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Metal Coordination-Directed Hydroxylation of Steroids with a Novel Artificial P-450 Catalyst

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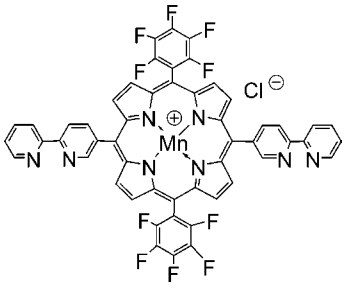
ABSTRACT



A novel catalyst has been synthesized in which a manganese–porphyrin unit is linked to two 2,2′-bipyridyl groups and two pentafluorophenyl groups in *trans* fashion on its four meso positions. Relative to a previous catalyst in which the manganese–porphyrin had four 2,2′-bipyridyl groups, the new catalyst, in the presence of Cu^{2+} ions as coordinating linkers, catalyzes the oxidation of a steroid substrate with much better regioselectivity and higher turnover numbers.

We have described hydroxylation of steroids by mimics of the enzyme cytochrome P-450 class. In our earliest examples, we used metalloporphyrins carrying cyclodextrin groups to bind hydrophobic substrates in water. When the cyclodextrins were linked to *p*-phenylene groups attached to the porphyrin meso positions in catalyst **1**, we saw highly selective hydroxylation at the C-6 α position of a steroid derivative **2** doubly bound into the cyclodextrins (Figure 1).[1] However, there were only about 10 turnovers before the catalyst was itself oxidatively destroyed. When instead the phenylene linkers in the catalyst were replaced by tetrafluorophenylene groups in catalyst **3**, we still saw hydroxylation selectively at C-6 α, but now with 187 turnovers before destruction of the catalyst (Figure 1).[2] That same perfluorinated catalyst was also able to hydroxylate the steroid in the C-9 alpha position when a substrate was hydrophobically bound to three cyclodextrins of the catalyst.[3]

There could be advantages in changing the mode of substrates/catalyst binding. Hydrophobic binding is somewhat ill-defined geometrically, and it is seen only in water solvent. We had used double metal-ion coordination to bind a substrate to a metalloporphyrin and a metallosalen, and had observed good selective epoxidation of the substrate.[4] Thus, we used manganese porphyrin **4** to bind and oxidize substrates, e.g., **5**, in the presence of coordinating metals such as Cu^{2+} ions (Figure 2).[5] However, the oxidation was not selective, with observed formation of six almost evenly distributed products, including **6**. Moreover, the turnover number was only 5, low compared to the 187 turnovers we observed with catalyst **3**.

The poor catalytic performance in this biomimetic study might result from two factors—the intrinsic reactivity and

(1) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535.

(2) (a) Breslow, R.; Gabriele, B.; Yang, J. *Tetrahedron Lett.* **1998**, *39*, 2887. (b) Yang, J.; Breslow, R., *Angew. Chem. Int. Ed.* **2000**, *39*, 2692; (c) Breslow, R.; Fang, Z., *Tetrahedron Lett.* **2002**, *43*, 5197; (d) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057.

(3) Breslow, R.; Yan, J.; Belvedere, S. *Tetrahedron Lett.* **2002**, *43*, 363.

(4) Breslow, R.; Brown, A. B.; McCullough. R. D.; White, P. W. *J. Am. Chem. Soc.* **1989**, *111*, 4517.

(5) Belvedere, S.; Breslow, R. *Bioorg. Chem.* **2001**, *29*, 321.

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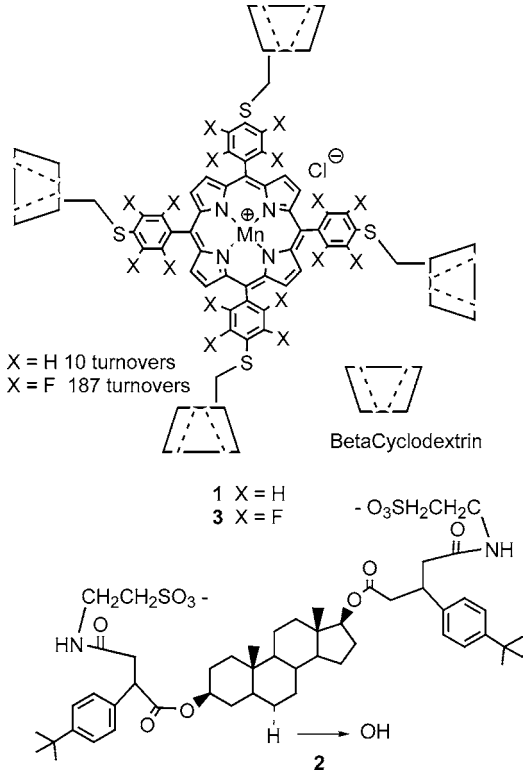


