Tweezer-Based C-H Oxidation Catalysts Overriding the Intrinsic Reactivity of Aliphatic Ammonium Substrates

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Abstract: The site-selective C-H oxygenation of alkyl chains as well as deactivated positions remains a great challenge for chemists. Here, we report the synthesis and application of four new supramolecular tweezer-based oxidation catalysts. They consist of the well-explored M(pdp/mcp) oxidation moiety and a molecular tweezer capable of binding ammonium salts. All catalysts display preferential oxidation of the strongly deactivated C3/C4 positions, however to different degrees. Furthermore, the best performing catalyst **Fe(pdp)Twe** was explored with an expanded substrate scope. It was demonstrated that the deactivated positions C3/C4 are also preferentially oxidized in these cases.

Introduction

Oxygenated hydrocarbon skeletons are abundant in nature and are crucial in many biological interactions. In nature, enzymes like cytochrome P450 enable the selective C-H oxygenation of unactivated positions in complex hydrocarbon frameworks, even if those are intrinsically the least reactive ones.[1] Due to the enormous scientific work over the last decades, chemists have learned to mimic such C-H oxygenations of unactivated positions with man-made catalysts.[2] The intrinsic reactivity of C-H bonds is now well-understood and even predictable, as shown by the groups of White,[2b, 3] and Baran.[2a] Moreover, the groups of White[4] and Costas[5] reported catalysts that favor oxidation at less hindered sites over more electron-rich ones. Despite these great advances, the site-selective oxidation of unactivated C-H bonds still represents a great challenge for synthetic chemists. Especially when it comes to longer flexible carbon chains (alkyl groups), as they feature a multitude of C-H bonds with very similar reactivity and steric hindrance, leading to mixtures of products. Even more challenging is the oxidation of *de*activated C-H bonds close to electron-withdrawing substituents. Related to the field of C-H oxygenation, similar challenges exist for other C(sp³)-H bond functionalizations.[6]

One way of addressing the selectivity issue of flexible carbon chains (alkyl groups) and *de*activated C-H bonds is the development of catalysts capable of binding and orientating substrates via non-covalent supramolecular recognition.[7] One of the first pioneering supramolecular C(sp³)-H oxidation catalysts was developed by Breslow and coworkers. They reported a manganese porphyrin catalyst with up to four cyclodextrin

moieties capable of binding and precisely orientating covalently modified steroid substrates.[8] Further impressive examples were reported by Brudvig and Crabtree[9] as well as by Bach and coworkers.[10] They developed catalysts that bind substrates via hydrogen bonding, however, oxidation was limited in both cases to activated benzylic positions.
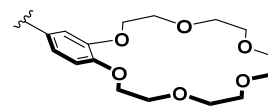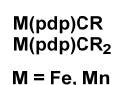
A few years ago, Costas and coworkers reported the site-selective C-H oxidation of unactivated methylene units in aliphatic
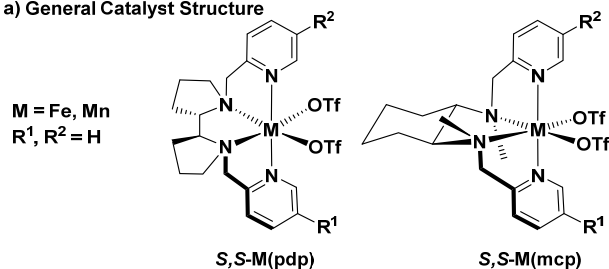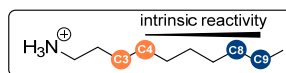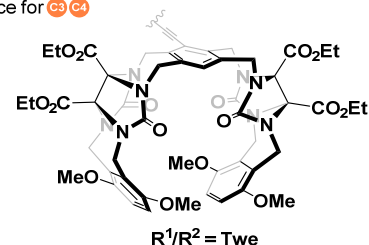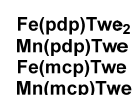

Figure 1. Supramolecular C-H oxidation catalysts for the oxidation of linear aliphatic ammonium salts.

ammonium salts by merging the **Fe(pdp)**[3] and **Mn(pdp)**[11] catalysts (Figure 1a) with two crown ether (CR) units (Figure 1b).[12] They achieved high selectivities for the C8/C9 positions of

