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Accepted Article

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Authors: Giorgio Olivo, Giulio Farinelli, Alessia Barbieri, Osvaldo Lanzalunga, Stefano Di Stefano, and Miquel Costas

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Supramolecular recognition allows remote, site-selective C-H oxidation of methylenic sites in linear amines

Giorgio Olivo,^{[a]*} Giulio Farinelli,^[b] Alessia Barbieri,^[b] Osvaldo Lanzalunga,^[b] Stefano Di Stefano^{[b]*} and Miquel Costas^{[a]*}

Abstract: Site-selective C-H functionalization of aliphatic alkyl chains stands as a longstanding challenge in oxidation catalysis, given the comparable relative reactivity of the different methylenes. Herein, we describe a supramolecular, bioinspired approach to address this challenge. We designed a Mn complex, able to catalyze C(sp³)-H hydroxylation with H₂O₂, equipped with 18-benzocrown-6 ether receptors that bind ammonium substrates *via* hydrogen bonding. Reversible pre-association of protonated primary aliphatic amines with the crown ether selectively exposes remote positions (C8 and C9) to the oxidizing unit, resulting in a site-selective oxidation. Remarkably, such control of selectivity retains its efficiency for a whole series of linear amines, overriding the intrinsic reactivity of C-H bonds, no matter the chain length.

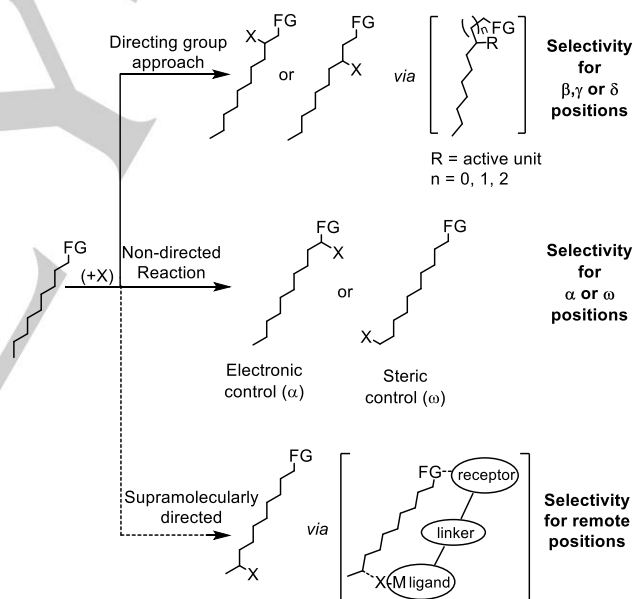
Unfolding the great potential of C-H oxidations in synthesis requires a precise and predictable control over reaction site-selectivity. Nature masters this control by precisely orienting the substrates towards the enzyme active site by means of multiple weak interactions. Conversely, artificial catalysts struggle to achieve such selectivity.¹ The problems faced are well highlighted in the selective hydroxylation of alkyl chains, a longstanding challenge in oxidation catalysis. The strength of their C-H bonds (~96 kcal mol⁻¹) coupled with the lack of appreciable differences in electronic and steric properties makes the internal methylenes practically indistinguishable (Scheme 1).¹ As a consequence, oxidation of alkyl chains affords statistical mixtures of products, only slightly affected by the use of very bulky catalysts.² A good selectivity can be only attained *via* intramolecular reactions, using a directing group^{1a,3,4} or incorporating the reactant into the substrate⁵ (Scheme 1). However, this strategy has two limitations: it cannot access C-H bonds outside a short range (β , γ or δ positions) and requires stoichiometric, preinstalled directing (or reactive) groups.⁶

Supramolecular chemistry may offer a way past these limitations.^{8,9} Reversible binding of the substrate to a receptor anchored to the catalyst can expose specific C-H bonds to the oxidizing unit, thus determining the selectivity of the hydroxylation (Scheme 1). Seminal works¹⁰ demonstrated the feasibility of this

approach, although the strict shape and size complementarity required for recognition limited the scope to few, well-crafted substrates (Figure 1).