Figure 1. Selective hydroxylation by a catalyst with attached cyclodextrins.

the oxidative stability of catalyst **4** are significantly lower compared with catalyst **3**, and the nitrogen atoms from

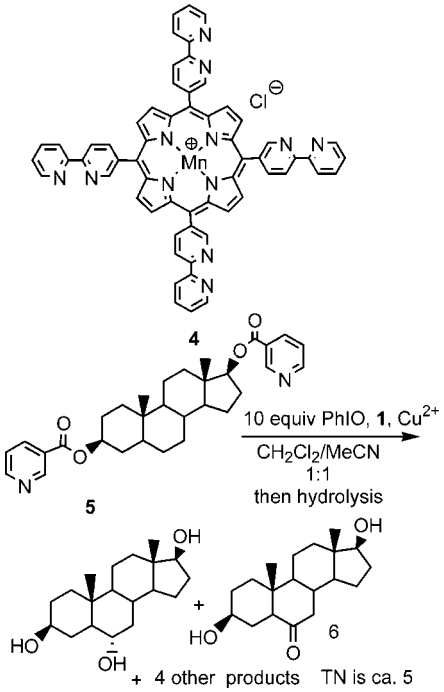


Figure 2. Metal coordination-directed oxidation.

both the manganese porphyrin and the substrate are easily oxidized to *N*-oxides under the hydroxylation conditions.[6] Once *N*-oxides are formed, the nitrogens lose the ability to coordinate to the metal center. Indeed, we isolated an initial undesired substrate oxidation product, the bis *N*-oxide of **5** from the hydroxylation experiments before basic hydrolysis;[7] this was not further hydroxylated under the same conditions.

To avoid the undesired substrate oxidation, we attached different metal ligands to the steroid, two α-phosphonoacetyl groups in substrate **7** (Figure 3).[8,9] When **7** was subjected to

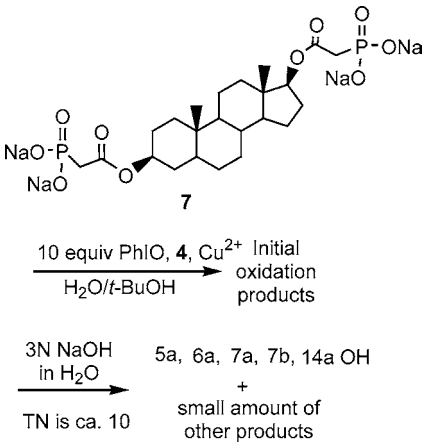


Figure 3. Hydroxylation of substrate **7** with catalyst **4**.

hydroxylation with iodosobenzene and the manganese porphyrin **4** in a mixture of H_2O and *t*-BuOH (1:1), products resulting from hydroxylation on the 5α, 6α, 7α, 7*β*, 12α, and 14α positions were identified by ^{1}H NMR.[10,11] Ten catalytic turnovers were observed.

To further address the poor regioselectivity as well as the low turnover in the metal coordination-directed oxidation, we designed a new catalyst **8** with the introduction of two C_6F_5 groups on its meso positions.

(6) Posakony, J. J.; Pratt, R. C.; Rettig, S. J.; James, B. R.; Skov, K. A. *Can. J. Chem.* **1999**, *77*, 182.

(7) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, 2H, J = 6.0 Hz), 8.37 (d, 2H, J = 6.2 Hz), 7.90 (d, 2H, J = 7.8 Hz), 7.40 (t, 2H, J = 6.5 Hz), 4.97 (m, 1H, C3α-H), 4.86 (t, 1H, J = 7.7 Hz, C17α-H), 0.91 (s, 1H, C19-Me), 0.84(s, 1H, C18-Me). CI-MS: 535.3 $[M + H]^+$.

