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TEMPO-linked metalloporphyrins as efficient catalysts for selective oxidation of alcohols and sulfides

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Abstract—Six new TEMPO-linked porphyrins and metalloporphyrins were synthesized and they exhibited efficient catalytic activity for selective oxidation of alcohols and sulfides to the corresponding aldehydes, ketones and sulfoxides using NaOCl as oxidant.

The importance of metalloporphyrins as chemical models of heme-containing enzymes and their use as catalysts for selective and controlled oxidation reactions have prompted extensive studies[1] of their reactions with a variety of oxidants including hydroperoxides,[2] monoperoxysulfate,[3] iodosylbenzene,[4] iodobenzene diacetate,[5] peracids,[6] pyridine *N*-oxide,[7] and hypochlorite.[8] As cytochrome P-450 mimics, simple Fe- or Mn–porphyrin complexes were found to be good catalysts for transferring oxygen atoms from these oxidants with formation of epoxides from alkenes,[2,9] alcohols or ketones from alkanes,[3,5,10] ketones from alcohols,[7a] and sulfoxides from sulfides.[8b,11] On the other hand, stable nitroxyl radicals, such as 2,2,6,6-tetramethyl-piperidyl-1-oxy (TEMPO), have been found to be another kind of efficient oxidation catalysts[12] to oxidize alcohols,[13] diols,[14] sulfides,[15] benzylic ethers,[16] phosphines,[17] naphthols,[17] and amines.[18] Generally, TEMPO oxidation system is similar to metalloporphyrin oxidation system because they are suitable for the same oxidation substrates and/or oxidants. As a part of our works on metalloporphyrin-catalyzed oxidation reactions,[10a] we are interested in the metalloporphyrin catalysts containing a TEMPO moiety. For this reason, we synthesized several TEMPO-attached porphyrins and metalloporphyrins, and investigated their catalytic abilities to selectively oxidize alcohols and sulfides using NaOCl as oxidant. We report herein the results of this effort.

As shown in Scheme 1, porphyrins **3a** and **3b** were synthesized from aromatic aldehydes **1** (1 equiv), **2** (3 equiv) and pyrrole (4 equiv) according to Lindesy method.[19] Porphyrins **3a** and **3b** were hydrolyzed using NaOH to give acids **4a** and **4b**, respectively. Esterification of acids **4** with 4-hydroxyl-TEMPO in the presence of DCC and DMAP afforded the TEMPO-linked porphyrins **5a** and **5b**, which exhibit a three-line peak character of ESR spectra of nitroxyl.[20] TEMPO-linked metalloporphyrins **6** and **7**[20] were obtained by chelating **5** with $FeCl_2$ and $MnCl_2$ according to the published method.[21]

Initially, we evaluated the TEMPO-linked metalloporphyrins for their catalytic activity for epoxidation of styrene using H_2O_2 as oxidant. However, **6** and **7** were found to be unstable to oxidant and bleached within 10 min. Fortunately, we found that the TEMPO-linked porphyrins and metalloporphyrins were stable in NaOCl solution, and they could efficiently catalyze the selective oxidization of alcohols and sulfides using NaOCl as oxidant.

The oxidation of benzyl alcohol to benzaldehyde was used as a model reaction (Table 1). The catalytic oxidation system includes catalyst (1 mol %), KBr (10 mol %) and aqueous NaOCl (l.25 equiv, pH 8.6). The catalysts TEMPO, Mn(TDCPP)Cl,[1a] TEMPO-linked porphyrins **5a** and **5b** as well as TEMPO-linked metalloporphyrins **6a**, **6b**, **7a** and **7b** were examined. We found that in the absence of the catalyst, the yield was rather poor (Table 1, entry 1). Catalysts **5**–**7** (Table 1, entries 4–9) gave higher yields than TEMPO (Table 1, entry 2) and Mn(TDCPP)Cl (Table 1, entry 3). The Mn complexes **7a** and **7b** exhibited better catalytic activity (Table 1, entries 8 and 9) than the corresponding porphyrins **5a** and **5b** (Table 1, entries 4 and 5) and Fe complexes **6a** and **6b**

