyst survival (%)
1	**1a** (06.89)	5.58	14.56	**2a** (17 ± 2)	7 ± 3
2	**1a** (09.00)	5.58	14.41	**2a** (46 ± 2)	10 ± 3
3	**1a** (11.07)	5.58	14.41	**2a** (57 ± 2)	30 ± 5
4	**1a** (21.15)	5.58	14.50	**2a** (67 ± 2)	51 ± 3
5	**1a** (32.00)	5.58	15.60	**2a** (99 ± 2)	88 ± 4
6	**1b** (05.83)	5.58	13.72	**2b** (31 ± 2)	12 ± 2
7	**1b** (15.73)	5.58	13.69	**2b** (98 ± 2)	78 ± 3
8	**1b** (30.49)	5.58	13.69	**2b** (99 ± 2)	7 ± 3

[a] With respect to the total H_2O_2 added. The yields reported are measured spectrophotometrically (see text).

In this oxidizing system, when $Cl_8TPPFe^{III}Cl$ was used as a catalyst, 26−27% of CH_3OH in CH_2Cl_2 has been found to be the best solvent.[8] Thus, from a typical reaction mixture of **1a** (2.58 mg, 4.5 mM), $Cl_8TPPFe^{III}Cl$ (13.8 μM), and H_2O_2 (1 μL, 28.5% 5.58 mM) 25% of **2a** was produced in 2 h.[9] When the initial concentration of **1a** was increased (19.15 mg, 33.34 mM), the yield of **2a** was improved up to 32%. In both cases the maximum yields were from 26 to 27% of CH_3OH in CH_2Cl_2 only. In neat CH_2Cl_2 there was no observable reaction, and in solvents of any other compositions of methanol in dichloromethane, the yields were lower. In this reaction it has been observed that at the end of the reaction the catalyst was completely deactivated. Thus, when an additional batch of oxidant was added to the reaction mixture after 2 h, there was no increase in the yield of **2a**. No other oxidized products of **1a** have also been detected.

In this oxidation reaction when $TMPFe^{III}Cl$ was used as a catalyst, we could not observe any oxidation of **1a**. Thus in a typical reaction when **1a** (2.66 mg, 4.63 mM), $TMPFe^{III}Cl$ (13.46 μM), and H_2O_2 (1 μL, 28.5%, 5.58 mM) were reacted in 20% CH_3OH in CH_2Cl_2 we could not observe any trace of **2a** up to 18 h.[8] The result remained the same even when the experiments were conducted at a higher concentration of **1a** (ca. 36 mM) and in any other solvent ratios of methanol in dichloromethane. In this study no new oxidation product of **1a** has been detected, and **1a** was recovered almost quantitatively.

In these studies we have not been able to detect any product where the thioether functionality of **1a** has been oxidized.[6] We believe that the oxoiron(IV) porphyrin cation radical is generated by the reaction of $F_{20}TPPFeCl$ and H_2O_2 and, in the presence of an excess of H_2O_2, oxoiron(IV) porphyrin cation radical abstracts a hydrogen atom from H_2O_2 and hydroperoxy radical ($HOO^\bullet$) becomes the major reactive species in the present oxidizing system.[11] Selected samples where the yields of **2a** were lower than quantitative were analyzed by HPLC, and appreciable amounts of formic acid have been detected. This acid may have been produced by the competitive oxidation of CH_3OH, especially when the oxidation reaction was carried out at a lower concentration of **1a**.

An efficient method has been developed for selective oxidation of a carbon−palladium bond by H_2O_2 using the most electronegatively substituted iron(III) porphyrin catalyst. This observation is in accord with the known iron(III) porphyrin catalyzed oxidation reaction of alkanes and alkenes by hydroperoxides.[11] Oxidation of palladium−carbon bonds by inorganic and organic peroxides are known, where the total reaction time is 12−24 h, whereas the present oxidizing system oxidizes the palladium−carbon bonds in 1.5 h.[3a] To the best of our knowledge the present method is the first one to selectively and quantitatively oxygenate a C−Pd bond by hydrogen peroxide under mild reaction conditions, which may find its utility in the oxidation of industrial/pharmaceutical compounds containing multiple functionalities. The catalytic oxygenation of palladium−carbon bonds of other organopalladium compounds by hydrogen peroxide is under investigation.

Acknowledgment. We thank the Department of Science and Technology (Project No. SP/S1/F22/97) and the Council of Scientific and Industrial Research (Project No. 01 (1634)/EMR-II), Government of India, for financial assistance.

OM000538D

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(10) In a typical reaction **1a** (18.4 mg, 32 mM) and a small magnetic bar was placed in a small screw-headed vial (5 mL capacity) and the vial was sealed with the screw cap, which had a Sure-seal septum. The vial was filled with argon, and argon-saturated $CH_3OH-CH_2Cl_2$ (1:2) solvent (1.5 mL) was added into the vial through a gastight syringe. A concentrated dichloromethane solution of $F_{20}TPPFe^{III}Cl$ (3−4 μL) was added to the vial such that the final concentration of the catalyst was 15.6 μM. The oxidant hydrogen peroxide (1 μL, 28.5%, 5.58 mM) was added at the end to initiate the reaction. The homogeneous solution was thermostated at 25 ± 1 °C and was stirred magnetically. The formation of **2a** was monitored at 520 nm ($\epsilon = 7752$), by removing and diluting a small aliquot (5−10 μL) of the reaction mixture in CH_2Cl_2 (1.5 mL) in a quartz cell and by recording the spectrum of this solution.[5] The reaction was completed in about 1.5 h, and the yield of **2a**, measured specrophotometrically, was 99 ± 2%.[9] The solvent was evaporated under a stream of dry argon, and the solid mass was purified by column chromatography. Compound **2a** was the only oxidized product obtained from the column. The pure band of **2a** was collected in a round-bottom flask, the solvent was evaporated to dryness under vacuum, and the mass was redissolved in known volume of dichloromethane and the yield of the pure isolated product was measured spectrophotometrically (yield 80 ± 5%). The same reaction was also conducted inside the spectrophotometer cell (2 mm path length), the absorbance at 580 nm ($\epsilon = 1673$) was measured with time, and the rate of production of **2a** was measured by the initial rate method. After the first set of the reaction was over (in 1.5−2.0 h) a second aliquot of the oxidant (1 μL) was added and the rate was measured again. The comparison of the rate data was used to measure the percentage survival of the catalyst.

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