Nevertheless, we reasoned that this approach may permit the elusive remote oxidation of alkyl chains.^{1b,3b,6,11} Towards this aim, we designed catalysts **1-Mn** and **1-Fe** (Scheme 2, synthesis and characterization in the SI, pages 16-38) equipped with 18-benzocrown-6 ether (BC) receptors to bind and orient primary ammonium ions¹⁵ (Figure 1). The catalytic center is a Mn¹² or Fe¹³ PDP complex (**2-M**, Scheme 2), known to catalyze aliphatic C-H hydroxylation with H₂O₂ and acetic acid (AcOH).¹⁴ Simple protonation of linear alkyl amines would provide optimal substrates to test our hypothesis.¹⁶

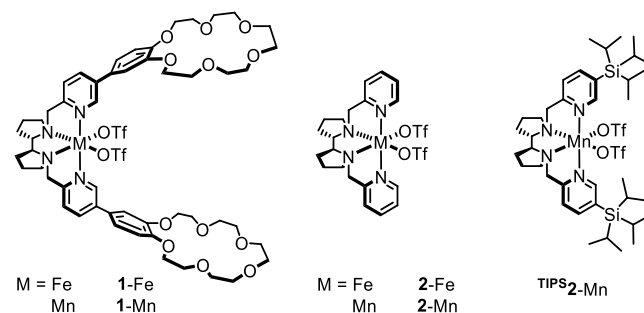
As anticipated, titration of **1-Fe** with protonated decylamine **3** results in a strong 1:2 binding (both $K_{\text{ass}} \geq 10^4$ M⁻¹, pages 39-43 in SI) in CD₃CN at -40°C. At this temperature the complex, that is



Scheme 1. Different approaches to the selective oxidation of alkyl chains.

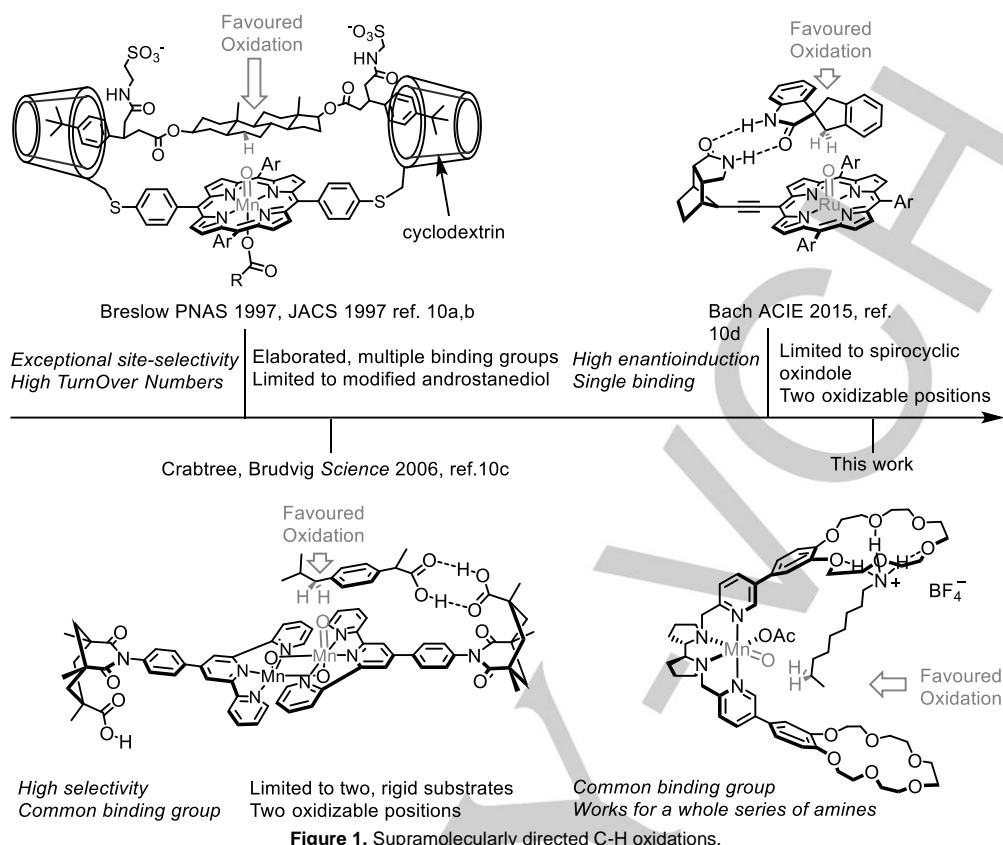
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Scheme 2. Catalysts used in this work.