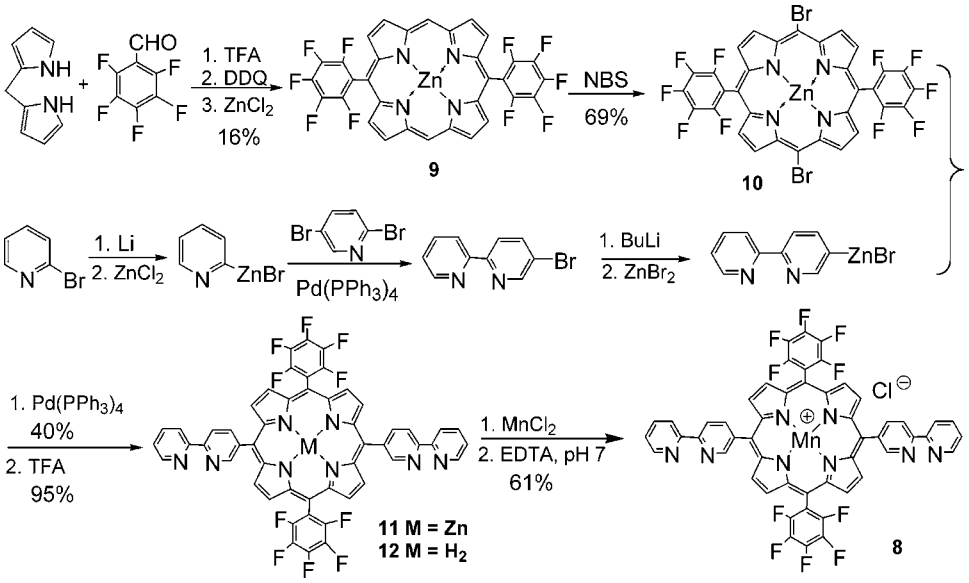
(8) Da Costa, C. P.; Song, B.; Gregan, F.; Sigel, H. *J. Chem. Soc., Dalton Trans.* **2000**, 899.

(9) Compound **7** was synthesized from the commercially available 3*β*,-17*β*-androstanediol and 2-dibenzylphosphonate acetic acid in a three-step procedure. ^{1}H NMR (400 MHz, D_2O): δ = 4.47 (m, 1H, C3α-H), 4.40 (t, J = 8.0 Hz, 1H, C17α-H), 2.55−2.41 (dd, 4H), 0.670 (s, 3H, C19-Me), 0.639 (s, 3H, C18-Me).

(10) The chemical shifts of C19 and C18 angular methyl protons in the identified steroid products ($CDCl_3$, 400 MHz). 3*β*,17*β*-Androstanediol (starting material): δ = 0.819 (C19-Me), 0.732 (C18-Me). 3*β*,5α,17*β*-Androstanetriol: δ = 1.003 (C19-Me), 0.738 (C18-Me), calcd 1.00, 0.73. 3*β*,6α,17*β*-Androstanetriol: δ = 0.833 (C19-Me), 0.738 (C18-Me). Identical to authentic sample; 3*β*,7α,17*β*-androstanetriol: δ = 0.823 (C19-Me), 0.741 (C18-Me); calcd 0.81, 0.74. 3*β*,7*β*,17*β*-Androstanetriol: δ = 0.850 (C19-Me), 0.763 (C18-Me), calcd 0.85, 0.76; 3*β*,14α,17*β*-Androstanetriol: δ = 0.844 (C19-Me), 0.864 (C18-Me), calcd 0.82, 0.85.

(11) Bhacca, N. S.; and Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field*; Holden-Day: San Francisco, 1964; p 21.

Scheme 1



Compared to the previous manganese porphyrin catalyst **4**, the new artificial P-450 catalyst **8** brought the following advantages: (1) The incorporation of two strongly electron-withdrawing pentafluorophenyl groups (C_6F_5) increased the enzyme's reactivity and oxidative stability, and (2) the "*trans*" geometrical relationship between the two bipyridyl ligands eliminates the possibility of undesired *cis*-binding between the artificial P-450 enzyme and the substrate, which may be the cause of some of the side reactions with catalyst **4**.

