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Manganese Porphyrins Catalyze Selective C−H Bond Halogenations

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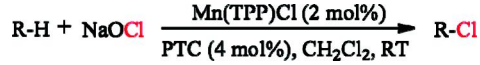
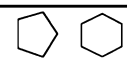
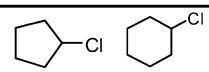
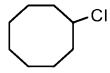
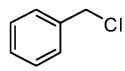
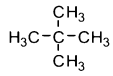
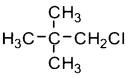
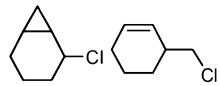
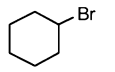
Abstract: We report a manganese porphyrin mediated aliphatic C−H bond chlorination using sodium hypochlorite as the chlorine source. In the presence of catalytic amounts of phase transfer catalyst and manganese porphyrin Mn(TPP)Cl **1**, reaction of sodium hypochlorite with different unactivated alkanes afforded alkyl chlorides as the major products with only trace amounts of oxygenation products. Substrates with strong C−H bonds, such as neopentane (BDE =∼100 kcal/mol) can be also chlorinated with moderate yield. Chlorination of a diagnostic substrate, norcarane, afforded rearranged products indicating a long-lived carbon radical intermediate. Moreover, regioselective chlorination was achieved by using a hindered catalyst, Mn(TMP)Cl, **2**. Chlorination of *trans*-decalin with **2** provided 95% selectivity for methylene-chlorinated products as well as a preference for the C2 position. This novel chlorination system was also applied to complex substrates. With 5α-cholestane as the substrate, we observed chlorination only at the C2 and C3 positions in a net 55% yield, corresponding to the least sterically hindered methylene positions in the A-ring. Similarly, chlorination of sclareolide afforded the equatorial C2 chloride in a 42% isolated yield. Regarding the mechanism, reaction of sodium hypochlorite with the Mn^{III} porphyrin is expected to afford a reactive Mn^{V}=O complex that abstracts a hydrogen atom from the substrate, resulting in a free alkyl radical and a Mn^{IV}—OH complex. We suggest that this carbon radical then reacts with a Mn^{IV}—OCl species, providing the alkyl chloride and regenerating the reactive Mn^{V}=O complex. The regioselectivity and the preference for CH_2 groups can be attributed to nonbonded interactions between the alkyl groups on the substrates and the aryl groups of the manganese porphyrin. The results are indicative of a bent [Mn^{v}=O---H---C] geometry due to the C−H approach to the Mn^{v}=O (dπ−pπ)* frontier orbital.

Halogenated organic compounds play a central role in organic chemistry,[1] affording important components of a variety of biologically and pharmacologically active molecules. Alkyl chlorides also find widespread use as intermediates in organic synthesis, such as in cross-coupling reactions.[2] Accordingly, the development of new chemoselective and regioselective approaches to the synthesis of alkyl halides remains an important challenge, especially for unactivated C−H bonds.

Manganese porphyrins and Schiff base complexes have long been known to be effective catalysts for the oxygenation of both unsaturated and saturated hydrocarbons.[3] Notably, small amounts of halogenation were described in the original reports[3a,4] and subsequently.[5] However, these reactions uniformly resulted in poor selectivity and low yields for nonoxygen functionalization. Selective chlorination was reported by Ricci et al. for a Ni(salen)/−OCl system, but the substrate scope was limited and the reaction was likely propagated by chloroxy radicals.[6]

Table 1. Halogenation of Simple Hydrocarbons[a]



	Substrate	Product	Yield[b]
1			69%, 57%
2			74%
3			38%
4[c]			31%
5			12%, 28%
6[d]			49%

[a] Standard conditions: Substrate/oxidant/**1**/PTC = 300:100:2:4. [b] Yield based on oxidant. Yield determined by GC. [c] Mn(TMP)Cl was used as catalyst. [d] NaOBr, prepared by treatment of NaOCl with a slight excess of NaBr, was used as the oxidant.