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paramagnetic at 25°C, turns diamagnetic due to a temperature dependent spin crossover, enabling $^1\text{H-NMR}$ spectroscopy (see SI pages 21-22). The paramagnetism of **1-Mn** does not allow NMR titration, but mass spectrometry reveals analogous **3** binding (see SI page 44). Remarkably, the recognition tolerates the competitive hydrogen bond partners (AcOH and H_2O) required for H_2O_2 activation,¹⁴ and is specific for primary ammonium ions (see SI pages 45-50).¹⁵

The electronic properties of **1-Fe** are hardly affected by the build-up of positive charge due to cation binding. Neither the $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ redox potential nor the energy of the MLCT Vis band nor the catalytic hydroxylation of **1-Fe** and **1-Mn** are significantly altered upon coordination of NH_4^+ , K^+ , Ca^{2+} or Ba^{2+} cations (see SI pages 78-81, 86). The only notable changes are related to the BC moiety, which becomes harder to oxidize both chemically and electrochemically (see SI pages 78, 85).

At this point, we selected decylammonium **3** as a model substrate to test our approach. Non-directed oxidation with **2-Mn** yields a mixture of ketone products (K3-K9, ketones at C3-C9, Table 1, entry 1). The first positions (up to C5) are shielded by the nearby ammonium positive charge,¹⁶ the last positions are slightly activated due to improved sterical accessibility (C8 and C9, 53% of the total yield), and a statistical oxidation occurs in the middle of the chain (C6, C7). To our delight, catalyst **1-Mn** substantially modified this selectivity, enhancing the selectivity for C8 and C9 positions up to 81% (entry 2).¹⁷ A concomitant decrease (C5-C7) or suppression (C3, C4) of the oxidation on the other sites is

observed. A similar, but lower, effect was also found for Fe-based complexes (entries 3 and 4).

