



A Journal of the Gesellschaft Deutscher Chemiker

# Angewandte Chemie

GDCh

International Edition

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## Accepted Article

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**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.202004242

**Link to VoR:** <https://doi.org/10.1002/anie.202004242>

## COMMUNICATION

# Overriding Intrinsic Reactivity in Aliphatic C–H Oxidation: Preferential C3/C4 Oxidation of Aliphatic Ammonium Substrates

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In memory of Rolf Huisgen.

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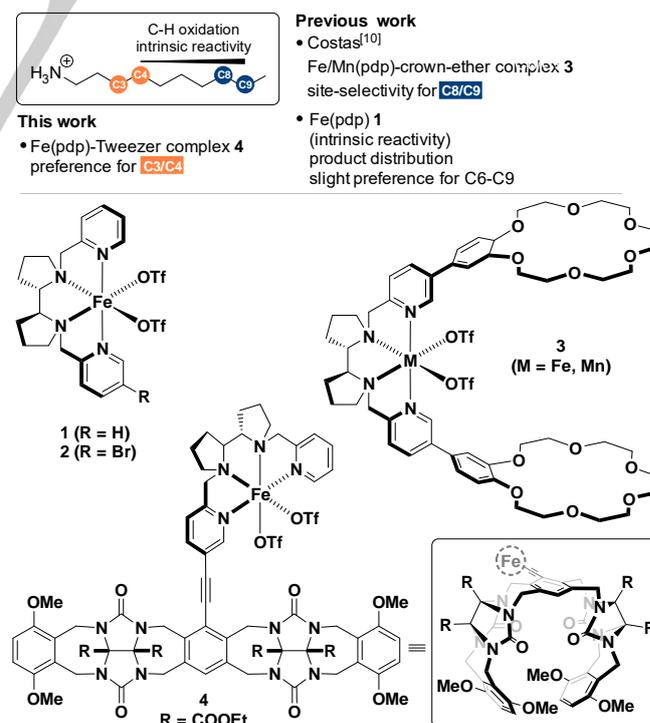
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**Abstract:** The site-selective C–H oxidation of unactivated positions in aliphatic ammonium chains poses a tremendous synthetic challenge for which a solution has not been found yet. Here, we report preferential oxidation of the strongly deactivated C3/C4 positions of aliphatic ammonium substrates by employing a novel supramolecular catalyst. This chimeric catalyst was synthesized by linking the well-explored catalytic moiety Fe(pdp) to an alkyl ammonium binding molecular tweezer. The results highlight the vast potential of overriding the intrinsic reactivity in chemical reactions by guiding catalysis using supramolecular host structures that enable a precise orientation of the substrates.

Over the last decades, synthetic methodology has progressed enormously. However, the site-selective oxidation of unactivated C(sp<sup>3</sup>)–H bonds still poses a remarkable challenge.<sup>[1]</sup> While it is possible to predict and exploit differences in the intrinsic reactivity of the C–H bonds in a given molecule, the oxidation of less reactive positions generally remains elusive.<sup>[2]</sup> Arguably, such methodology would considerably simplify the synthesis of complex oxygenated organic molecules. Nature, in many cases a role model for chemists, clearly demonstrates the potential of such methodology utilizing complex cytochrome P450 enzymes.<sup>[3]</sup> The optimized binding pocket of the active site is crucial in orienting a specific C–H bond towards the oxidant that is not necessarily the most reactive one. Mimicking such selective binding modes with synthetic catalysts has been very challenging.<sup>[4]</sup>

