A Journal of the Gesellschaft Deutscher Chemiker

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201710676
Angew. Chem. 10.1002/ange.201710676

Link to VoR: http://dx.doi.org/10.1002/anie.201710676
http://dx.doi.org/10.1002/ange.201710676

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Selective C-H Halogenations with A Highly Fluorinated Manganese Porphyrin

Gang Li,[a] Andrew K. Dilger,[b] Peter T. Cheng,[b] William R. Ewing[b] and John T. Groves*[a]

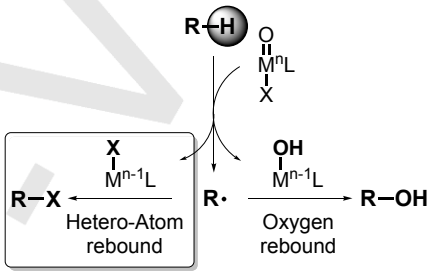
Abstract: Selective C-H functionalizations of aliphatic molecules remain a challenge in organic synthesis. While radical chain halogenations provide an efficient way to access many halogenated molecules, application of typical protocols to selectively halogenate electron-deficient and strained aliphatic molecules are rare. Herein, we report selective C-H chlorinations and fluorinations that use an electron-deficient manganese pentafluorophenyl porphyrin catalyst, Mn(TPFPP)Cl. This catalyst displays superior properties for aliphatic halogenations of recalcitrant, electron-deficient and strained substrates with unique regio- and stereoselectivity. *In operando* UV-vis analyses indicate that an oxoMn(V) species is responsible for hydrogen atom abstraction. The observed stereoselectivity results from steric interactions between the bulky porphyrin ligand and the intermediate substrate radical in the halogen rebound step.

Free radical halogenations of unactivated C-H bonds offer high potential for late stage diversification and building block synthesis by providing an efficient means to functionalize inaccessible sites in key molecules.[1] Alkyl bromides and chlorides are important coupling partners in organic synthesis providing highly flexible avenues for diversification.[2] Alkyl fluorides are particularly important in drug candidates since sites of Phase I metabolism can be blocked by the fluorine substituent and tighter binding to protein targets is often achieved.[3] Classical radical halogenations are severely limited, however, by poor regioselectivity, often harsh conditions and undesirable polyhalogenation.[4]

Recent improvements in N-chloro methodology have been effective for selective radical chlorination, albeit only with simple aliphatic and benzylic substrates.[4-5]

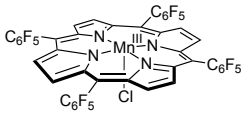
Nature utilizes metalloenzymes[6] such as the heme protein chloroperoxidase (CPO)[7] and non-heme iron proteins such as SyrB2,[8] to effect C-H halogenations. The latter enzyme employs a chloro-oxoiron(IV) intermediate to cleave the substrate C-H bond and then to direct the incipient substrate radical to the chloride ligand. The high efficiency and exquisite substrate selectivity of SyrB2 has offered insight and impetus to explore chlorination reactions catalyzed by transition-metal complexes.[9]

We have previously reported that electron-rich manganese porphyrins catalyze the efficient chlorination of aliphatic and benzylic C-H bonds.[10] This method, which employs hetero-atom rebound catalysis[11] similar to that of SyrB2 (Scheme 1), has shown remarkable chemo- and regioselectivity. Based on these initial results, we discovered that these manganese catalysts also mediated C-H fluorination using fluoride ion,[12] azidation with aqueous sodium azide[13] and isocyanation as a route to ureas.[14] Recently, Burns *et al*. applied this protocol to chlorinate a sensitive hydrocarbon ladderane, enabling the total synthesis of an unusual membrane phospholipid.[15] Zhou and co-workers have successfully synthesized a porphyrinic MOF system using a water-soluble manganese porphyrin. With this immobilized system, they were able to catalyze the chlorination of simple hydrocarbons in high yields.[16]



Scheme 1. Concept of hetero-atom rebound wherein an incipient substrate radical is captured by M-X instead of M-OH.

Missing from this repertoire is a general method to halogenate substrates bearing electron-withdrawing groups and strained sp^3 C-H sites. Herein, we report the development of an electron-deficient manganese porphyrin, Mn(TPFPP)Cl (Figure 1) as an efficient catalyst for selective C-H halogenations of a variety of difficult and recalcitrant substrates. Moreover, this catalyst shows *enzyme-like selectivity*.



Mn(TPFPP)Cl
TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrinate

Figure 1. Structure of Mn(TPFPP)Cl.

