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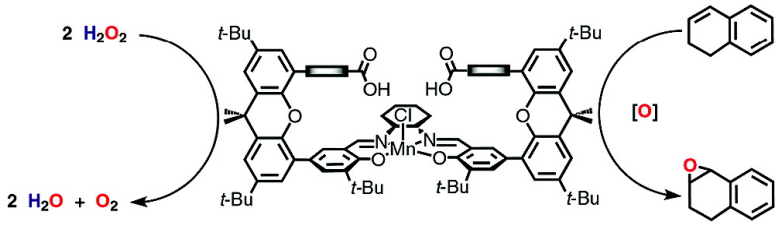

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Catalase and Epoxidation Activity of Manganese Salen Complexes Bearing Two Xanthene Scaffolds

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Abstract: A series of manganese Hangman salen ligand platforms functionalized by *tert*-butyl groups in the 3 and 3′ positions using the Suzuki cross-coupling methodology are presented. The Hangman platforms support multielectron chemistry mediated by proton-coupled electron transfer (PCET), as demonstrated by their ability to promote the catalytic disproportionation of hydrogen peroxide to oxygen and water via a high-valent metal oxo. The addition of the steric groups to the salen macrocycle leads to enhanced catalase activity by circumventing side reactions that sequester the catalyst off pathway. The stereochemistry imposed by the cyclohexanediamine backbone of the salen platform is revealed by the epoxidation of 1,2-dihydronapthalene by a variety of oxidants. Improved enantiomeric excess and catalase activity as compared to sterically unmodified counterparts establishes the efficacy of the *tert*-butyl groups in promoting PCET catalysis on the Hangman platform.

Introduction

Metallocofactors of proteins and enzymes are the sites of confluence for coupling the protons and electrons needed for the activation of small molecule substrates.[1,2] We have captured the proton-coupled electron transfer (PCET) reactivity of metallocofactors by designing "Hangman" constructs.[3−7] In the Hangman architecture, the proton-transfer function of the secondary coordination sphere of the enzyme is assumed by an acid−base functional group that is suspended over the face of a redox-active macrocycle, which serves as the site for both the redox and substrate binding functions.[8−10] We previously reported the synthesis of a series of Hangman salen ligands that incorporated two functionalized xanthene scaffolds and a chiral cyclohexanediamine backbone in the macrocyclic ring.[7] Compared to the redox-only salen complex, the Hangman salen complexes, HSX* and H_{ph}SX*, (Chart 1) catalytically enhance the dismutation of hydrogen peroxide

$$2\ H_2O_2 \xrightarrow{\text{catalase}} 2\ H_2O + O_2 \qquad (1)$$

by at least an order of magnitude.[7] The increased catalase activity by the Hangman salens is particularly compelling in view of the efficacy of manganese salen complexes as therapeutic agents of reactive oxygen species (ROS) in biological systems.[11] The removal of cytotoxic amounts of hydrogen peroxide in animals[12−16] and human tissue[17] by manganese bis(3-methoxysalicylidene)-1,2-ethylenediamine chloride (EUK-134) and manganese bis(salicylidene)-1,2-ethylenediamine chloride (EUK-8) has prompted structure−reactivity[11,18] and computational[19,20] investigations aimed at elucidating key intermediates in the catalytic cycle. To this end, the ability to control catalase reactivity with the hanging group of Hangman salens establishes this platform as an ideal venue in which to define the structural and electronic properties of salen complexes that are critical to enhanced ROS activity. We now show that the superior catalase activity of Hangman salen complexes is

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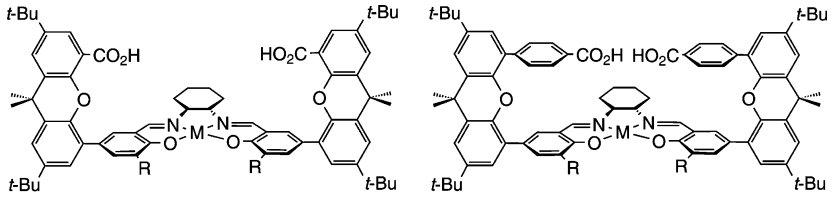
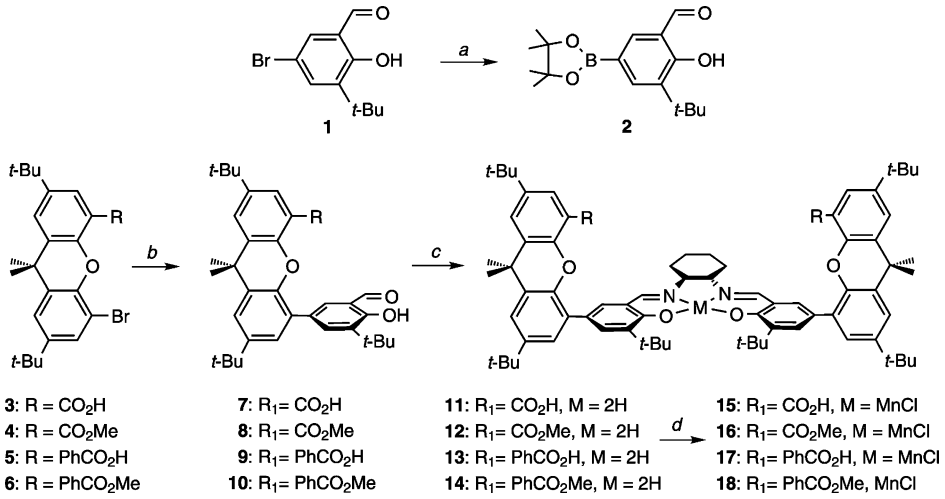
Chart 1