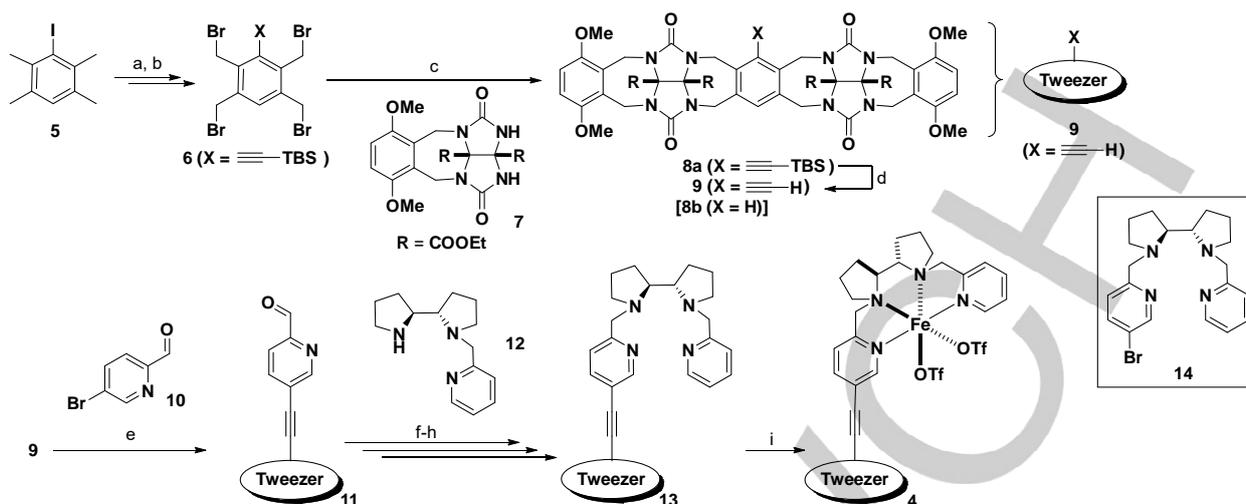
One promising approach is the covalent merger of a well-developed oxidation catalyst with a supramolecular binding motif.<sup>[4b-d, 5]</sup> For instance, seminal work by Breslow involved cyclodextrin (CD)-modified metalloporphyrin complexes.<sup>[4b, 6]</sup> Several covalently modified substrates (to enable binding to the CD-moieties of the catalyst) were selectively oxidized using this strategy. The selective oxidation without the covalent attachment of recognition moieties to the substrate has been less successful, although remarkable examples were reported by Crabtree and

Brudvig,<sup>[7]</sup> and Bach.<sup>[8]</sup> The oxidation of unactivated positions remains problematic.<sup>[4d]</sup> Longer alkyl chains comprise one of the most challenging substrate classes for selective oxidation, as the methylene C–H bonds hardly differ in their reactivity.<sup>[9]</sup> For instance, oxidation of a decyl ammonium substrate (Fig. 1) utilizing the White-Chen<sup>[1a, 2d, 10]</sup> catalyst **1** yields mixtures of ketone products with a preference for oxidation at carbons C6 and higher.<sup>[11]</sup> Remarkably, the Costas group recently reported a novel method for selective oxidation of alkyl ammonium substrates



**Figure 1.** C–H Oxidation catalysts with different selectivities for alkylammonium chains.

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**Scheme 1.** Synthesis of the Fe(pdp)-functionalized tweezer Fe-Twe **4**. a) TBS-acetylene, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, Et<sub>3</sub>NH, 50 °C, 16 h, 97%. b) NBS, AIBN, CCl<sub>4</sub>, 95 °C, 72 h, 58%. c) 7, KOtBu, **6**, DMSO, rt, 16 h, 44%. d) TBAF, THF, 0 °C, 2 h, 80%. e) **10**, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, PPh<sub>3</sub>, THF, μw, 120 °C, 90 min, 76%. f) NaCNBH<sub>3</sub>, TFA, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 h, 96%. g) PBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C → rt, 16 h, 75%. h) **11**, K<sub>2</sub>CO<sub>3</sub>, TBAB, MeCN, 90 °C, 16 h, 97%. i) Fe(OTf)<sub>2</sub>(MeCN)<sub>2</sub>, MeCN, rt, 2.5 h, 58%. AIBN: *N*-bromosuccinimide. TBS: (*tert*-butyldimethylsilyl), TBAB: tetra-*n*-butylammonium bromide, TBAF: tetra-*n*-butylammonium fluoride, TFA: trifluoroacetic acid, NBS: *N*-bromosuccinimide.