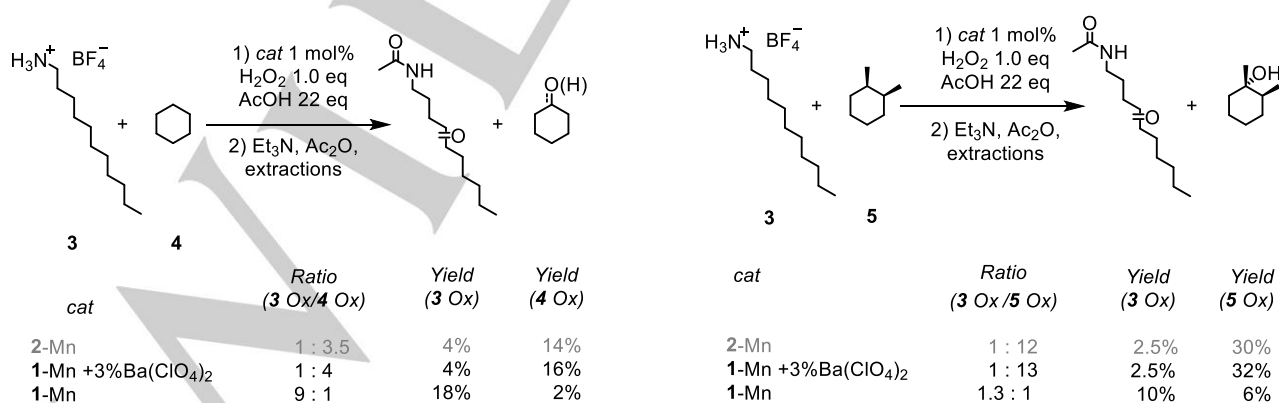
A series of control experiments were carried out to assess whether the observed change in selectivity were really due to supramolecular recognition. **i)** Addition of free BC does not modify the selectivity of the parent **2-Mn** complex, indicating that substrate binding to BC does not affect its reactivity (entries 5-7). Increasing BC loadings reduce conversion, probably because of competitive ether oxidation. **ii)** The selectivity amplification does not derive from increased steric hindrance, since the bulky catalyst $\text{TIPS}^2\text{-Mn}^{18}$ affords the same selectivity pattern of **2-Mn** (entry 8). **iii)** Saturation of the receptor by prior coordination of $\text{Ba}(\text{ClO}_4)_2$ fully suppresses the selectivity amplification of **1-Mn** (entry 9). **iv)** Replacement of NH bonds in **3** with N-methyl ones ($\text{DecNH}_2\text{Me}^+$, DecNHMe_2^+) undermines the affinity of the substrate for the crown ether and yields the same selectivity pattern, no matter the catalyst used (entries 10-14). However, when there are no cationic guests that shield the BC moiety from oxidation (see SI page 85), low product yields are obtained with **1-Mn**. Consistently, addition of readily exchangeable NH_4^+ (3mol%) increases the yield (entry 14). **v)** Competitive oxidation of **3** and a neutral, more reactive substrate with methylene units (**4**) or weak tertiary C-H bonds (**5**) results in preferential hydrocarbon oxidation with **2-Mn** (Scheme 3). **1-Mn** induces a full reversal of this selectivity, which is lost upon addition of Ba^{2+} (Scheme 3). All these experiments consistently point to a recognition-driven selectivity, which overrides the intrinsic reactivity of the substrate C-H bonds.

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Table 1: 3 oxidation mediated by different catalysts.^a

Entry	cat	Substrate (BF ₄ ⁻ anion)	Additive mol%	Conv/ tot yield (%)	AcHN							C8 + C9 Selectivity ^b
					K3	K4	K5	K6	K7	K8	K9	
1	2-Mn	DecNH ₃ ⁺ (3)		43/34	0.5%	2%	2.5%	5.5%	5.5%	8%	10%	53%
2	1-Mn	"		50/36	-	-	0.5%	1.5%	5%	13%	16%	81%
3	2-Fe	"		48/36	-	0.5%	4%	8%	8%	7%	10%	45%
4	1-Fe	"		36/30	-	-	0.5%	5%	6%	6%	12%	61%
5	2-Mn	"	BC 2%	41/35	0.5%	1.5%	3%	6%	6%	7.5%	10%	51%
6	2-Mn	"	BC 10%	25/21	0.5%	1%	1.5%	3%	3%	5%	6%	54%
7	2-Mn	"	BC 100%	8/traces	-	-	-	-	-	-	-	-
8	TIPS ₂ -Mn	"		62/34	traces	1%	2%	5%	8%	8%	10%	53%
9	1-Mn	"	Ba ²⁺ 3% ^c	47/27	traces	2%	2%	5%	5%	6%	8%	58%
10	1-Mn	DecNMeH ₂ ⁺		9/7	traces	0.5%	0.5%	1.5%	1.5%	2%	2%	50%
11	2-Mn	"		28/26	0.5%	1%	3%	4.5%	4.5%	5%	7.5%	49%
12 ^d	1-Mn	DecNMe ₂ H ⁺		11/3	traces	traces	traces	0.5%	0.5%	0.5%	0.5%	50%
13 ^d	2-Mn	"		60/47	-	2.5%	5%	7.5%	7.5%	10%	14%	52%
14 ^d	1-Mn	"	NH ₄ ⁺ 3% ^e	12/6	traces	0.5%	0.5%	1%	1%	1%	2%	50%