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aliphatic ammonium substrates despite the very similar reactivity of all the methylene groups remote from the electron-withdrawing ammonium group (C6 and higher). Subsequently, they also applied the crown ether catalysts in the oxidation of steroid substrates and demonstrated impressive predictability in these cases.[13]

Examples in which intrinsically deactivated positions are oxidized in the presence of more reactive C-H bonds, however, are still limited, despite the significant interest in such functionalizations. For instance, very recently Costas and coworkers reported the site-selective γ-lactonization of very strong primary C-H bonds in carboxylic acid substrates even in the presence of more reactive secondary and tertiary bonds, enabled via a directed intramolecular oxidation strategy.[14] Our group merged the White-Chen catalyst **Fe(pdp)**[3a] with a molecular glycoluril-based tweezer[15] to deliver **Fe(pdp)Twe** (Figure 1b).[16] A molecular tweezer is a host molecule with an open cavity defined by two rigid arms.[17] Similar to crown ethers, this tweezer moiety is capable of binding ammonium salts.[15] The shorter distance between the oxidation site and the binding site resulted in the preferential oxidation of C3/C4, positions that are strongly deactivated due to the nearby positive charge of the ammonium moiety. As catalyst-directed oxygenations of deactivated positions remain underexplored, we decided to further expand our initial investigations by increasing the catalyst and substrate scope. We here report the synthesis of four new supramolecular catalysts and their application to the oxidation of challenging aliphatic ammonium substrates.