Scheme 1



augmented by structurally imposing a bulky *tert*-butyl group ortho to the phenol (HSX*-^{t}Bu and H_{ph}SX*-^{t}Bu in Chart 1). The initial step of catalase reactivity involves the PCET activation of the O−O bond of hydrogen peroxide within the Hangman cleft by heterolysis to produce the high-valent metal oxo species,[21] which reacts with a second molecule of hydrogen peroxide to complete the dismutation reaction. Kinetically stable intermediates that are deleterious to dismutation are averted by the presence of the bulky *tert*-butyl groups. Moreover, we show that this structural modification is general to enhanced enantioselective reactivity of the high-valent manganese oxo. Because the ligand also incorporates a chiral cyclohexanediamine bridge, which has proven to be extremely effective in the transfer of chiral information in oxygen atom transfer chemistry,[22] the Hangman salens are capable of converting olefins to epoxides enantoselectively. Improved enantiomeric excess of the epoxide products for the manganese HSX*-^{t}Bu and H_{ph}SX*-^{t}Bu catalysts as compared to their unmodified manganese HSX* and H_{ph}-SX* congeners establishes the benefits of a sterically circumscribed Hangman salen platform for the PCET activation of small molecule substrates.

Results and Discussion

The synthesis of the Hangman family of salens substituted with *tert*-butyl groups in the 3 and 3′ positions is presented in Scheme 1. Ligand construction begins with the commercially available 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene. One of the bromides can be selectively functionalized to the carboxylic acid with 1 equiv of phenyllithium, followed by treatment with carbon dioxide and an acidic workup to furnish **3**.[5] Methyl ester **4** is obtained smoothly by using a catalytic amount of sulfuric acid in methanol.[5] Incorporation of the phenylene spacer between the xanthene scaffold and carboxylic acid requires the stepwise functionalization of the xanthene to deliver the benzoic acid methyl ester **6**,[6] which can be deprotected with sodium hydroxide to give the corresponding acid **5**.[7] The acid- and ester-functionalized xanthene spacers **3**−**6** retain a bromo group, which serves as the site for addition of the boronic ester derivative of 3-*tert*-butylsalicylaldehyde (**2**) using Suzuki cross-coupling methodology.[23] Synthesis of the boronic ester **2** required a two-step procedure. First, the commercially available 3-*tert*-butyl-2-hydroxybenzaldehyde was functionalized with a bromo group in the 5 position as described in the literature.[24] The bromo was then replaced with a boronic ester functionality by palladium-catalyzed cross-coupling methods[25] to give **2**. Synthon **2** serves as a good nucleophilic substrate for the conversion of xanthene precursors **3**−**6** to **7**−**10**, respectively.[26] Hangman ligands **11**−**14** are provided by the condensation of **7**−**10** with 0.5 equiv of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane. The amount of product depends critically on the stoichiometry of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane. If more than 0.5 equiv is used, varying amounts of product with an incompletely formed macrocycle are obtained; only one imine forms to make an −(ONN)− tridentate ligand impurity. This

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Table 1. Observed TON and Initial Rate Constant (k_{init}) for H_2O_2 Disproportionation by Manganese Hangman Catalysts[a]

catalyst	TON	k_{init} (M^{-1} s^{-1})
Mn(HSX*-COOH)Cl	1574[b]	6
Mn(HSX*-^{t}Bu-COOH)Cl (**15**)	5328	14
Mn(H_{ph}SX*-COOH)Cl	792[b]	5
Mn(H_{ph}SX*-^{t}Bu-COOH)Cl (**17**)	2495	10
Mn(HSX*-^{t}Bu-COOMe)Cl (**16**)	59	
Mn(H_{ph}SX*-^{t}Bu-COOMe)Cl (**18**)	1207	
Mn(salen)Cl[c]	164	
Mn(salen)Cl[c,d]	182	

[a] In 2:1 dichloromethane/methanol at 25 °C. [b] Data taken from ref 9. [c] salen = (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]. [d] Two equivalents of benzoic acid.

unintended product can be identified by ^{1}H NMR and mass spectrometry; spectra for the incomplete macrocycle resulting from the condensation reaction to produce **13** can be found in Figures S1.1 and S1.2. When 0.5 equiv of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane is employed, ^{1}H NMR integrations of **11**−**14** establish the presence of one cyclohexanediamine per two xanthene scaffolds.

Manganese acetate serves as an efficient metalation agent of **11**−**14**. The oxidized Mn(III) products **15**−**19** are obtained when the metalation is performed in air followed by a workup in aqueous sodium chloride. Computations on the analogous compounds lacking the *tert*-butyl groups suggest that the carboxylic acids on the Hangman ligand (**17**) can easily span the face of the macrocycle to form a carboxylic acid dimer.[7] Solid state infrared spectra of **17** are congruent with this finding; a doublet at $\nu = 1285$ and 1272 cm^{-1} is indicative of the C−O stretching band in carboxylic acid dimers.[27] The band is not seen in the spectra of the methyl ester analogue (**18**).