^aReaction conditions: cat 1 mol% (3 mol% for Fe cat.), substrate 1 eq (95 mM, 0.38 mmol), H₂O₂ 2.5 eq (15 min. addition by syringe pump), AcOH 22 eq (7 eq for Fe cat.), CH₃CN, 0°C. After 30 min., internal standard (biphenyl), Et₃N, Ac₂O and CH₂Cl₂ were added. After 1 hour, the mixture was washed with H₂O, H₂SO₄ 1M, sat. NaHCO₃, H₂O, dried and analysed by GC. All reactions have been carried out in triplicate. Error ± 0.5%. Traces of acetylated alcohols were detected, with a selectivity pattern superimposable to that of the main ketone products. ^bDefined as (K8+K9)/tot. yield). ^cBa(ClO₄)₂. ^dDifferent workup, see SI page 80. ^eNH₄PF₆.

**Scheme 3: Competition experiments.**

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Then, we investigated the oxidation of a series of protonated, linear amines, whose chain length spans from C6 to C14, aiming at determining the precise oxidation site of **1-Mn** (Scheme 4). No oxidation occurs with short amines (C₆-NH₃⁺), likely due to the strong deactivation exerted by the proximal positive charge. As the chain length increases, ketone products are formed. Catalyst **2-Mn** (Figure 2A) affords an almost statistical distribution of ketone products, except for C3-C5 (electronically deactivated) and the last two methylene units (sterically activated). Conversely, the distribution obtained with **1-Mn** (Figure 2B) reveals a bell-shaped profile, with the maximum yields on C8 and C9 sites, no matter the chain length. K10 becomes a secondary product in

long-chain amines, while oxidation on positions before C8 and after C10 fade away. Such bell-shaped profile is again consistent with a supramolecular site-selectivity, with the receptor placing mainly C8 and C9 C-H bonds in the reach of the oxidizing species.

To sum up, we designed a supramolecular catalyst that oxidizes linear amines with a predictable site selectivity for C8 and C9 positions. To the best of our knowledge, this is the first report of a selective, remote C-H functionalization of alkyl chains. The key for such selectivity lies in a substrate recognition that brings these C-H bonds in the range of the active unit. Remarkably, this control of selectivity is not affected by the chain length or the presence of more (sterically) activated positions.

C ₈ -NH ₃ ⁺	
	K7 K6 K5 K4 K3
2-Mn	3% 2% 1% 0.5% <0.5%
1-Mn	6% 2%
C ₉ -NH ₃ ⁺	
	K8 K7 K6 K5 K4 K3
2-Mn	7.5% 5% 5% 3% 1.5% 0.5%
1-Mn	11% 3.5% 1.5%
C ₁₀ -NH ₃ ⁺ (3)	
	K9 K8 K7 K6 K5 K4 K3
2-Mn	10% 8% 5.5% 5.5% 2.5% 2% 0.5%
1-Mn	16% 13% 5% 1.5% 0.5%
C ₁₁ -NH ₃ ⁺ (a)	
	K10 K9 K8 K7 K6 K5 K4 K3
2-Mn	8% 5.5% 6.5% 6% 5% 3.5% 2% 1.5%
1-Mn	14% 18% 20% 6% 4% 1%
C ₁₂ -NH ₃ ⁺ (a)	
	K11 K10 K9 K8 K7 K6 K5 K4 K3
2-Mn	8.5% 9% 6.5% 5.5% 4.5% 4.5% 2.5% 1%
1-Mn	7% 9% 17% 21% 4% 3% 1%
C ₁₄ -NH ₃ ⁺ (a)	
	K13 K12 K11 K10 K9 K8 K7 K6 K5 K4 K3
2-Mn	9% 6% 6% 7% 7% 6% 6% 4% 3.5% 2.5% 1.5%
1-Mn	1.5% 2% 3.5% 6% 19% 26% 3% 2.5% 1%

(a) 15 eq. of H₂O₂, see SI page 85

Scheme 4.