We initiated this study by exploring the chlorination of methyl cyclobutanecarboxylate, **1**, used as the limiting reagent. Typical chlorination reagents applied to this substrate result either in low conversion or low selectivity. Our original manganese porphyrin catalyst, Mn(TMP)Cl,[10] also gave low product conversions. When Mn(TPFPP)Cl was used, we were pleased to observe that the conversion was significantly improved along with a high 3-chloro selectivity (Table 1, entry 6). Homogenous reaction conditions were found to be beneficial for chlorination. Higher yields were achieved and the use of a phase transfer catalyst could be avoided when acetonitrile was used as the solvent (Table 1, entry 7). Moreover, use of deuterated solvents significantly improved the conversion of substrate since the

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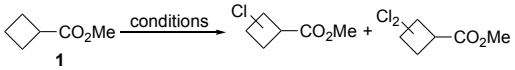
10.1002/anie.201710676

solvent oxidization is suppressed by a significant isotope effect, which is typical of manganese porphyrin catalysis (Table 1, entry 8, a more thorough condition optimization is provided in the Supporting Information).[1f, 10]

Table 1. Chlorination of **1** with substrate as the limiting reagent.[a]



1

Entry	Conditions	% Conversion	% 3- chloro (cis:trans)	% dichloro
1	NCS, AIBN 60 °C, C_6H_6, N_2	14	9 (64:36)	N/A
2	$SOCl_2$, BPO, 85 °C, C_6H_6, N_2	43	11 (57:43)	24
3	N-chloroamide, Cs_2CO_3, *hv*, 55 °C, C_6H_6, N_2	37	26 (56:44)	N/A
4	Ni(salen), NaOCl (aq), CH_2Cl_2, rt (biphasic)	29	16 (55:45)	N/A
5	Mn(TMP)Cl, NaOCl (aq), CH_2Cl_2, rt (biphasic)	6	4 (67:33)	N/A
6	Mn(TPFPP)Cl, NaOCl (aq), CH_2Cl_2, rt (biphasic)	40	34 (56:44)	2
7	Mn(TPFPP)Cl, NaOCl (aq), CH_3CN, rt	56	49 (52:48)	1
8	Mn(TPFPP)Cl, NaOCl (aq), CD_3CN, rt	92	83 (57:43)	4

[a] Yields and ratios were determined by GC-MS.

With optimized conditions for the C-H chlorination, a variety of cyclobutane derivatives were tested (Figure 2). Reactions were generally complete within 3-8 h. Ketone, ester and amide functional groups were well tolerated as well as di-functionalized substrates. Building blocks of this sort are particularly difficult to prepare, usually requiring multiple steps. For instance, the previous known synthesis of **5** takes 3 steps and only about 30% overall yield was achieved.[17]

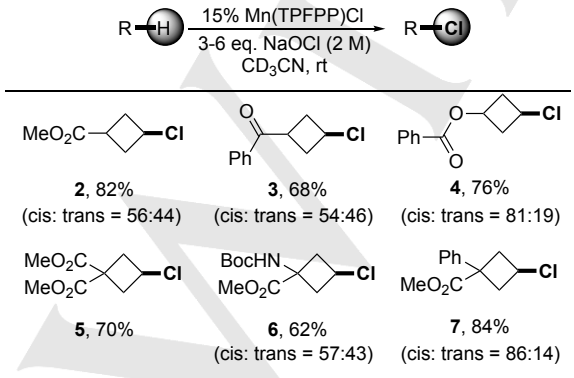


Figure 2. Chlorination of cyclobutane derivatives. Isolated yields were reported. Diastereomer ratio was determined by GC-MS.

Considering the bulkiness of the porphyrin ligand, we anticipated that this catalytic system might provide unique stereoselectivities with appropriate sterically hindered substrates. Thus, we set out to apply this method to the chlorination of challenging, bridged bicyclic lactones, which are both electron-deficient and sterically hindered. The optimized method showed superb reactivity as well as regio- and stereoselectivity of chlorination of these lactones (Figure 3). *Only a single stereoisomer was obtained in high yield* as determined by NOESY NMR. To the best of our knowledge, this is the only chlorination method that can achieve such *enzyme-like* regio- and stereoselectivity to date. Ready access to such halogenated intermediates expands the versatility of alkyl halide cross-coupling and related strategies.[18]

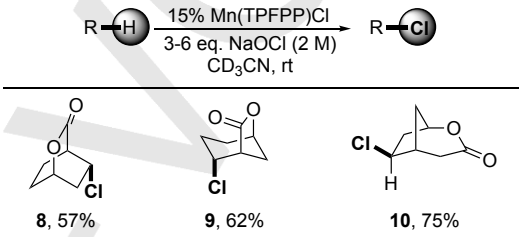


Figure 3. Chlorination of lactones. Isolated yields were reported.