Results and Discussion

Catalyst Scope

First, the catalyst scope was expanded. In particular, we were interested in the attachment of two molecular tweezer units to the pdp backbone instead of only one (Figure 2b). This was of interest to us, as the original catalyst **Fe(pdp)Twe** (Figure 2a) suffered to some extent from an unspecific background reaction.[16] We hypothesized that it might be caused by the relatively open structure of the catalyst that may enable oxidation even without specific tweezer-substrate binding. The synthesis of the difunctionalized catalyst **Fe(pdp)Twe₂** involved the double alkylation of bipyrrolidine (**4**) with the tweezer bromide **3** (see Scheme 1) that was accessed via our route developed earlier.[16] Subsequent complexation with Fe(OTf)$_2$(MeCN)$_2$ resulted in the desired *S,S*-**Fe(pdp)Twe₂** in a similar step count (10 steps) as the original catalyst. To our surprise, the oxidation of decylammonium tetrafluoroborate (**7**) with **Fe(pdp)Twe₂** in the presence of H$_2$O$_2$ and acetic acid gave inferior results to the monofunctionalized **Fe(pdp)Twe** (Table 1). As no increase in yield and an even lower selectivity for C3/C4 oxidation were observed, the monofunctionalization of the catalyst was obviously not the cause of the background reaction observed. Therefore, the focus of the remaining study was put on novel mono-functionalized catalysts. Next, the scope of the catalysts was expanded to the mcp-ligand (Figure 1a), as well as to the manganese metal center. The synthesis of the supramolecular catalysts started from tweezer bromide **3** that was reacted with amines **5**[18] and **6**[19] resulting in the two free ligands *S,S*-**(mcp)-Twe** and *S,S*-**(pdp)-Twe**, respectively (Scheme 1). Complexation with either FeCl$_2$/AgOTf or Mn(OTf)$_2$ gave the desired complexes. Furthermore, the established unfunctionalized *S,S*-**Fe(pdp)**[3a] and *S,S*-**Fe(mcp)**[20] complexes as well as the two Mn versions *S,S*-**Mn(pdp)**[11] and *S,S*-**Mn(mcp)**[21] were synthesized and compared with the respective tweezer complexes *S,S*-**Fe(pdp)Twe**, *S,S*-**Fe(mcp)Twe**, *S,S*-**Mn(pdp)Twe**, and *S,S*-**Mn(mcp)Twe** in the oxidation of decylammonium tetrafluoroborate (**7**, Table 2, Figure 3a-b). Whereas the *S,S*-**Mn(pdp)Twe** and *S,S*-**Mn(mcp)Twe**
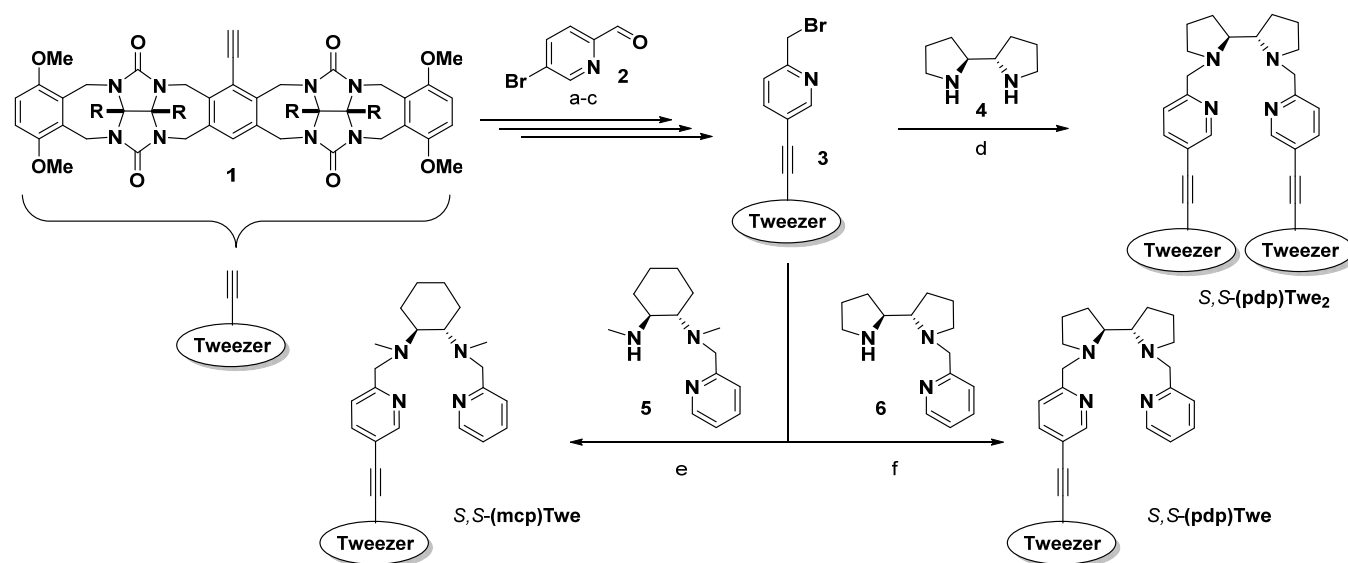
Scheme 1. Synthesis of the three ligands *S,S*-**(pdp)Twe**, *S,S*-**(mcp)Twe** and *S,S*-**(pdp)Twe₂**. The Synthesis of tweezers **1** and **3,** compound **6**, and ligand *S,S*-**(pdp)-Twe** was previously reported.[16] a) **2**, PdCl$_2$(PPh$_3$)$_2$, CuI, PPh$_3$, THF, mw, 120 °C, 90 min, 76%. B) NaCNBH$_3$, TFA, MeOH, CH$_2$Cl$_2$, rt, 4 h, 96%. C) PBr$_3$, CH$_2$Cl$_2$, 0 °C → rt, 16 h, 75%. D) **3** (2 equiv.), **4** (1 equiv.), K$_2$CO$_3$, TBAB, MeCN, 90 °C, 16 h, 88%. E) **3** (1 equiv.), **5**[18] (1 equiv.), K$_2$CO$_3$, TBAB, MeCN, 90 °C, 16 h, 94%. F) **3** (1 equiv.), **6**[19] (1 equiv.), K$_2$CO$_3$, TBAB, MeCN, 90 °C, 16 h, 97%. TBAB: tetra-*n*-butylammonium bromide, TFA: trifluoroacetic acid.
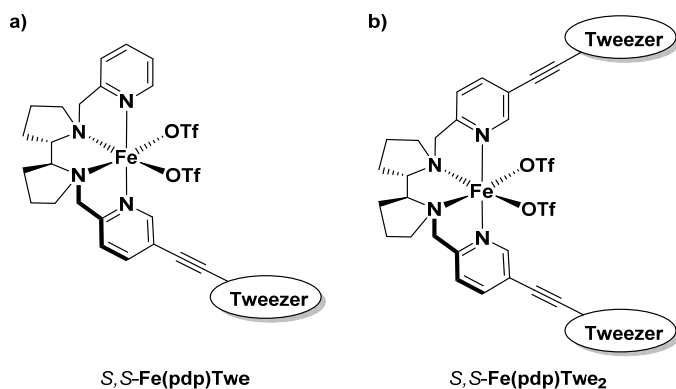
Figure 2. Depiction of *S,S*-**Fe(pdp)Twe** and *S,S*-**Fe(pdp)Twe₂**.