favoring the positions C8/C9 (Fig.1).<sup>[11]</sup> The catalyst utilized in their work features a catalytic center (Mn- or Fe-*N,N*-bis(2-pyridylmethyl)-2,2'-bipyrrrodine (Mn- / Fe(pdp)) attached to two 18-benzocrown-6 ether (BC) receptors (**3**) able to bind primary aliphatic ammonium ions.<sup>[11]</sup>

Our recent interest in molecular tweezers,<sup>[12]</sup> combined with their ability to bind alkyl ammoniums prompted us to investigate their potential for selective C–H oxidation. Molecular tweezers are host molecules with an open cavity defined by two rigid arms.<sup>[13]</sup> Specifically, we decided to utilize a framework similar to the glycoluril-based tweezer **8b** (Scheme 1) originally developed by Isaacs.<sup>[14]</sup> We speculated that it may bind alkylammonium cations more rigidly than the flexible crown ethers in catalyst **3**; potentially delivering an increased oxidation selectivity. Here we report the synthesis of the chimeric tweezer-oxidation catalyst **4**, and its unprecedented selectivity for the deactivated positions C3/C4.

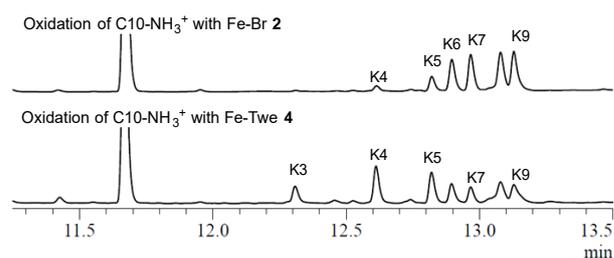
Although the ability of tweezer **8b** (R = COOH, Scheme 1) to bind alkyl ammonium species in water was documented,<sup>[14]</sup> this project depended on binding in acetonitrile, the standard solvent for oxidations utilizing catalyst **1** and its derivatives.<sup>[2e, 10–11, 15]</sup> The binding constant of decyl ammonium tetrafluoroborate (C10-NH<sub>3</sub><sup>+</sup>) to **8b** (R = COOEt) in acetonitrile was determined via NMR titration experiments (see Supporting Information, p. S95–96) and indicated reasonably strong binding ( $K_a = 210 \pm 7.6 \text{ M}^{-1}$ ,  $K_d = 4.77 \text{ mM} \pm 0.17 \text{ mM}$ ). Under the general oxidation concentrations adapted from Costas (1.0 eq. substrate, 74 mM in MeCN; 5 mol% Fe-Twe **8b**; vide infra),<sup>[11]</sup> > 93% of tweezer **8b** would be occupied with substrate.

Encouraged by these initial results, we decided to explore a synthetic route towards the tweezer-catalyst **4**, which comprises the well-explored catalytic moiety Fe(pdp)<sup>[1a, 10]</sup> linked to the tweezer binding motif by an alkyne residue. Initially, we envisioned a convergent approach based on the coupling of tweezer **9** and ligand **14** (Scheme 1). However, attempts to achieve such a coupling failed which led us to develop a more linear approach. Commercially available iododurene (**5**) was

coupled with TBS acetylene under Sonogashira coupling conditions. Subsequent tetrabromination with NBS and AIBN yielded compound **6**, which was linked via alkylation with two equivalents of **7**<sup>[14]</sup> to produce tweezer **8a**. TBS deprotection using TBAF resulted in tweezer **9**, which subsequently was coupled with 5-bromo-2-pyridine carboxaldehyde (**10**). Surprisingly, reductive amination with **12** resulted in low yields under a variety of conditions. Therefore, the desired ligand **13** was constructed via alkylation (after reduction of the aldehyde and Appel-like bromination). The final complex **4** was obtained via coordination of **13** with Fe(OTf)<sub>2</sub>(MeCN)<sub>2</sub>.<sup>[11]</sup> As a reference oxidation catalyst lacking the tweezer binding motif but carrying a substituent at the pyridine 5-position, catalyst **2** (Figure 1) was also synthesized (see Supporting Information).