Hangman complexes **15**−**18** were examined for their catalytic activity. Table 1 shows the turnover numbers (TON) for hydrogen peroxide dismutation by the Hangman systems over the course of 1 h. These results are compared to two control system: a manganese salen lacking a xanthene scaffold but with the *tert*-butyl groups in the 3 and 3′ positions and a Hangman platform in which the proton is absent from the hanging group (achieved by the replacement of the acid by a methyl ester). The unsubstituted control, [1,2-cyclohexanediamino-*N*,*N*'-bis-(3,5-di-*tert*-butylsalicylidene)] manganese chloride, demonstrates negligible TONs, even with the addition of 2 equiv of benzoic acid to serve as an intermolecular proton source. Conversely, Hangman platforms show high TONs, but only if a proton is present on the hanging group; **15** exhibits TONs that are appreciably higher than **16**, where the acid functionality has been replaced by an ester. The activity of **17**, with the acid extended from the xanthene with a phenylene group, also demonstrates increased activity with respect to its methyl ester analogue **18**, albeit to a lesser extent. We note that the activity of **18** (Figure S2.1 in the Supporting Information) is complicated by ester hydrolysis. Oxygen evolution is initially slow and ceases completely within 15 min of hydrogen peroxide addition. At this point, a marked increased in activity is observed and TONs are obtained that are higher than expected from the initial rate. Mass spectrometry of Mn-containing species obtained from quenched reaction mixtures (∼20 min) reveals the presence of manganese salen complexes with the methyl ester deprotected (Figure S2.2). Deprotection of methyl esters to give the acid derivative with hydrogen peroxide is possible owing to the high pK_a of the conjugate acid. Moreover, it has been shown that HOO^- can nucleophilically cleave the methyl ester in some cases.[28]

The effect of substitution at the 3 and 3′ positions is revealed by comparison of the activity of **15** and **17** to Mn(HSX*-COOH)Cl and Mn(H_{ph}SX*-COOH)Cl, respectively. An approximately 3-fold increase in the catalase activity is observed upon substitution of the *tert*-butyl groups. The overall TONs are closely tied with the reaction rates in the first 2 min of the reaction. The initial rate constants (k_{init}) for H_2O_2 consumption by the four acid-functionalized manganese Hangman complexes are listed in Table 1. **15** and **17** display k_{init} values that are roughly double that of their respective unsubstituted congeners. Though the reactions are run under biphasic conditions with methanol serving as a phase transfer reagent between dichloromethane/catalyst solution and the aqueous hydrogen peroxide phase, reaction rates and TON are not limited by the biphasic nature of the reaction. Dissolution of the more soluble **15** in tetrahydrofuran and methanol yields a homogeneous reaction mixture. Addition of the aqueous hydrogen peroxide to this solution results in TONs that are commensurate to those obtained under the biphasic conditions (see Figure S3).

Experimental[21] and theoretical[19,20] studies have led to the proposal that the catalase reaction at Mn salens proceeds by the cycle shown in Scheme 2. Oxidation of the metal by hydrogen peroxide forms a high-valent manganyl oxo and water. Evidence for the oxo is provided by stopped flow studies; spectra consistent with an oxo intermediate are obtained when the catalytic cycle is arrested by the replacement of hydrogen peroxide by aryl peroxide.[21] Whereas a proton transfer to the coordinated aryl peroxide is necessary to promote cleavage of the O−O bond to form the Mn(V) oxo, this step does not show rate-determining kinetics. Alternatively, oxidation of the second equivalent of peroxide appears to be rate-determining.[20,21] A detailed theoretical study on this step has concluded that the orientation of the second hydrogen peroxide to the Mn(V) oxo center is critical to catalysis.[20] An end-on approach leads to substrate oxidation in a one-step, low activation energy process. Alternatively, the side-on approach was computed to form an intermediate (depicted as B in Scheme 2), which is stabilized by hydrogen bond formation with a ligand oxygen. Propagation of the side-on intermediate requires several high-energy steps, making it an "energetic trap"; this trap is avoided by an end-on approach.[20] The temporary deactivation of the catalyst from the formation of intermediate B limits overall catalase efficiency. It is at this step that the hanging acid−base group of the Hangman platform is manifest to increased catalase activity. The Hangman construct can maintain the catalyst on cycle by promoting the end-on assembly of H_2O_2 via a hydrogen-bonding network (intermediate A in Scheme 2). Geometry-optimized calculations on the manganese Hangman salens[7] support the contention that the carboxylic acid in both the acid and benzoic acid-functionalized xanthenes is sufficiently proximate to the metal center to hydrogen bond with a ligated hydroperoxide. The presence of the large *tert*-butyl groups at the 3 and 3′

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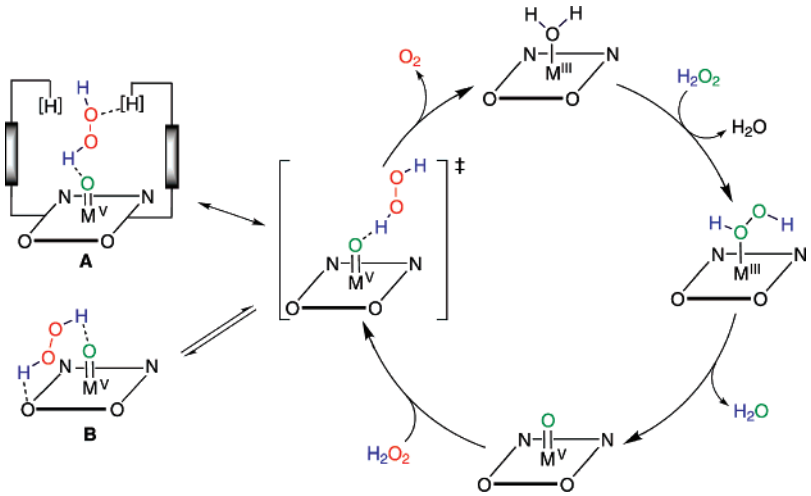
Scheme 2



positions provides a further bias for intermediate A vs intermediate B by preventing hydrogen peroxide approach to the Mn(V) oxo near the phenolic oxygens.[20] We believe that it is the confluence of the hydrogen-bonding scaffold of the Hangman platform and the steric blocking groups in the 3 and 3′ positions of **15** and **17** that keeps the system on cycle and leads to the enhanced rates and TONs for catalase activity.