The synthesis of catalyst **8** was first attempted using either a statistical approach under standard Alder−Longo conditions[12] or an approach developed by Lindsey toward the synthesis of *trans*-A_2B_2-porphyrins prepared by reaction of an aldehyde and a dipyrromethane.[13] However, these two attempts failed. Finally, **8** was successfully synthesized following a Negishi-coupling approach (Scheme 1). The dipyrromethane[14] and the commercially available pentafluorobenzaldehyde were condensed under acid conditions followed by DDQ oxidation to form a porphyrin which was immediately protected as the zinc complex **9**.[15] Then **9** was regioselectively brominated with NBS[16] to give compound **10**,[17] which was coupled with a bipyridyl zinc bromide[18] under Negishi conditions to give zinc porphyrin **11**.[19] This was demetalated with trifluoroacetic acid to give porphyrin **12**,[20] which was then metalated with $MnCl_2$ in air to give catalyst **8**.[21]

As hoped, **8** catalyzed the hydroxylation of substrate **7** very regioselectively (90% of the product) at the 6α position with a significantly improved turnover number of 32 (Figure 4). The significant increase in the turnover number is not surprising, considering the nonoxidizable nature of the *substrate*'s coordination groups. The formation of an *N*-oxide of **8**, along with other oxidative degradations, are probably the major factors that limit the turnover number to 32 in the hydroxylation of **7**.

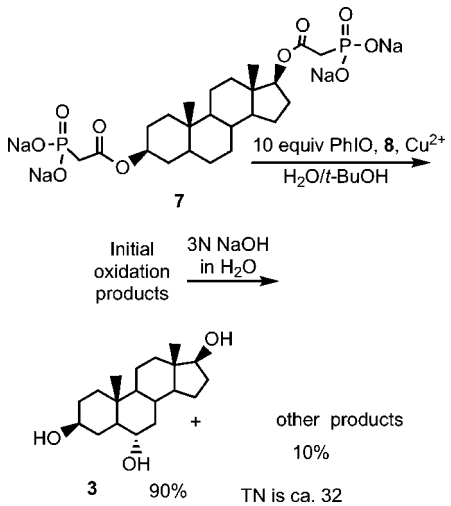


Figure 4. Hydroxylation of substrate **7** with catalyst **8**.

Both the selectivity and turnover number of metal coordination directed steroid hydroxylation are not yet quite as

(12) Alder, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.

(13) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org.* Chem. **2000,** *65*, 7323.

(14) Wang, Q. M.; Bruce, D. W. *Synlett* **1995**, 1267.

(15) ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.51 (s, 2H, meso proton), 9.61 (d, 2H, J = 4.5 Hz), 9.27 (d, 2H, J = 4.5 Hz). CI-MS: 705.7 $[M]^+$.

(16) DiMagno, S. G.; Lin, V.; Therien, M. J. *J. Org. Chem.* **1993,** *58*, 5983.

(17) ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.77 (d, 4H, J = 4.7 Hz), 9.16 (d, 4H, J = 4.7 Hz). CI-MS: 863.0 $[M]^+$.

(18) Simkovsky, N. M.; Erman, M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1847.

(19) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 2H), 9.06 (d, 4H, J = 4.7 Hz), 8.96 (d, 4H, J = 4.7 Hz), 8.87 (m, 4H), 8.70 (m, 4H), 8.00 (m, 2H), 7.51 (m, 2H). FAB-MS: 1013 $[M]^+$.

good as the hydrophobic interaction directed steroid hydroxylation by **3**. However, both the regioselectivity and catalytic turnover in the hydroxylation of steroids are probably good enough for synthetic applications. This system may also be more practical since it will not require a water solvent and substrate water solubility for effective catalyst/substrate binding.

(20) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.50 (s, 2H), 8.99 (d, 4H, J = 4.8 Hz), 8.86 (m, 8H), 8.68 (m, 4H), 7.96 (m, 2H), 7.45 (m, 2H), −2.80 (s, 2H, pyrrole NH). MS (FAB): 951 $[M]^+$. UV−vis (CH_2Cl_2, nm): 376 (Soret), 437, 470, 504, 544.

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Supporting Information Available: Experimental procedures for the syntheses and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) UV−vis (CH_2Cl_2, nm): 331, 435 (Soret), 535, 573.