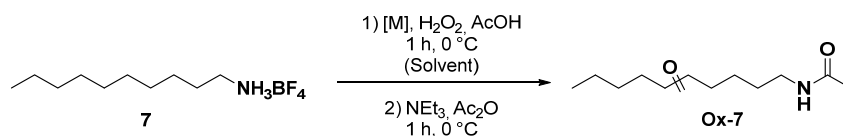**Table 1.** Oxidation of decylammonium **7** with **Fe(pdp)Twe** and **Fe(pdp)Twe₂**.[a]

Catalyst	Conv [%]	Total Yield[b] [%]	K3/K4 Selectivity[c] [%]	K3-K5 Selectivity[c] [%]
Fe(pdp)Twe	47	25	28	43
Fe(pdp)Twe₂	34	24	19	34

[a] General reaction conditions: substrate (9.25 μmol, 1.0 equiv.), Fe (463 nmol, 5 mol%), AcOH (74.0 μmol, 8.0 equiv.), H₂O₂ (139 μmol, 15 equiv., addition *via* a syringe pump over 90 min), MeCN, 0 °C. After 15 min, internal standard (biphenyl, 4.63 μmol, 0.5 equiv.), NEt₃ (50 μL), Ac₂O (75 μL), 0 °C. After 1 h, washing with H₂O, 2 M H₂SO₄, NaHCO₃, dried (Na₂SO₄) and analyzed by GC. [b] Total yield refers to the mixture of all isomers. [c] Selectivity refers to the yield of selected ketones/total yield.

resulted in active catalysts, **Fe(mcp)Twe** gave only low conversions and yields in the oxidation experiments (Table 2, entry 6) despite repeated attempts of synthesizing it under various reported conditions.[20, 22] Interestingly, the Fe(mcp) combination is often excluded in catalytic studies, potentially indicating that it is generally less accessible/active.[13-14]

In agreement with previous results,[12-13] the manganese complexes gave higher yields at lower catalyst loading as compared to the **Fe(pdp)Twe** catalyst (1 vs. 3 mol%). They also displayed a significant increase in C3/C4 selectivity (5.8 vs. 14, and 7.2 vs. 13, respectively) compared to their unfunctionalized counterparts **Mn(mcp)** and **Mn(pdp)** (Table 2, entries 1-4, Figure 3a). However, the selectivity increase was not as marked as for the **Fe(pdp)**-series (Table 2, entries 7-8). A closer inspection of the results revealed that both K3 and K4 selectivity are affected to a similar extent (Figure 3b). Furthermore, for both Mn Twe catalysts, a distinct increase in C5 oxidation is observed compared to their unfunctionalized versions.

This is in stark contrast to the original **Fe(pdp)Twe**, which shows only a slight increase in K5 product compared to its unfunctionalized counterpart. A comparison of the two catalyst backbones reveals that the **Mn(mcp)Twe** not only gives slightly better selectivities for the proximal C3-C5 positions compared to **Mn(pdp)Twe** but also higher yields (Table 2). In conclusion, both **Fe(pdp)Twe** and **Mn(mcp)Twe** possess interesting features. The first displays the best selectivity for the deactivated positions C3/C4 of all the catalysts investigated, whereas the second one gives the best yields and the highest selectivity for the K5 product. Since to us the oxidation of the strongly deactivated positions C3 and C4 was most interesting, we decided to focus on the **Fe(pdp)Twe** catalyst in the subsequent oxidation experiments that aimed at expanding the substrate scope.

Solvent screening

Before expanding the substrate scope, we decided to explore alternative solvents besides acetonitrile. Specifically, we wanted to investigate the polar solvents trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP). Both solvents are known to activate H₂O₂, and therefore facilitate the hydrogen atom transfer (HAT) to form the reactive [LMᵛ(O)OAc]²⁺ species in Fe and Mn catalyzed C-H oxidation reaction.[23] Since these solvents also deactivate the α C-H bond of the alcohols formed,[24] higher amounts of alcohol products are observed (in HFIP almost exclusively). Being not aware of this strong deactivation of the α C-H bond in the past, led to a misinterpretation in our initial publication.[16]