The Mn(V) oxo generated in the catalase cycle is believed to be the enantioselective oxidant in manganese salen epoxidation reactions.[29] This manganyl oxo is formed by the activation of the O−X bond of various oxidants.[30] Computational[31] studies performed on the O−O bond cleavage of acylperoxo manganese salen complexes in acidic and neutral media identify the proton as a means to promote O−O bond heterolysis and prevent O−O bond homolysis to produce the less reactive Mn(IV) oxo. Such acid−base-induced bond activation chemistry, classically known as the "pull effect" in heme oxidations,[32−37] is responsible for the enhanced olefin epoxidation observed in Hangman porphyrin complexes.[5] Similar oxygen atom transfer chemistry has been observed for doubly strapped Hangman salen complexes. However, in the absence of 3 and 3′ substitution, these oxidations proceed with small enantiomeric excess (ee).[7]

To investigate whether the presence of the acid Hangman moiety in conjunction with 3 and 3′ substitution leads to an increase in yield of enantiomeric oxidation products, a comparative study was undertaken of the epoxidation of the prochiral olefin, 1,2-dihydronapthalene by **15** and **17** versus the unsubstituted Hangman salens, Mn(HSX*-COOH)Cl and Mn(H_{ph}-SX*-^{t}Bu-COOH)Cl, and the non-Hangman catalyst (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)]manganese(III) chloride (Jacobsen's catalyst[22]). Table 2 lists the TONs measured by GC/MS for the various catalysts and oxidants. In view of the foregoing catalase studies, hydrogen peroxide is limited in its utility as an oxidant owing to its proclivity to disproportionate.[38,39] Hence, low TONs are observed for H_2O_2 as an oxidant even when dilute hydrogen peroxide was added by a syringe pump to high concentrations of substrate. Conversely, the more commonly used oxidants, sodium hypochlorite (NaOCl) under biphasic reaction conditions of dichloromethane and water, and iodosobenzene (PhIO) in dichloromethane, result in higher TONs that are commensurate with the unmodified platform. Both acid-functionalized Hangman complexes **15** and **17** give products with 53% ee. By comparison, the analogous Hangman compounds lacking the *tert*-butyl groups in the 3 and 3′ positions on the macrocycle yield epoxidized product at 23% ee.[7] Steric functionalities at the 3 and 3′ positions on the salicylide have been shown to be a critical element for good enantioselectivity by maximizing stereochemical communication between the manganyl oxo and substrate.[22,40] As with the unmodified Mn salen catalysts, the Hangman systems gain a considerable boost to the enantioselectivity when the salen macrocycle is substituted with steric-directing *tert*-butyl groups.

In summary, the activity of the oxo catalyst of Mn salens is enhanced by the positioning of an acid−base group over the salen that is modified with steric blocking groups at the 3 and 3′ positions of the macrocycle. These design principles are general for the oxidation catalysis of Mn salens, as demonstrated by the variant oxidation chemistry of catalase-like oxygen evolution and mono-oxygenase epoxidation. For catalase conversion, the hydrogen-bonding network established by the Hangman scaffold and the steric blocking groups work in concert to promote the end-on assembly of the second equivalent of the hydrogen peroxide in conformation that is productive for its subsequent oxidation by the manganyl oxo. Similarly, the *tert*-butyl groups on the macrocycle confer the chirality of the diamine backbone of the macrocycle to substrate. These design principles should find utility for the construction of

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Table 2. TON for Epoxidation of 1,2-Dihydronapthalene in Dichloromethane

		catalyst		
oxidant	*t* (h)	Mn(salen)Cl[a]	Mn(HSX*-^{t}Bu)Cl (**15**)	Mn(H_{ph}SX*-^{t}Bu)Cl (**17**)
NaOCl	3	21	12	29
NaOCl	24	76	59	69
PhIO	3	22	28	25
PhIO	24	89	79	85
PhIO[b]	3	24	31	25
PhIO[b]	24	80	75	85
H_2O_2	4	3	2	2
H_2O_2[b]	4	6	9	4

[a] salen = (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]. [b] With 1 equiv of *N*-methylimidazole.

general Mn salen catalysts displaying enhanced ROS and organic substrate oxidation activity.

Experimental Methods

Materials. Silica gel 60 (70−230 and 230−400 mesh) was used for column chromatography. Analytical thin layer chromatography was performed using F254 silica gel (precoated sheets, 0.2-mm thick). Solvents for synthesis were reagent grade or better and used as received or dried according to standard methods.[41] 3-*tert*-Butyl-2-hydroxybenzaldehyde, potassium acetate, (1*R*,2*R*)-(−)-1,2-diaminocyclohexane, 1,2-dihydronapthalene, and dodecane (Aldrich), bis(pinacolato)diboron (Frontier Scientific), bis(tricyclohexylphosphine)palladium(0), tetrakis(triphenylphosphine)palladium(0), sodium carbonate, manganese(II) acetate tetrahydrate, and (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]manganese(III) chloride (Strem Chemicals), 30% aqueous solution of hydrogen peroxide (Alfa Aesar), and iodosobenzene (TCI America) were used as received. The following compounds were obtained using published protocols and their purity was confirmed by ^{1}H NMR: 5-bromo-3-*tert*-butylsalicylaldehyde (**1**),[42] 4-hydroxycarbonyl-5-bromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene (**3**),[5] 4-methoxycarbonyl-5-bromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene (**4**),[5] 4-(5-bromo-2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthen-4-yl)-benzoic acid (**5**),[7] and 4-(5-bromo-2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthen-4-yl)-benzoic acid methyl ester (**6**).[6]

Physical Measurements. ^{1}H NMR spectra were recorded on $CDCl_3$ (Cambridge Isotope Laboratories) solvents at 25 °C on an Inova 500 spectrometer housed in the MIT Department of Chemistry Instrumentation Facility (DCIF). All chemical shifts are reported using the standard δ notation in parts-per-million relative to tetramethylsilane, and spectra have been internally calibrated to the monoprotio impurity of the deuterated solvent used. High-resolution mass spectral analyses were carried out by the MIT DCIF on a Bruker APEXIV47e.FT-ICR-MS using an Apollo ESI source.