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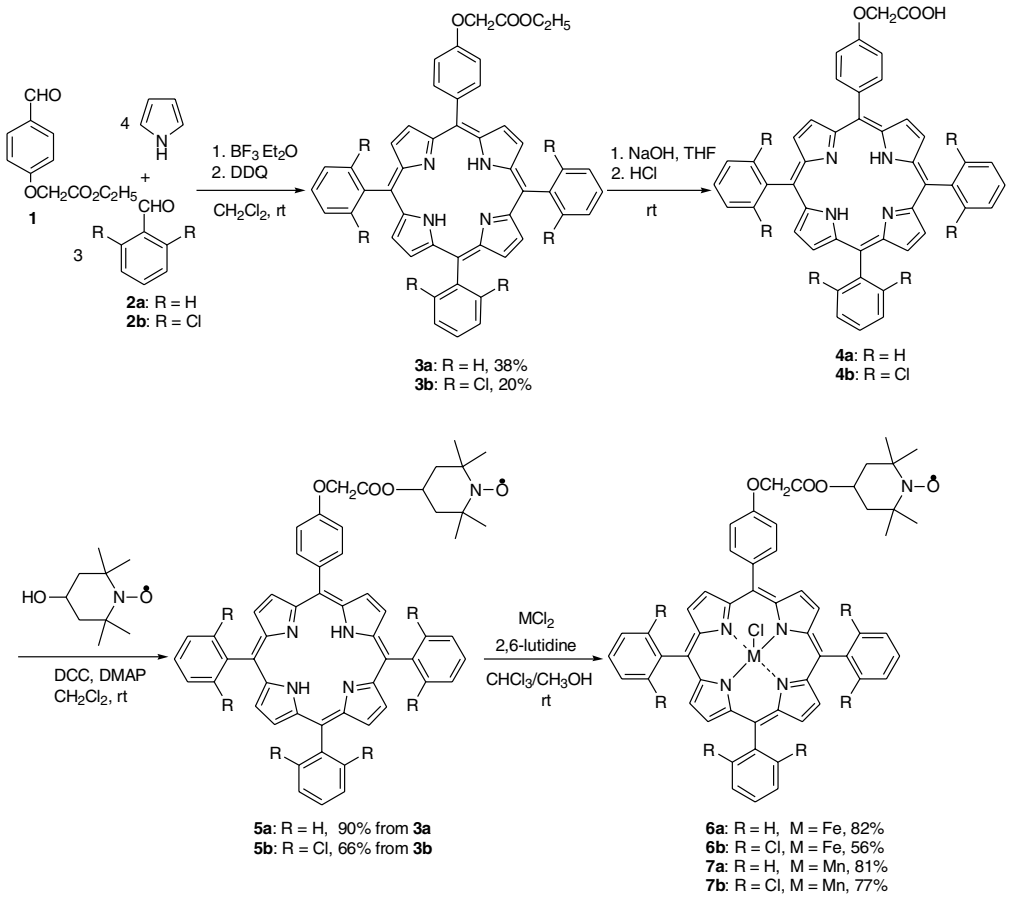
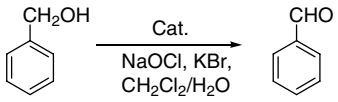


Scheme 1. Synthesis of TEMPO-linked porphyrins and metalloporphyrins.