Inspired by these chlorination results, we further investigated the ability of Mn(TPFPP)Cl to catalyze the direct C-H fluorination of these electron-deficient and steric-hindered molecules. Only rare examples of C-H fluorination addressing electron deficiency have been reported.[19] Under the published fluorination protocol,[12a] cyclobutane derivatives presented considerable challenges and no desired fluorinated products were observed. However, when the lactone substrates were subjected to these fluorination conditions, reasonable yields were observed (Figure 4). More interestingly, a bridged cyclic lactam substrate also reacted smoothly, resulting the corresponding fluorinated product in a moderate yield. Similar to the chlorination reactions, *only a single stereoisomer was obtained for each reaction*.

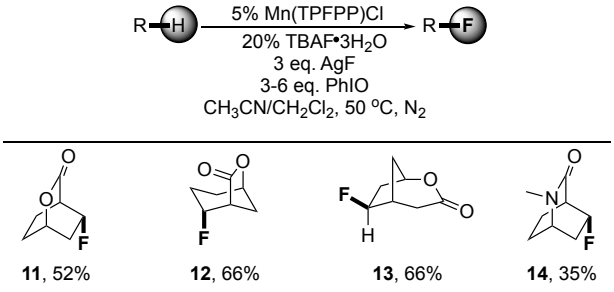


Figure 4. Fluorination of lactones and lactam. Isolated yields are reported.

In our previous work, we proposed a mechanism for this manganese porphyrin-catalyzed C-H chlorination that involves a hypochloritomanganese(IV) intermediate as the chlorine atom source (Figure 5).[10] Chlorine atom abstraction from Mn^{IV}-OCl would serve both to generate the alkyl chloride product and regenerate the reactive oxoMn^{V} intermediate. Spectroscopic

interrogation of the reaction mixture was made difficult by the heterogeneous conditions, however. The homogeneous conditions developed here have allowed us to elucidate the mechanism more fully.

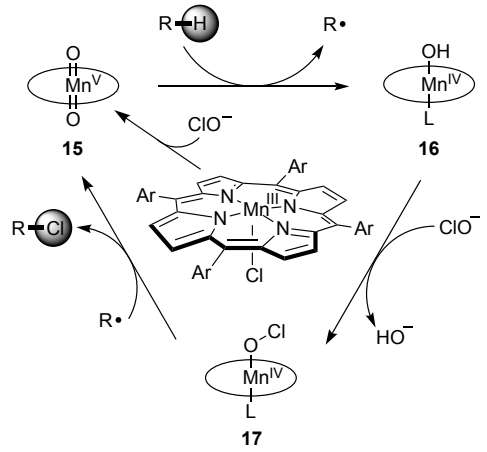


Figure 5. Proposed mechanism for Mn-catalyzed C-H chlorination.

We have shown that the oxidation of Mn(TPFPP)Cl in basic acetonitrile produces a stable *trans*-dioxomanganese(V) species,[20] which becomes an active oxidant upon protonation.[21] Similarly, UV-vis spectral changes were observed upon adding oxidants into an acetonitrile solution of Mn(TPFPP)Cl at room temperature under halogenation conditions. Mn(TPFPP)Cl shows a split Soret band at 359 and 470 nm and a Q band at 566 nm, typical of Mn(III) porphyrins. After the addition of 20 equiv of NaOCl, the band at 470 nm quickly disappeared. A new Soret band at 432 nm was observed, which gradually disappeared over 30 s (Figure 5a). At the same time, the band at 566 nm also faded and a new Q band at 552 nm was formed, which also gradually disappeared over 30 s (Figure 5b). The 432 nm and 552 nm absorbances match a previous report for an oxoMn^{V} species,[22] indicating the formation of the dioxoMn(V) compound **15**. Decomposition of **15** would produce the corresponding oxoMn(IV) species with a Soret band at 418 nm and a Q band at 542 nm in the absence of substrate.[23]

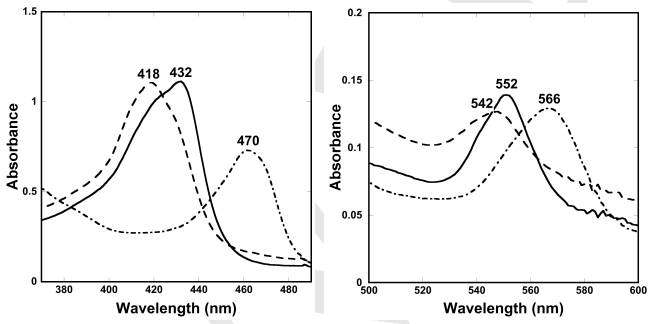


Figure 6. UV-vis spectra observed upon adding NaOCl to Mn(TPFPP)Cl. *a*), Soret Band; *b*), Q Band. Dotted line, Mn(TPFPP)Cl (10 μM) in MeCN. Solid line, 0.5 s after adding 20 equiv of NaOCl. Dashed line, 30 s after adding 20 equiv of NaOCl.