Surprisingly, the determination of the binding constant of decyl ammonium tetrafluoroborate and Fe-Twe **4** resulted in rather weak binding ( $K_a = 29.5 \pm 1.9 \text{ M}^{-1}$ ,  $K_d = 34.0 \text{ mM} \pm 2.2 \text{ mM}$ ). Subsequent dilution titration experiments, however, revealed that Fe-Twe **4** displays a relatively large dimerization constant ( $K_{\text{dim}} = 160 \pm 2.2 \text{ M}^{-1}$ ) in contrast to tweezer **8b** which did not show significant aggregation (see Supporting information's, p S94–99).

Initially, decyl ammonium tetrafluoroborate was chosen as a model substrate and investigated in the oxidation reactions with



**Figure 2.** GC Chromatograms of the oxidation of C10-NH<sub>3</sub><sup>+</sup> with Fe-Br **2** (top) and Fe-Twe **4** (bottom).

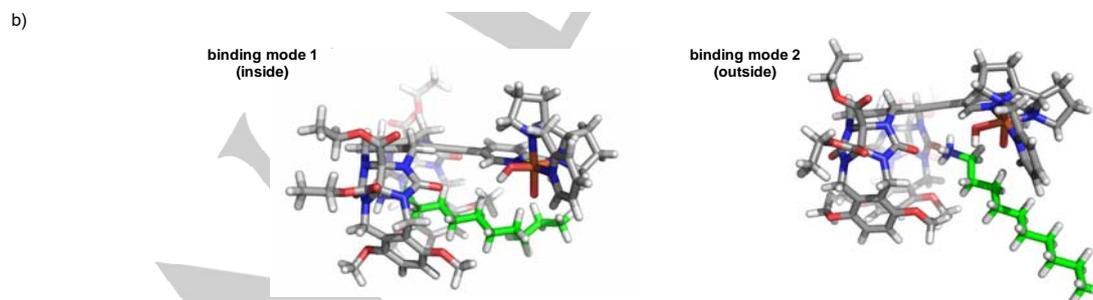
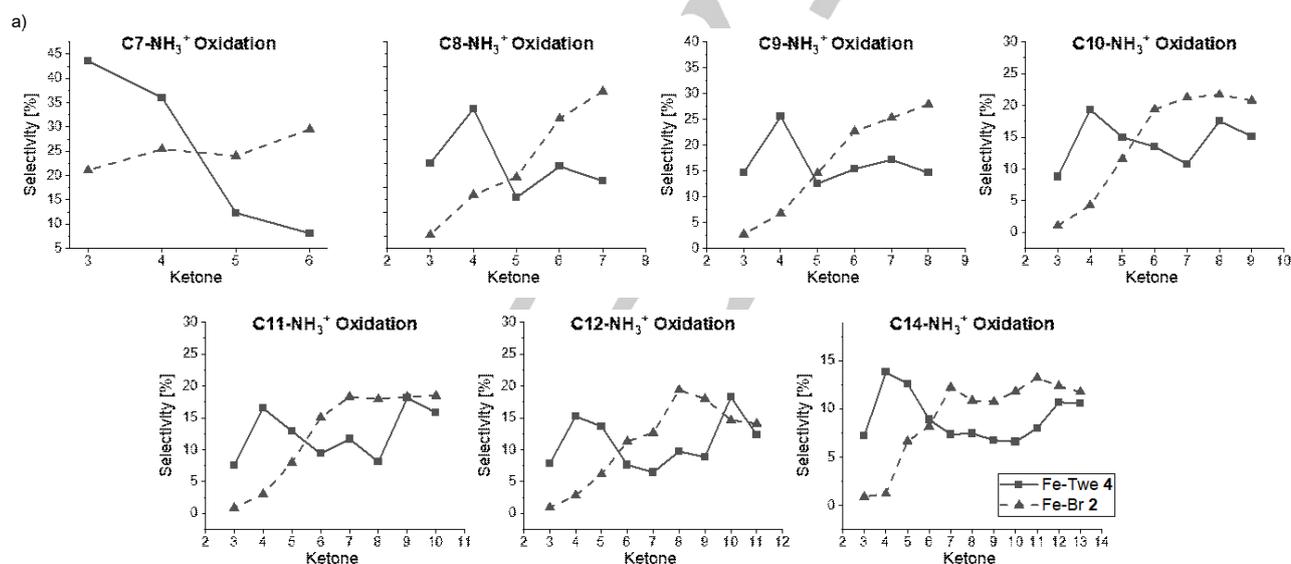
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**Table 1.** Oxidation of aliphatic ammonium salts by catalyst Fe-Br **2** and Fe-Twe **4**.