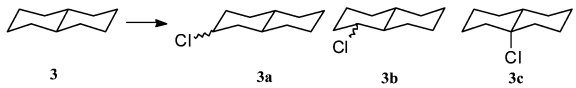
The development of metalloporphyrin-catalyzed halogenations of unactivated hydrocarbons could provide a significant new avenue for late-stage drug candidate diversification. Further, the realization of such a process could provide insight into the mechanisms of halogenating enzymes[7] such as chloroperoxidase, a heme-containing chlorinating enzyme, and Syr3, a nonheme Fe(II) α-ketoglutarate-dependent halogenase.[8] We report herein a manganese porphyrin catalyzed chlorination reaction that shows remarkable chemo- and regioselectivity even with complex substrates. Conveniently, the process uses hypohalites as the halogen source.

We have found that a biphasic system with catalytic amounts of Mn(TPP)Cl (**1**), tetrabutylammonium chloride as a phase transfer catalyst (PTC), and sodium hypochlorite transformed a variety of simple alkanes to alkyl chlorides with high selectivity (Table 1). Only trace amounts of oxygenated and other chlorinated products were detected under optimal conditions. There was negligible reaction in the absence of the Mn or PTC catalysts. Interestingly, even substrates with strong C−H bonds, such as neopentane (BDE =∼100 kcal/mol)[9] could be chlorinated with a useful yield by using Mn(TMP)Cl (**2**) as the catalyst. When toluene was used as the substrate, the benzylic position was chlorinated exclusively. Interestingly, cyclohexane and toluene were found to have similar reactivities in a competitive reaction, despite the 11 kcal/mol difference in C−H BDE. Moreover, when norcarane was used as a diagnostic substrate, the major product was rearranged, indicating

the involvement of a long-lived radical intermediate,[3a,10] similar to manganese porphyrin mediated hydroxylation reactions.[3a] The chlorination reaction could be expanded to bromination simply by replacing NaOCl with NaOBr. The bromination of cyclohexane provided cylcohexyl bromide as the main product with insignificant amounts of cyclohexyl chloride, indicating that the hypohalite is the halogen source rather than the solvent or the axial ligand.

The chlorination of *trans*-decalin catalyzed by **1** and **2** was very revealing. With commonly employed chlorinating agents such as *N*-chlorosuccinimide (NCS)[11] or hypochlorous acid[12] this substrate provides a mixture of products with poor regioselectivity and tertiary/secondary selectivities of ∼1.4 and ∼3, respectively. Significantly, chlorination of *trans*-decalin with **1** as the catalyst provided *95% selectivity for methylene-chlorinated products* (Scheme 1). Furthermore, when the more hindered catalyst **2** was used, 2-chlorodecalins (**3a**) were obtained with 76% selectivity. Such a high selectivity for chlorination of unactivated methylene C−H bonds has not been observed before.

Scheme 1. Chlorination of *trans*-Decalin



3		3a	3b	3c
	yield		distribution	
Mn(TPP)Cl/NaOCl	55%	38%	58%	4%
Mn(TMP)Cl/NaOCl	51%	76%	19%	5%

Encouraged by the highly regioselective chlorination of *trans*-decalin, we sought to apply this system to complex substrates (Figure 1). We first examined the chlorination of 5α-cholestane, a saturated steroid that contains 48 unactivated C−H bonds. Remarkably, despite six tertiary C−H bonds and 13 possible methylene sites of chlorination, we observed chlorination *only* at the C2 and C3 positions, the least sterically hindered methylene positions in the A-ring, in a net 55% yield. Notably, the C2 chlorination afforded a 15:1 selectivity for the equatorial chloride (**4a**), while a mixture of epimers was found at C3. This example highlights the capacity of steric factors to produce high selectivity for the chlorination of secondary C−H bonds in a simple, intermolecular event.

Sclareolide (**5**, Figure 1) is a plant-derived terpenoid with antifungal and cytotoxic activities. This substrate has been utilized recently to demonstrate the selectivity of a bulky nonheme iron oxygenation catalyst toward the C2 and C3 positions.[13] Significantly, the Mn(TMP)Cl catalyzed chlorination of **5** afforded a 42% isolated yield of the C2 equatorial chloride **5a**. The structure was confirmed by observing the signature triplet of triplets at δ 4.22 (J = 12.1, 4.2 Hz) in the ^{1}H NMR of **5a**. The C2/C3 selectivity was 7:1.