3-*tert*-Butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (2). Under nitrogen, a mixture of 5-bromo-3-*tert*-butylsalicylaldehyde (**1**) (1.00 g, 3.89 mmol), bis(pinacolato)diboron (1.087 g, 4.28 mmol), potassium acetate (0.572 g, 5.83 mmol), and bis(tricyclohexylphosphine)palladium(0) (0.130 g, 0.194 mmol) was combined with 24 mL of dry dioxane and heated to 85 °C for 36 h. Upon cooling, 20 mL of water was added and the mixture was extracted with 4 × 50 mL of benzene. The organic portions were combined and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, 7:3 hexane/dichloromethane) to give the desired product (0.715 g, 60.4%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 12.00 (s, 1H), 9.90 (s, 1H), 7.93 (s, 1H), 7.91 (s, 1H), 1.43 (s, 9H), 1.35 (s, 12H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 197.72, 163.81, 140.21, 140.18, 137.62, 120.61, 84.15, 35.04, 30.40, 29.44, 25.08. HRESI-MS ([M + H]$^+$) calcd for $C_{17}H_{26}BO_4$ *m/z*, 305.1933, found 305.1922.

2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthene-4-carboxylic Acid (7). Under nitrogen, 4-hydroxycarbonyl-5-bromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene (**3**) (0.400 g, 0.898 mmol), 3-*tert*-butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-benzaldehyde (**2**) (0.300 g, 0.988 mmol), sodium carbonate (0.139 g, 1.35 mmol), and tetrakis(triphenylphosphine)-palladium(0) (0.062 g, 0.053 mmol) were combined with 18 mL of DMF and 2 mL of deionized water, and the mixture was heated to 90 °C for 36 h. Upon cooling, 30 mL of dichloromethane was added and the solution was washed with 10 mL of water. The aqueous layer was then extracted with 2 × 10 mL of dichloromethane, and the combined organic portions were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, 3:7 diethyl ether/pentane) to give the desired product (0.265 g, 54%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.92 (s, 1H), 9.95 (s, 1H), 8.06 (d, J = 2 Hz, 1H), 7.71 (d, J = 2 Hz, 1H), 7.63 (d, J = 2 Hz, 1H), 7.57 (d, J = 2 Hz, 1H), 7.51 (d, J = 2 Hz, 1H), 7.24 (d, J = 2 Hz, 1H), 1.76 (s, 6H), 1.48 (s, 9H), 1.40 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 197.29, 165.26, 161.25, 148.08, 147.57, 146.93, 144.52, 139.44, 135.25, 132.60, 131.19, 130.14, 129.00, 128.73, 128.54, 128.33, 126.68, 122.34, 120.88, 116.29, 35.32, 35.16, 34.91, 32.11, 31.72, 31.52, 29.32. HRESI-MS ([M + H]$^+$) calcd for $C_{35}H_{43}O_5$ *m/z*, 543.3105, found 534.3109.

2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthene-4-carboxylic Acid Methyl Ester (8). Under nitrogen, 4-methoxycarbonyl-5-bromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene (**4**) (0.100 g, 0.218 mmol), 3-*tert*-butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (**2**) (0.073 g, 0.239 mmol), sodium carbonate (0.034 g, 0.327 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.013 mmol) were added to 9 mL of DMF and 1 mL of deionized water. The mixture was heated to 90 °C for 24 h. Upon cooling, 10 mL of deionized water was added, and the solution was extracted with 3 × 20 mL of dichloromethane. The combined organic portions were washed with 10 mL of deionized water and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, 1:9 diethyl ether/pentane) to give the desired product (0.084 g, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.87 (s, 1H), 10.03 (s, 1H), 7.78 (d, J = 2.5 Hz, 1H), 7.68 (d, J = 2.5 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 3.46 (s, 3H), 1.71 (s, 9H), 1.49 (s, 9H), 1.38 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 198.41, 198.12, 167.24, 160.40, 147.40, 146.11, 145.31, 145.28, 137.72, 136.22, 134.02, 130.92, 129.98, 129.46, 128.44, 126.50, 126.16, 125.81, 121.99, 120.30, 120.28, 119.65, 52.04, 35.14, 35.08, 34.78, 34.72, 32.47, 31.75, 31.58, 29.45. HRESI-MS ([M + Na]$^+$) calcd for $C_{36}H_{44}NaO_5$ *m/z*, 579.2903, found 579.2911.

4-[2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthen-4-yl]-benzoic Acid (9). Under nitrogen, 4-(5-bromo-2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthen-4-yl)-benzoic acid (**5**) (0.312 g, 0.598 mmol), 3-*tert*-butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (**2**) (0.200 g, 0.657 mmol), sodium carbonate (0.092 g, 0.897 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.041 g, 0.036 mmol) were added to 18 mL of DMF and 2 mL of deionized water. The mixture was heated to 90 °C for 36 h. Upon cooling, 30 mL of dichloromethane was added, and the solution was washed with 10 mL of water. The aqueous layer was then extracted with 2 × 15 mL of dichloromethane, and the combined organic portions were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, 2:8 ethyl acetate/pentane) to give the desired product (0.273 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.72 (s, 1H), 9.36 (s, 1H), 7.80 (d, J = 8 Hz, 2H), 7.50 (m, 2H), 7.48 (d, J = 2 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 7.22 (J = 2 Hz, 1H), 7.20

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(m, 2H), 1.78 (s, 6H), 1.45 (s, 9H), 1.40 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 196.78, 170.83, 160.39, 145.95, 145.89, 145.78, 145.72, 143.74, 138.02, 135.02, 135.33, 133.63, 130.69, 130.38, 129.75, 129.62, 128.90, 128.69, 128.20, 127.69, 125.59, 122.75, 121.90, 120.39, 35.39, 35.08, 34.81, 31.14, 31.80, 31.77, 29.45. HRESI-MS ($[M + H]^+$) calcd for $C_{41}H_{47}O_5$ *m/z*, 619.3418, found 619.3414.