Acknowledgements

MC acknowledge MINECO of Spain (CTQ2015-70795-P), the Catalan DIUE (2009SGR637, ICREA Academia award) and STR of UdG for experimental support. S.D.S acknowledges MIUR, PRIN 2010CX2TLM and Sapienza Università di Roma (Ricerca

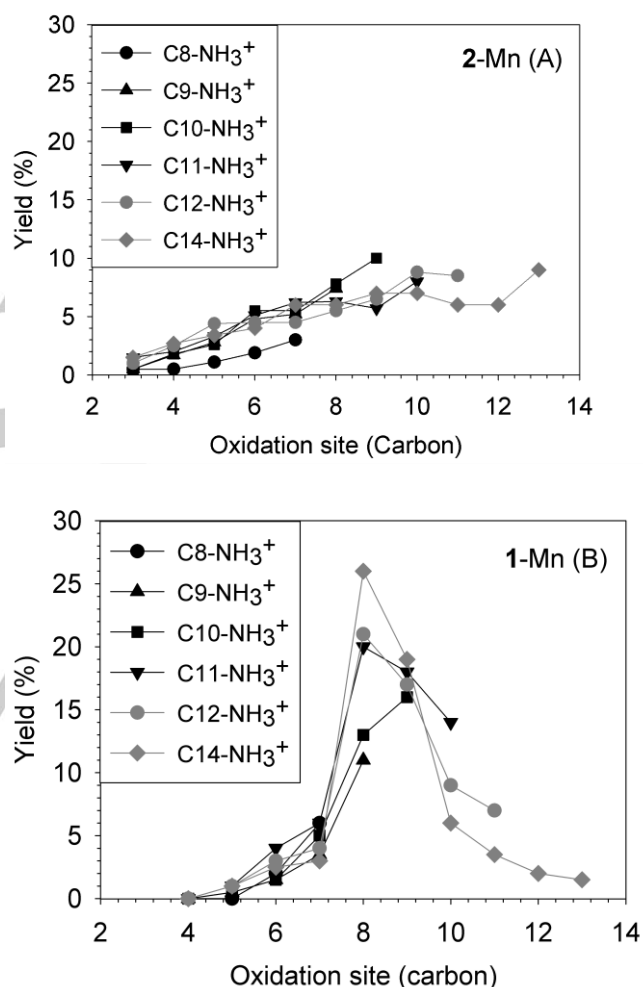


Figure 2: Distribution of oxidation products in **2-Mn** (A) and **1-Mn** (B) catalyzed oxidation of linear amines.

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Keywords: Bioinspired catalysis • Supramolecular chemistry • C-H oxidation • Regioselectivity • Molecular recognition

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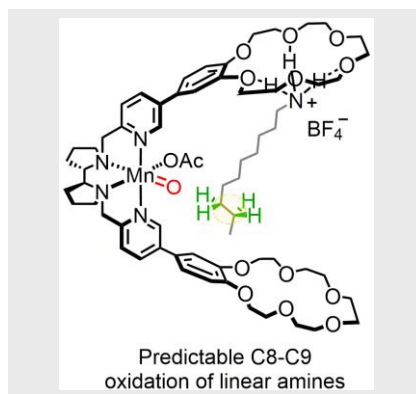
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Supramolecular C-H oxidation:

Supramolecular recognition of protonated primary amines on 18-crown-6 receptors exposes specific, remote methylenes to the Mn active site. Linear alkyl chains can thus be selectively oxidized on C8 and C9 positions with H₂O₂, overriding the intrinsic reactivity of C-H bonds.



Giorgio Olivo,* Giulio Farinelli, Alessia Barbieri, Osvaldo Lanzalunga, Stefano Di Stefano* and Miquel Costas*

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