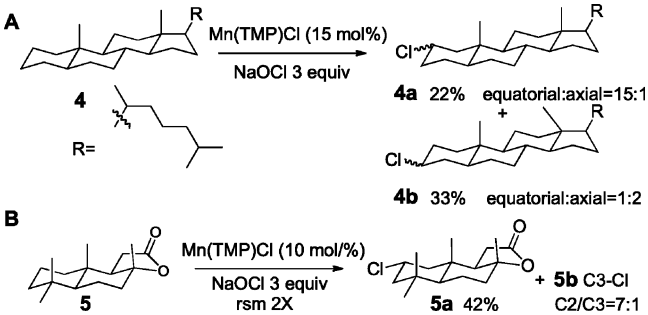
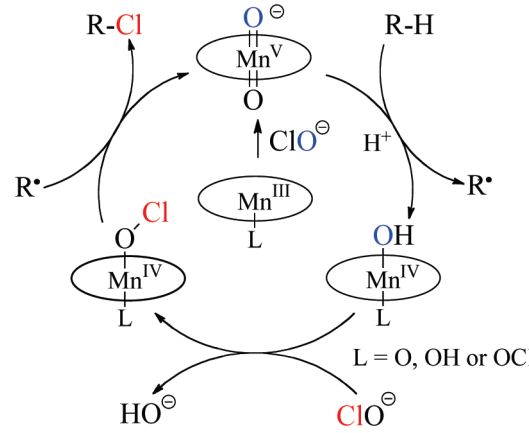


Figure 1. (A) Steric effects lead to selective chlorination of 5α-cholestane at the C2 and C3 positions. NMR yields. (B) C2-selective chlorination of sclareolide. Isolated yield.

Regioselective chlorinations of unactivated methylene C−H bonds are rare, with the few known examples involving the use of internal directing groups.[14] In our system, the regioselectivity derives solely from intermolecular interactions as opposed to structurally enforced positioning of the catalyst.[15]

Scheme 2. Proposed C−H Chlorination Mechanism



A likely mechanism for this new transformation is outlined in Scheme 2. While the details are yet to be elucidated, we note that only the O=Mn^{IV}−OH porphyrin or a very similar species were observed during catalysis and that the C−H selectivity was clearly dependent upon the nature of the porphyrin meso-substituent. It is expected that basic sodium hypochlorite will oxidize the starting Mn^{III} porphyrin[16] to a dioxo- or oxohydroxoMn^V complex.[17] Subsequent hydrogen atom abstraction from the substrate would afford an alkyl radical and a hydroxoMn^{IV} complex.[3a] For the product-forming step we suggest chlorine atom transfer from the L−Mn^{IV}−OCl complex[5c] to the incipient carbon radical center also regenerating the reactive oxoMn^V species. For this chain reaction to work, the initially formed alkyl radical must escape the [L−Mn^{IV}−OH •R] cage, as evidenced by the rearrangement accompanying the chlorination of norcarane. We expect that a second ligating hydroxide, or hypochlorite anion, would lower the redox potential of the L−Mn^{IV}−OH intermediate under these basic conditions (pH 12 in the aqueous phase),[18] thus slowing down the rebound rate of the alkyl radical and preventing the formation of the oxygenated products. Other axial ligands such as pyridines led to a loss of the selectivity for halogenation. Further, the formation of Mn^{IV} porphyrin species during C−H oxygenation reactions has been noted recently at high pH.[19]

We attribute the preference for the least hindered methylene position to intermolecular nonbonded catalyst−substrate interactions resulting from the approach of the scissile C−H bond to the Mn^v=O ($d\pi$−$p\pi$)* frontier orbital.[20] A collinear [Mn^v=O---H---C] transition state geometry with σ-symmetry would not explain this obvious preference for methylene sites, whereas a bent, π-approach for H-atom abstraction would result in significant interactions between the meso-aryl groups of the Mn-porphyrin catalyst and steric bulk flanking the substrate C−H bond (cf. TOC graphic).

The results demonstrate that highly regioselective aliphatic halogenations can be achieved predictably with catalysts as simple as **1** and **2** and halogenating agents as ubiquitous as hypochlorite or hypobromite. Since oxoMn^V species can also oxygenate halogen ions,[17a,c] we anticipate the possibility that similar halogenations may be accessible with other oxidants.

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Supporting Information Available: Experimental procedures, GC data for **4a** and **4b**, and ^{1}H NMR data for **4a**, **4b**, and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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