Reaction scheme: Aliphatic ammonium salt (n = 1 - 6, 8) reacts with 1) Cat. H<sub>2</sub>O<sub>2</sub>, AcOH, 90 min, 0 °C and 2) NEt<sub>3</sub>, Ac<sub>2</sub>O, 1 h, 0 °C (MeCN) to form a ketone product with carbonyl groups at positions K1 and K2.

Entry	Substrate	Catalyst	Conv. [%]	Total Yield <sup>a</sup> [%]	Yield K3-4 [%]	Yield K3-5 [%]	Selectivity <sup>b</sup> K3-4 [%]	Selectivity <sup>b</sup> K3-5 [%]
1 vs 2 <sup>c</sup>	C10-NH <sub>3</sub> <sup>+</sup>	Fe-Br <b>2</b> vs Fe-Twe <b>4</b>	75 vs 47	34 vs 25	1.8 vs 7.0	5.9 vs 11	5.3 vs 28	17 vs 43
3 vs 4	C10-NH <sub>3</sub> <sup>+</sup>	Fe-Br <b>2</b> vs Fe-Br <b>2</b> + <b>8b</b>	75 vs 52	34 vs 19	1.8 vs 1.5	5.9 vs 3.4	5.3 vs 7.8	17 vs 18
5 vs 6	C10-NMeH <sub>2</sub> <sup>+</sup>	Fe-Br <b>2</b> vs Fe-Twe <b>4</b>	57 vs 43	27 vs 18	1.9 vs 2.9	5.5 vs 5.6	7.1 vs 16	20 vs 32
7 <sup>d</sup> vs 8 <sup>d</sup>	C10-NMe <sub>2</sub> H <sup>+</sup>	"	60 vs 41	32 vs 14	1.7 vs 0.9	5.3 vs 2.4	5.2 vs 6.2	17 vs 17
9 vs 10	C7-NH <sub>3</sub> <sup>+</sup>	"	34 vs 34	3.8 vs 6.4	1.8 vs 5.1	2.7 vs 5.9	46 vs 80	70 vs 92
11 vs 12	C8-NH <sub>3</sub> <sup>+</sup>	"	37 vs 22	17 vs 8.2	3.2 vs 4.2	6.1 vs 5.2	19 vs 51	36 vs 64
13 vs 14	C9-NH <sub>3</sub> <sup>+</sup>	"	49 vs 39	30 vs 16	2.9 vs 6.6	7.3 vs 8.7	10 vs 40	24 vs 53
15 vs 16	C11-NH <sub>3</sub> <sup>+</sup>	"	57 vs 36	42 vs 24	1.6 vs 5.7	5.0 vs 8.7	3.9 vs 24	12 vs 37
17 vs 18	C12-NH <sub>3</sub> <sup>+</sup>	"	63 vs 39	28 vs 10	1.0 vs 2.4	2.8 vs 3.8	3.8 vs 23	9.9 vs 37
19 vs 20	C14-NH <sub>3</sub> <sup>+</sup>	"	77 vs 68	33 vs 18	0.7 vs 3.8	2.9 vs 6.1	2.1 vs 21	8.8 vs 34