4-[2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthen-4-yl]-benzoic Acid Methyl Ester (10). The addition of 4-(5-bromo-2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthen-4-yl)-benzoic acid methyl ester (**6**) (0.100 g, 0.187 mmol), 3-*tert*-butyl-2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (**2**) (0.063 g, 0.205 mmol), sodium carbonate (0.029 g, 0.280 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.013 g, 0.011 mmol) to 9 mL of DMF and 1 mL of deionized water was performed under N_2. The mixture was heated to 90 °C for 24 h. Upon cooling, 10 mL of deionized water was added, and the solution was extracted with 3 × 20 mL of dichloromethane. The combined organic portions were washed with 10 mL of deionized water and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography (silica gel, 1:9 diethyl ether/pentane) to give the desired product (0.106 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 11.66 (s, 1H), 9.29 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 2.5 Hz, 7 Hz, 2H), 7.27 (d, J = 2.5 Hz, 1H), 7.25 (s, 1H), 7.18 (m, 2H), 7.16 (d, J = 2.5 Hz, 1H), 3.98 (s, 3H), 1.76 (s, 6H), 1.42 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, δ): 197.00, 196.93, 166.84, 160.27, 145.93, 145.87, 145.70, 142.88, 137.86, 135.39, 133.71, 130.64, 130.39, 129.63, 129.06, 128.92, 128.57, 128.40, 128.26, 125.76, 125.54, 122.64, 121.93, 120.35, 52.20, 35.38, 35.03, 34.79, 32.13, 31.78, 31.75, 29.43. HRESI-MS ($[M + Na]^+$) calcd for $C_{42}H_{48}O_5Na$ *m/z*, 655.3185, found 655.3196.

H_2[HSX*-^{t}Bu-COOH] (11). 2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthene-4-carboxylic acid (**7**) (0.100 g, 0.184 mmol) was added to (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (0.010 g, 0.092 mmol) to 6 mL of absolute ethanol. The mixture was heated to reflux for 12 h. Upon cooling, the solvent was removed by rotary evaporation and the residue was washed with 1 mL of cold methanol and then dried under vacuum to give the bright yellow product (0.105 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.61 (s, 2H), 7.66 (s, 2H), 7.58 (bs, 2H), 7.51 (s, 2H), 7.46 (d, J = 2 Hz, 2H), 7.41 (d, J = 2 Hz, 2H), 7.31 (d, J = 2 Hz, 2H), 3.16 (bs, 2H), 2.97 (m, 2H), 2.31 (m, 2H), 1.83 (s, 12H), 1.52 (s, 18H), 1.50 (s, 4H), 1.39 (18H), 1.35 (18H). HRESI-MS ($[M - H]^-$) calcd for $C_{76}H_{93}N_2O_8$ *m/z*, 1161.6926, found 1161.6884.

H_2[HSX*-^{t}Bu-COOMe] (12). 2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthene-4-carboxylic acid methyl ester (**8**) (0.040 g, 0.072 mmol) was added to (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (0.004 g, 0.036 mmol) in 4 mL of absolute ethanol and heated to reflux for 12 h. Upon cooling, the solvent was removed by rotary evaporation and the residue was washed with 1 mL of cold deionized water and then dried under vacuum to give the bright yellow product (0.042 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 13.92 (bs, 2H), 8.46 (s, 2H), 7.55 (d, J = 2.5 Hz, 2H), 7.51 (d, J = 2.5 Hz, 2H), 7.37 (m, 4H), 7.29 (d, J = 2 Hz, 2H), 7.15 (d, J = 2 Hz, 2H), 3.46 (d, J = 10 Hz, 2H), 3.18 (s, 6H), 2.02 (d, J = 7 Hz, 2H), 1.92 (d, J = 10 Hz, 2H), 1.80 (d, J = 7 Hz, 2H), 1.69 (s, 6H), 1.68 (s, 6H), 1.53 (m, 2H), 1.40 (s, 18H), 1.34 (s, 18H), 1.33 (s, 18H). HRESI-MS ($[M + H]^+$) calcd for $C_{78}H_{99}N_2O_8$ *m/z*, 1191.7396, found 1191.7342.

H_2[H_{ph}SX*-^{t}Bu-COOH] (13). 4-[2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthen-4-yl]-benzoic acid (**9**) (0.050 g, 0.081 mmol) was added to (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (0.005 g, 0.040 mmol) to 5 mL of absolute ethanol. The mixture was refluxed for 12 h. Upon cooling, the solvent was removed by rotary evaporation and the residue was washed with 1 mL of cold methanol and dried under vacuum to give the yellow product (0.051 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.82 (m, 6H), 7.49 (d, J = 2 Hz, 2H), 7.43 (d, J = 2 Hz, 2H), 7.34 (m, 6H), 7.22 (m, 4H), 6.92 (s, 2H), 3.74 (m, 2H), 3.66 (bs, 2H), 3.51 (bs, 2H), 2.02 (bs, 4H), 1.76 (s, 12H), 1.56 (s, 18H), 1.39 (s, 18H), 1.38 (s, 18H). HRESI-MS ($[M + H]^+$) calcd for $C_{88}H_{103}N_2O_8$ *m/z*, 1315.7709, found 1315.7704.