Table 1. Catalyzed oxidation of benzyl alcohol with NaOCl[a]



Entry	Catalyst	Yield (%)[b]	Bleached time of catalyst (min)
1	None	5	
2	TEMPO	85	>30
3	Mn(TDCPP)Cl	48	>30
4	**5a**	89	>30
5	**5b**	90	>30
6	**6a**	86	>30
7	**6b**	92	>30
8	**7a**	97	>30
9	**7b**	96	>30

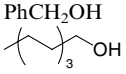
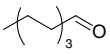
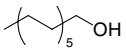
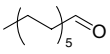
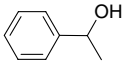
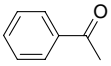
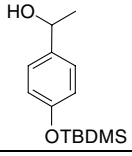
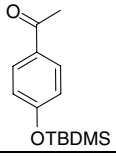
[a] Benzyl alcohol (1 mmol) was oxidized by NaOCl (1.25 mmol, pH 8.6) in the presence of TEMPO (1 mol %), porphyrins (1 mol %) or metalloporphyrins (1 mol %) and KBr (10 mol %) in CH_2Cl_2/H_2O = 1:1 (8 mL) at 0 °C for 30 min.
[b] Isolated yields.

(Table 1, entries 6 and 7). The yields were almost quantitative when Mn complexes **7** were used (Table 1, entries 8 and 9).

The oxidations of various alcohols were investigated using the selected catalyst **7a**.[22] As shown in Table 2, primary alcohols were oxidized to the corresponding aldehydes (Table 2, entries 2–4) and secondary alcohols were oxidized to the corresponding ketones (Table 2, entries 1, 5 and 6). The yields are good to excellent (87–99%). It is noteworthy that the silyl ether protecting group (TBDMS) is stable under the reaction conditions (Table 2, entry 6).

The selective oxidation of sulfide to sulfoxide was also investigated. Glycosyl sulfide phenyl 4,6-*O*-benzylidene-1-*S*-β-D-gluco-pyranoside (**8**), an important synthetic intermediate containing one sulfide and two hydroxyl groups, was used as substrate. The reaction was performed with NaOCl, TEMPO-linked metalloporphyrins (1 mol %), KBr (10 mol %) and Bu_4NBr (5 mol %) in CH_2Cl_2/saturated aq $NaHCO_3$ solution at 0 °C (Table 3). The sulfide **8** was oxidized to sulfoxide **9** with high selectivity even using excess of NaOCl (2.0 equiv) (Table 3, entries 1–4 and 6–8). The Fe complexes **6a** and **6b** gave lower yields due to their instability to oxidant (Table 3, entries 1 and 2), while the Mn complexes **7a** and **7b** afforded the oxidation product **9** in satisfactory yields (Table 3, entries 3 and 4). It is noteworthy that the hydroxyl groups of substrate molecule were not oxidized. In our oxidation system, TEMPO-linked metalloporphyrin **7b** is more efficient than the published metalloporphyrin catalysts Mn(TPP)Cl,[1a] Mn(TDCPP)Cl and TEMPO.

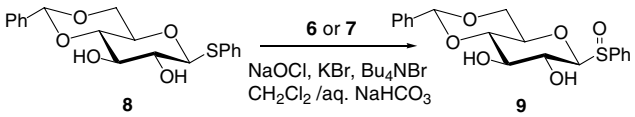
Table 2. **7a**-Catalyzed oxidation of alcohols with NaOCl[a]

Entry	Substrate	Product	Yield (%)
1			96[b]
2	$PhCH_2OH$	PhCHO	97[c]
3			93[b]
4			95[b]
5			99[b]
6			87[c]

[a] Alcohol (1 mmol) was oxidized by NaOCl (1.25 mmol, pH 8.6) in the presence of **7a** (1 mol %) and KBr (10 mol %) in $CH_2Cl_2/H_2O = 1:1$ (8 mL) at 0 °C for 30 min.
[b] Yields were determined by GC analyses based on substrates used.
[c] Isolated yields.

The generality of this protocol was examined by a variety of sulfides using **7b** as catalyst.[23] As shown in Table 4, sulfides were oxidized to the corresponding sulfoxides and no overoxidation to sulfone was observed on the basis of TLC analysis. The yields are excellent (88–96%) and the protective groups and hydroxyl groups remained intact during the reactions (Table 4, entries 8 and 9).