General reaction conditions:<sup>[11]</sup> substrate (18.5 μmol, 1.0 equiv.), catalyst (925 nmol, 5 mol%), AcOH (148 μmol, 8.0 equiv.), H<sub>2</sub>O<sub>2</sub> (278 μmol, 15 equiv., addition via a syringe pump over 90 min), MeCN, 0 °C. After 15 min, internal standard (biphenyl, 9.25 μmol, 0.5 equiv.), NEt<sub>3</sub> (100 μL), Ac<sub>2</sub>O (150 μL), 0 °C. After 1 h, washing with H<sub>2</sub>O, 2 M H<sub>2</sub>SO<sub>4</sub>, NaHCO<sub>3</sub>, H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and analyzed by GC. [a] Total yield refers to mixture of all isomers. [b] Selectivity refers to yield of selected ketones/total yield. [c] 5 mol% of Tweezer **8b** was added additionally. [d] Different work-up, see SI.



**Figure 3.** a) Reaction selectivities of the possible ketone products for the oxidation of different aliphatic ammonium ions with Fe-Br **2** resp. Fe-Twe-**4**. b) Binding modes 1 and 2 of Fe-**4** and decyl ammonium (optimized at the PM3 level).

Fe-Br **2** (intrinsic reactivity) and Fe-Twe **4** (Figure 2). As expected,<sup>[11]</sup> the non-directed oxidation with Fe-Br **2** resulted in mixtures of ketone products (K4-K9, ketones at C4-C9). Oxidation

at the more proximal positions (K3/K4) was hardly detectable due to deactivation by the nearby ammonium moiety.<sup>[16]</sup> The main products were K6-K9 in nearly equal amounts. Employing catalyst

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Fe-Twe 4 also led to mixtures but resulted in an inversed selectivity. Interestingly, the deactivated positions K3-K5 were those preferred by the supramolecular catalyst 4, overriding the intrinsic reactivity of the substrate (Table 1, entry 1 vs 2).

Several control experiments were carried out to elucidate the role of the supramolecular recognition motif. First an experiment in which the two parts of Fe-Twe 4 were added as separate entities (tweezer 8b (5 mol%), and Fe-Br 2 (5 mol%)) was performed (Table 1, entry 4). The selectivity was significantly reduced and similar to the results of Fe-Br 2, demonstrating that the tweezer has to be covalently linked to the oxidation catalyst to achieve high selectivity. In separate experiments, we tried to reduce the binding ability of the substrate via methylation of the amine residue. The oxidation of C10-NMeH<sub>2</sub><sup>+</sup> already delivered reduced selectivities (entry 5 vs 6) while with dimethylated C10-NMe<sub>2</sub>H<sup>+</sup> as substrate, the selectivity was almost completely lost. These results strongly indicate that the substrate binds to the tweezer via hydrogen bonds. The yields in these two cases (entries 6 and 8) were only slightly reduced in comparison to entry 2 which suggest that oxidation without specific binding to the tweezer is taking place as a background reaction. This is also indicated by the oxidation of cyclohexane by both catalysts (see Supporting Information, p. S37). In a competition experiment, decylammonium and cyclohexane were subjected to the oxidation reactions with Fe-Br 2 and Fe-Twe 4 in equal amounts which resulted in only slightly increased selectivity for decylammonium with Fe-Twe 4. The background reaction was much less pronounced with 3,<sup>[11]</sup> presumably due to the oxidant being blocked from two sides by the crown ether moieties. A third series of control experiments was performed with the aim of inhibiting substrate binding inside Fe-Twe 4. As inhibitors, NH<sub>4</sub>PF<sub>6</sub>, NaOTf and methyl viologen dichloride hydrate were explored. The yields of the oxidation products, as well as the selectivity for C3-4 decreased. However, these results are difficult to interpret since the inhibitor, also inhibits oxidation of the regular catalyst Fe-Br 2 devoid of a tweezer moiety. However, due to the reduced selectivity these experiments also indicate some background oxidation with regular "solution" selectivity at C6-9.