H_2[H_{ph}SX*-^{t}Bu-COOMe] (14). 4-[2,7-Di-*tert*-butyl-5-(3-*tert*-butyl-5-formyl-4-hydroxyphenyl)-9,9-dimethyl-9*H*-xanthen-4-yl]-benzoic acid methyl ester (**10**) (0.050 g, 0.080 mmol) was added to (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (0.004 g, 0.040 mmol) to 6 mL of absolute ethanol, and the mixture was refluxed for 12 h. Upon cooling, the solvent was removed by rotary evaporation and the residue was washed with 1 mL of cold deionized water and dried under vacuum to give the yellow product (0.053 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 13.71 (bs, 2H), 7.48 (d, J = 8 Hz, 4H), 7.42 (d, J = 2.5 Hz, 2H), 7.39 (d, J = 2.5 Hz, 2H), 7.09 (m, 6H), 7.02 (d, J = 2 Hz, 2H), 6.97 (d, J = 2 Hz, 2H), 6.87 (d, J = 2 Hz, 2H), 2.91 (s, 6H), 3.32 (J = 10 Hz, 2H), 2.07 (bs, 2H), 2.04 (bs, 2H), 1.97 (d, J = 10 Hz, 2H), 1.72 (s, 6H), 1.70 (s, 6H), 1.55 (m, 2H), 1.34 (s, 18H), 1.31 (s, 18H), 1.14 (s, 18H). HRESI-MS ($[M + H]^+$) calcd for $C_{90}H_{107}N_2O_8$ *m/z*, 1343.8022, found 1343.8016.

Mn[HSX*-^{t}Bu-COOH]Cl (15). H_2[HSX*-^{t}Bu-COOH] (**11**) (0.105 g, 0.093 mmol) was added to manganese(II) acetate tetrahydrate (0.033 g, 0.140 mmol) in 6 mL of absolute ethanol, and the solution was refluxed in air for 2 h. Upon cooling, 1 mL of an aqueous saturated sodium chloride solution was added and the mixture was stirred for 10 min and then extracted with 3 × 10 mL of dichloromethane. The organic layers were combined and washed with 10 mL of water and then dried over $MgSO_4$. The solvent was removed by rotary evaporation to leave the brown product (0.112 g, 99%). HRESI-MS ($[M - Cl]^+$) calcd for $C_{76}H_{92}ClMnN_2O_8$ *m/z*, 1215.6229, found 1215.6241. Anal. Calcd for $C_{76}H_{92}ClMnN_2O_8$: C, 72.91; H, 7.41; N, 2.24. Found: C, 72.84; H, 7.46; N, 2.35.

Mn[HSX*-^{t}Bu-COOMe]Cl (16). H_2[HSX*-^{t}Bu-COOMe] (**12**) (0.020 g, 0.017 mmol) was added to manganese(II) acetate tetrahydrate (0.006 g, 0.025 mmol) in 4 mL of absolute ethanol, and the solution was refluxed in air for 2 h. Upon cooling, 0.5 mL of an aqueous saturated sodium chloride solution was added and the mixture was stirred for 10 min and then extracted with 3 × 10 mL of dichloromethane. The organic layers were combined and washed with 10 mL of water and then dried over $MgSO_4$. The solvent was removed by rotary evaporation to leave the brown product (0.021 g, 98%). HRESI-MS ($[M - Cl]^-$) calcd for $C_{78}H_{96}MnN_2O_8$ *m/z*, 1243.6542, found 1243.6582. Anal. Calcd for $C_{78}H_{96}ClMnN_2O_8$: C, 73.19; H, 7.56; N, 2.19. Found: C, 73.01; H, 7.76; N, 2.30.

Mn[H_{ph}SX*-^{t}Bu-COOH]Cl (17). H_2[H_{ph}SX*-^{t}Bu-COOH] (**12**) (0.025 g, 0.019 mmol) was combined with manganese(II) acetate tetrahydrate (0.007 g, 0.028 mmol) in 3 mL of absolute ethanol and refluxed in air for 2 h. Upon cooling, 0.5 mL of an aqueous saturated sodium chloride solution was added and the mixture was stirred for 10 min and then extracted with 3 × 10 mL of dichloromethane. The organic layers were combined and washed with 5 mL of water and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give the brown product (0.027 g, 100%). HRESI-MS ($[M - Cl]^+$) calcd for $C_{88}H_{100}MnN_2O_8$ *m/z*, 1367.6860, found 1367.7056. Anal. Calcd for $C_{88}H_{100}ClMnN_2O_8$: C, 75.27; H, 7.18; N, 2.00. Found: C, 75.15; H, 7.38; N, 2.13.

Mn[H_{ph}SX*-^{t}Bu-COOMe]Cl (18). H_2[H_{ph}SX*-^{t}Bu-COOMe] (**14**) (25 mg, 0.019 mmol) was combined with manganese(II) acetate tetrahydrate (6.8 mg, 0.028 mmol) in 4 mL of absolute ethanol and refluxed in air for 2 h. Upon cooling, 0.5 mL of an aqueous saturated sodium chloride solution was added and the mixture was stirred for 10 min and then extracted with 3 × 10 mL of dichloromethane. The organic layers were combined and washed with 5 mL of water and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give the brown product (0.026 g, 98%). HRESI-MS ($[M - Cl]^+$) calcd for $C_{90}H_{104}MnN_2O_8$ *m/z*, 1395.7168, found 1395.7136. Anal. Calcd for $C_{90}H_{104}ClMnN_2O_8$: C, 75.48; H, 7.32; N, 1.96. Found: C, 75.34; H, 7.45; N, 2.03.

Disproportionation Reactions. Dismutation reactions were performed at room temperature in a sealed (PTFE septum) 20-mL reaction vial equipped with a magnetic stir bar and a capillary gas delivery tube linked to an inverted graduated burette filled with water. The reaction vial was charged with a stock solution of the corresponding catalyst in CH_2Cl_2 (1.0 mL). MeOH (0.5 mL) was added followed by H_2O_2 (790 μL, 8.22 mmol; 10.4 M (30%) aqueous solution), and the reaction mixture was stirred vigorously. The time was set to zero immediately after addition of H_2O_2. The conversion was monitored volumetrically, and the amount of O_2 (*n*) produced was calculated using the ideal gas law.