Table 3. Catalyzed oxidation of sulfide **8** with NaOCl[a]



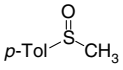
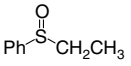
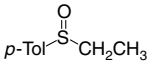
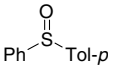
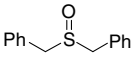
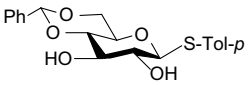
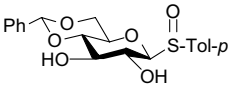
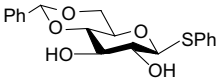
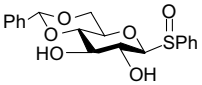
8 **9**

Entry	Catalyst	Yield (%)[b]	Bleached time of catalyst
1	**6a**	50	~20 min
2	**6b**	62	~30 min
3	**7a**	81	>30 min
4	**7b**	86	>30 min
5[c]	**7b**	88	>30 min
6	TEMPO	80	>30 min
7	Mn(TPP)Cl	78	>30 min
8	Mn(TDCPP)Cl	84	>30 min

[a] Compound **8** (0.5 mmol) was oxidized by NaOCl (1 mmol) in the presence of metalloporphyrins (1 mol %), KBr (10 mol %) and Bu_4NBr (5 mol %) in CH_2Cl_2/saturated aq $NaHCO_3 = 1:1$ (10 mL) at 0 °C for 30 min.
[b] Isolated yields.
[c] Using 1.25 equiv NaOCl.

In conclusion, we have synthesized six new TEMPO-linked porphyrins and metalloporphyrins, and found that Mn complexes of TEMPO-linked porphyrins could efficiently catalyze the selective oxidation of alcohols and sulfides using NaOCl as oxidant. Using this procedure, primary alcohols, secondary alcohols and sulfides were oxidized to the corresponding aldehydes, ketones and sulfoxides in high yields with excellent selectivity. This type of catalysts is more efficient in comparison with the conventionally used TEMPO, Mn(TPP)Cl

Table 4. **7b**-Catalyzed oxidation of sulfides with NaOCl[a]

Entry	Substrate	Product	Yield (%)[b]
1	$PhSCH_3$		93
2	*p*-$TolSCH_3$		89
3	PhSEt		95
4	*p*-$TolSCH_2CH_3$		92
5	PhSPh		96
6	PhSTol-*p*		95
7	$PhCH_2SCH_2Ph$		94
8			91
9			88

[a] Different sulfide (1 mmol) was oxidized by NaOCl (1.25 mmol, pH 8.6) in the presence of **7b** (1 mol %), KBr (10 mol %) and Bu_4NBr (5 mol %) in CH_2Cl_2/saturated aq $NaHCO_3 = 1:1$ (10 mL) at 0 °C for 30 min.
[b] Isolated yields.

and Mn(TDCPP)Cl, especially for the oxidation of alcohols.