Subsequently, we studied the oxidation of several aliphatic ammonium salts with different chain lengths (Table 1, Figure 3). For all oxidation reactions with Fe-Twe 4 a pronounced selectivity increase for the C3–C4 positions was observed compared to the non-directed oxidations. In fact, with most substrates, ketones K3 or K4 were the favored products for Fe-Twe 4 oxidation reactions. The yields, however, were generally lower for catalyst 4, which is presumably due to catalyst decomposition during the oxidation reaction (see Supporting Information, p. S39-42). The only exception is the oxidation of C7-NH<sub>3</sub><sup>+</sup> in which almost all positions are deactivated.<sup>[16]</sup> Moreover, substrates with longer alkyl chains mostly resulted in higher yields compared to the short ones, a trend also observed with 3.<sup>[11]</sup> Regarding the selectivities, in principle, two different binding motifs can be envisioned for catalyst 4 (Figure 3b): (1) The binding of the aliphatic chain inside the cavity of the tweezer. This binding mode is observed in aqueous solution, presumably due to the hydrophobic effect.<sup>[14]</sup> It would expose positions C6-C8 to the oxidant. (2) Without the hydrophobic effect, the sole binding to the polar end groups (urea carbonyl and methoxy oxygen) of the tweezer would be feasible, favoring the oxidation of positions C3-C5. The oxidation results obtained clearly suggest that the second binding mode is the predominant one. Molecular modeling was performed to investigate the suggested binding modes of the ammonium

substrate to the tweezer (see Supporting Information, p. S101-107). According to the calculations, the two binding modes are relatively close in energy indicating that C6-9 oxidation not only stems from a background reaction but also from binding mode 1. However, binding mode 2 (the cavity is filled with a acetonitrile solvent, not shown in Fig. 3) is preferred by approx. 5 kJ/mol, in accordance with the experimental results. Since binding mode 2 depends on the guest molecule acetonitrile, the observed selectivity for K3-5 should be solvent dependent. Indeed, the selectivity is greatly reduced with trifluoroethanol, and disappears completely with the larger hexafluoro isopropanol as solvent (see Supporting information, p. S35-36). These results provide further evidence that the observed oxidation of the unactivated positions C3-5 stem from substrate binding to the tweezer moiety of catalyst 4.

In summary, we reported the synthesis of a supramolecular oxidation catalyst capable of overriding the intrinsic reactivity in aliphatic C–H oxidation of alkyl ammonium salts. The main products formed were ketones at carbons C3 and C4, positions that are intrinsically strongly deactivated and therefore not formed to a significant degree with other catalysts. Although the selectivities have clearly to be improved to achieve synthetically useful yields, these results augur well for the selective oxidation of unactivated C–H positions on complex carbon frameworks.

## Acknowledgements

This work was supported by the Swiss National Science Foundation as part of the NCCR Molecular Systems Engineering program. The authors thank Fabian Bissegger for VT-NMR experiments, Dr. Michael Pfeffer for HR-MS analysis, and Dr. Joan Serrano Plana for helpful discussions. Calculations were carried out on the ETH Euler cluster.

**Keywords:** C–H oxidation • molecular recognition • regioselectivity • catalysis • supramolecular chemistry

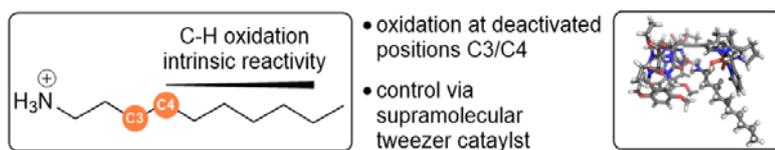
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## COMMUNICATION

## Entry for the Table of Contents



We report the synthesis of a supramolecular tweezer catalyst capable of oxidizing aliphatic ammonium salts at the deactivated methylene positions C3/C4. The catalyst is able to override the intrinsic reactivity in C–H oxidation of these substrates.

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