A number of high-valent metal-oxo species with porphyrin and non-heme ligands have been reported,[24] but all of them show modest reactivity in abstracting H atoms from strong sp^3 C-H bonds. In this report, due to the high electron-deficiency of the fluorinated porphyrin ligand, compound **15** is a highly oxidizing reagent and can rapidly abstract H• from C-H bonds even within electron-deficient substrates to afford a hydroxo Mn(IV) intermediate **16**.[25] In the presence of excess NaOCl, the predominant Cl-transferring Mn species would be **17**.[26] Such a ligand transfer step has been reported in a similar hydroxo-iron(III) porphyrin species Fe(TPFPP)OH system.[27]

The high stereoselectivities observed for both the chlorination and fluorination reactions are due to the halogen atom rebound step. DFT analysis of the transition states revealed a low-energy σ-approach geometry leading to products **8**-**14**, in which the substrate radical, the transferred halogen and the Mn(IV) center are collinear (Figure 7). In this arrangement, there is relatively little steric clash for the observed *endo*-isomers, whereas *exo*-approach suffers from strong interactions of the carbonyl oxygen electron lone pairs with the Mn porphyrin catalyst. Consequently, the *endo*-approach dominates the reaction and leads to the formation of the *endo*-selective products.

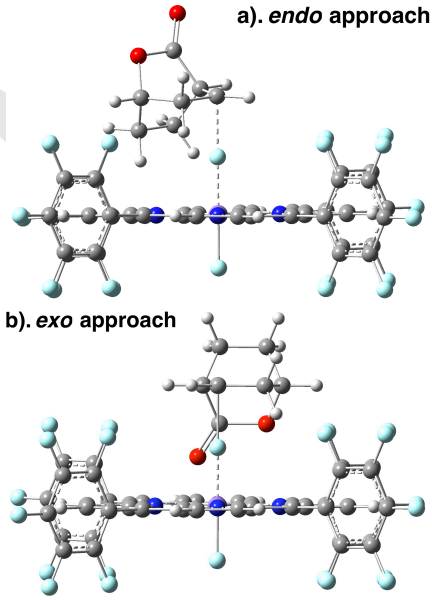


Figure 7. Two approaches in the radical rebound step (Formation of **11** is used as an example). a). ***endo*** approach, less repulsion. b). ***exo*** approach, more repulsion.

In conclusion, we have demonstrated in this work that a highly electron-deficient manganese porphyrin, Mn(TPFPP)Cl, efficiently and selectively catalyzes C-H chlorination of a panel of challenging substrates with small rings and strong electro-withdrawing groups. The reaction is operationally simple and proceeds under mild conditions, affording a range of useful synthons. Spectroscopic analyses of the reaction mixture show the formation of an oxoMn^{V} intermediate, which can efficiently abstract hydrogen atoms to initiate the catalytic cycle. The

formation of a hypochloritomanganese(IV) species via ligand exchange further leads to the high efficiency of chlorination.

Acknowledgements

This research was supported by the US National Science Foundation award CHE-1464578 (J.T.G.) and the BMS Center for Molecular Synthesis at Princeton University. We thank Robert Kaltenbach for the synthesis of the lactone precursor for compounds **8** and **11**.

Conflict of interest

The authors declare no conflict of interest.

Keywords: radical halogenation • nucleophilic fluorination • selective C-H activation• high-valent metal • manganese porphyrins

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Layout 1:

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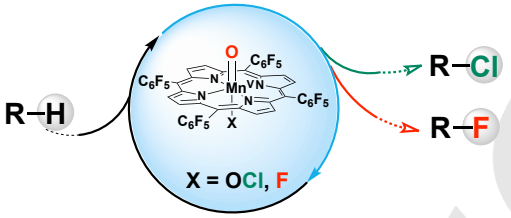
Power of electron deficiency: A highly electron-deficient manganese porphyrin is discovered to effectively catalyze radical halogenation of strained, electron-deficient aliphatic substrates. The bulkiness of catalyst results in unique stereo- and regioselectivity.



- **Aliphatic C-H Halogenation under Mild Condition**
- **High Reactivity on Strained, Electron-Deficient Substrate**
- **Unique Stereo- and Regioselectivity**

*Gang Li, Andrew K. Dilger, Peter T. Cheng, William R. Ewing, John T. Groves**

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Selective C-H Halogenations with A Highly Fluorinated Manganese Porphyrin