Acknowledgements

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20. Spectral data for selected compounds. Compound **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: −2.77 (s, 2H), 1.41 (t, $J = 7.2$ Hz, 3H), 4.41 (dd, $J = 7.2$ Hz, 14.2 Hz, 2H), 4.91 (s, 2H), 7.3 (d, $J = 8.3$ Hz, 2H), 7.73–7.77 (m, 9H), 8.13 (dd, $J = 2.2$ Hz, 8.3 Hz, 2H), 8.21 (d, $J = 5.1$ Hz, 6H), 8.85 (s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.5, 61.8, 66.0, 113.2, 119.8, 120.4, 126.9, 127.9, 134.8, 135.8, 142.4, 158.0, 169.3; MS (ESI) m/z: 717.1 ($[M+H]^+$). Compound **3b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: −2.62 (s, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 4.39 (dd, $J = 7.1$ Hz, 14.2 Hz, 2H), 4.90 (s, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.67–7.69 (m, 3H), 7.77 (d, $J = 7.9$ Hz, 6H), 8.12 (d, $J = 8.5$ Hz, 2H), 8.65 (d, $J = 7.6$ Hz, 6H), 8.85 (d, $J = 4.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.4, 61.7, 65.9, 113.1, 113.4, 114.3, 120.8, 127.8, 127.9, 130.6, 135.2, 135.6, 138.8, 138.9, 139.5, 139.8, 157.9, 169.1; MS (ESI) m/z: 923 ($[M+H]^+$). Compound **4a**: MS (ESI) m/z: 689 ($[M+H]^+$). Compound **4b**: MS (ESI) m/z: 895 ($[M+H]^+$). Compound **5a**: HMRS (ESI): Calcd for $C_{55}H_{49}N_5O_4$ ($[M+H]^+$) 843.3784, found 843.3776; ESR (1×10^{-4} mol L^{-1} in $CHCl_3$): 3 lines, $g_0 = 2.0059$, $A_N = 15.9$ Gs. Compound **5b**: HMRS (ESI): Calcd for $C_{55}H_{43}Cl_6N_5O_4$ ($[M+H]^+$) 1047.1446, Found 1047.1452. Compound **6a**: MS (ESI) m/z: 896.1 ($[M-Cl]^+$). Compound **6b**: MS (ESI) m/z: 1102.1 ($[M-Cl]^+$). Compound **7a**: MS (ESI) m/z: 895 ($[M-Cl]^+$). Compound **7b**: MS (ESI) m/z: 1101 ($[M-Cl]^+$).
21. Borovkov, V. V.; Lintuluoto, J. M.; Inoue, Y. *Synlett* **1999**, 61–62.
22. General procedure for the catalytic oxidation of alcohols to carbonyl derivatives. To a solution of alcohols (1 mmol) in CH_2Cl_2 (3 mL) was added the catalyst (1 mol %), KBr (10 mol %) and saturated $NaHCO_3$ solution (2 mL). 0.35 M NaOCl solution (2.86 mL, pH 8.6) was added at 0 °C and the mixture well stirred at the same temperature for 30 min. The organic phase was separated, dried over Na_2SO_4, and analyzed by GC or evaporated and then purified by column chromatography on silica gel.
23. General procedure for the catalytic oxidation of sulfides to sulfoxides. To a solution of sulfides (1 mmol) in CH_2Cl_2 (3 mL) was added the catalyst (1 mol %), Bu_4NBr (5 mol %), KBr (10 mol %) and saturated aq $NaHCO_3$ solution (2 mL). The mixture was cooled to 0 °C and then 0.73 M NaOCl in saturated $NaHCO_3$ solution (0.92 mL, 1.25 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min, and then the layers were separated. The aqueous phase was extracts with CH_2Cl_2 (3×3 mL) and the combined organic extracts were washed with water, brine and dried (Na_2SO_4). The products were purified by chromatography on silica gel. Compound **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.96 (s, 1H), 3.41–3.42 (m, 1H), 3.64 (t, $J = 9.4$ Hz, 1H), 3.75 (t, $J = 10.3$ Hz, 1H), 3.87 (t, $J = 9.6$ Hz, 1H), 4.17 (d, $J = 9.4$ Hz, 1H), 4.24–4.28 (m, 2H), 4.31 (s, 1H), 5.55 (s, 1H), 7.35–7.37 (m, 3H), 7.46–4.47 (m, 2H), 7.57–7.58 (m, 3H), 7.70–7.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 68.3$, 71.0, 73.4, 74.4, 79.7, 93.8, 102.2, 124.8, 126.5, 128.6, 129.5, 129.6, 132.3, 136.9, 141.6; MS (ESI) m/z: 399 ($[M+Na]^+$), 775 ($[2M+Na]^+$).