The amount of catalyst used to obtain the results of Table 1: (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]-manganese(III) chloride (1.0 mL from 6.0 mg into 10 mL of CH_2Cl_2 solution or 0.00095 mmol) to give an average of 3.7 mL of O_2 in 1 h. (1*R*,2*R*)-(−)-[1,2-Cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]manganese(III) chloride with 2 equiv of benzoic acid (1.0 mL from 6.0 mg). (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]manganese(III) chloride and 1.2 mg of benzoic acid into 10 mL of CH_2Cl_2 solution or 0.00095 and 0.0019 mmol, respectively, to give on average 4.2 mL of O_2 in 1 h. Mn(HSX*-^{t}Bu-COOH)Cl (**15**) (1.0 mL from 3.0 mg into 5 mL of CH_2Cl_2 solution or 0.000475 mmol) to give 60.7 mL of O_2 in 1 h. Mn(HSX*-^{t}Bu-COOMe)-Cl (**16**) (1.0 mL from 2.4 mg into 2 mL of CH_2Cl_2 solution or 0.00095 mmol) to give 1.4 mL of O_2 in 1 h. Mn(H_{ph}SX*-COOH)Cl (**19**) (1.0 mL from 1.3 mg into 2 mL of CH_2Cl_2 solution or 0.00095 mmol) to give 56.9 mL of O_2 in 1 h. Mn(H_{ph}SX*-COOMe)Cl (**20**) (1.0 mL from 2.7 mg into 2 mL of CH_2Cl_2 solution or 0.00095 mmol) to give 27.5 mL of O_2 in 1 h. The standard deviations on the TON measurements are derived from at least three data points and are as follows: compound **15** (±113), **16** (±11), **17** (±178), and **18** (±49).

Epoxidation of 1,2-Dihydronapthalene. The data from Table 2 were determined as follows: 0.2 mM solutions of the catalyst (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)]-manganese(III) chloride (1.3 mg in 10 mL of dichloromethane), **15** (2.5 mg in 10 mL of dichloromethane), and **17** (2.8 mg in 10 mL of dichloromethane) were prepared. A 20 mM solution of 1,2-dihydronapthalene and 10 mM dodecane (65 mg of 1,2-dihydronapthalene and 43 mg of dodecane in 25 mL) was prepared. For NaOCl as the oxidant, the oxidant solution was prepared by mixing 2 mL of 0.05 M $NaHPO_4$ and 5 mL of commercial bleach (Clorox) and 0.1 mL of 1 M NaOH solution and then cooling to 0 °C. A quantity of 1.5 mL of this solution was added to 0.5 mL of each catalyst solution and 0.5 mL of the 1,2-dihydronapthalene/dodecane solution, precooled to 0 °C. For PhIO as the oxidant, 4.0 mg of PhIO was added to 0.5 mL of each catalyst solution with 0.5 mL of the 1,2-dihydronapthalene/dodecane solution. For the trial with an equivalent of *N*-methylimidazole, 10 μL of a 0.0104 M solution (42.7 mg in 50 mL of dichloromethane) of *N*-methylimidazole was added to each reaction. For H_2O_2, the oxidant solution was prepared by diluting 1 mL of 30% H_2O_2 solution with 9 mL of H_2O. A 40 mM solution of 1,2-dihydronapthalene and 10 mM of dodecane was prepared (130 mg 1,2-dihydronapthalene and 43 mg of dodecane in 25 mL of dichloromethane). A quantity of 0.5 mL of this was added to 0.5 mL of each catalyst solution. The diluted solution of H_2O_2 was added over 3 h. Upon completion of the oxidant addition, the reaction was stirred for an additional hour before being sampled. The concentration of the substrate and epoxide product was determined by GC/MS with dodecane as the internal standard to determine the TON.

For the determination of ee, the epoxidation method and conditions were modified from that employed for previous epoxidation studies using manganese salen complexes for comparison to previous literature work.[43] Five milliliters of a 0.05 M solution of Na_2HPO_4 was added to 12.5 mL of commercial bleach (Clorox). The pH of this solution (~55 M in NaOCl) was adjusted to pH 12 by the dropwise addition of 1.0 M NaOH solution and cooled to 0 °C. A quantity of 4.8 mL was added to a precooled 0 °C solution of 1,2-dihydronapthalene (104 mg, 0.800 mmol) and Mn(HSX*-^{t}Bu-COOH) (**15**) (10 mg, 0.008 mmol, 1% catalyst loading) in 8 mL of dichloromethane. A quantity of 3.6 mL of the prepared bleach solution was added to a precooled 0 °C solution of 1,2-dihydronapthalene (78 mg, 0.600 mmol) and Mn(H_{ph}SX*-^{t}Bu-COOH) (**17**) (8.4 mg, 0.006 mmol, 1% catalyst loading) in 6 mL of dichloromethane. Upon being stirred for 12 h, the layers were separated and the aqueous layer was extracted with 2 × 6 mL of dichloromethane. The combined organic layers for each reaction were washed with 10 mL of water and 10 mL of a saturated sodium chloride solution and dried over $MgSO_4$. After solvent removal by rotary evaporation, the crude products were purified by column chromatography (silica gel, 98:2 pentane/ethyl acetate) to yield the epoxide product.

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Supporting Information Available: ^{1}H NMR and MS of the potential ligand impurity from synthesis of **13**, O_2 evolution and MS of **18** in the catalase reaction, and O_2 evolution by **15** under two different solvent conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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