Table 2. Oxidation of decylammonium tetrafluoroborate (**7**) using different catalysts and solvents.[a]

Entry	Catalyst	[Cat] [mol%]	Solvent	Conv. [%]	Total Yield[c] [%]	K3/K4 Selectivity[d] [%]	K3-K5 Selectivity[d] [%]
1 vs 2	**Mn(mcp)** vs **Mn(mcp)Twe**	1	MeCN	69 vs 58	55 vs 40	5.8 vs 14	15 vs 29
3 vs 4	**Mn(pdp)** vs **Mn(pdp)Twe**	1	MeCN	58 vs 45	32 vs 26	7.2 vs 13	16 vs 28
5 vs 6	**Fe(mcp)** vs **Fe(mcp)Twe**	3	MeCN	18 vs 6.8	15 vs 2.0	3.6 vs 9.0	7.9 vs 15
7 vs 8	**Fe(pdp)** vs **Fe(pdp)Twe**	3	MeCN	35 vs 17	31 vs 14	6.4 vs 27	13 vs 36
9[b] vs 10[b]	**Fe(pdp)** vs **Fe(pdp)Twe**	3	TFE	63 vs 38	34 vs 20	1.6 vs 5.6	9.5 vs 20
11[b] vs 12[b]	**Fe(pdp)** vs **Fe(pdp)Twe**	3	HFIP	94 vs 45	73 vs 30	0.7 vs 15	3.3 vs 34

[a] General reaction conditions: substrate (18.5 μmol, 1.0 equiv.), Fe (555 nmol, 3 mol%) or Mn catalyst (185 nmol, 1 mol%), AcOH (148 μmol, 8.0 equiv. or 407 μmol, 22 equiv., respectively), H₂O₂ (46.3 μmol, 2.5 equiv., addition *via* a syringe pump over 16 min), solvent, 0 °C. After 45 min, internal standard (biphenyl, 9.25 μmol, 0.5 equiv.), NEt₃ (100 μL), Ac₂O (150 μL), 0 °C. After 1 h, washing with H₂O, 2 M H₂SO₄, NaHCO₃, dried (Na₂SO₄) and analyzed by GC. [b] Additional IBX oxidation of alcohol products, see SI p. SXX. [c] Total yield refers to the mixture of all isomers. [d] Selectivity refers to the yield of selected ketones/total yield.
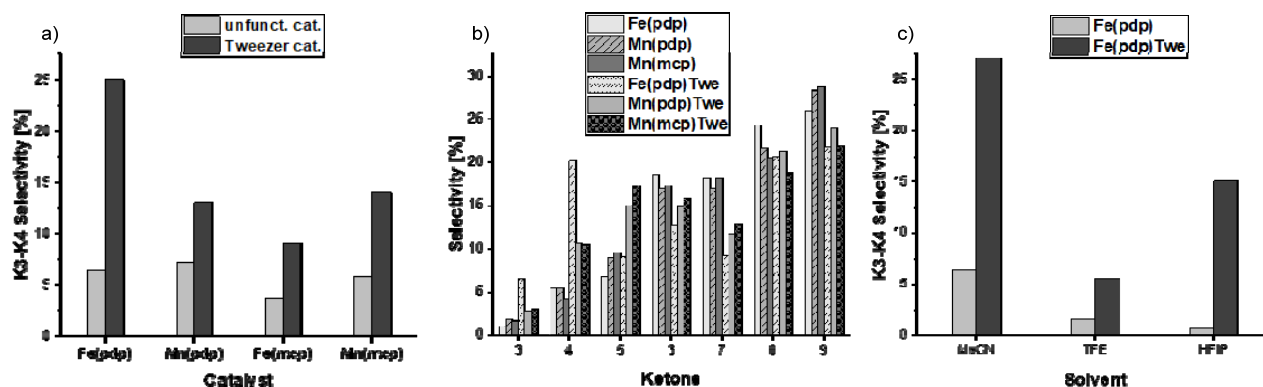
Figure 3. Graphical depictions of the decylammonium tetrafluoroborate (**7**) oxidation results from Table 2: a) the K3-K4 oxidation selectivity of various catalysts; b) the oxidation selectivity of the observed ketone products; c) the K3-K4 selectivity in different solvents in the oxidation with **Fe(pdp)** and **Fe(pdp)Twe**.

The alcohol products observed in the oxidation of decylammonium possess very similar retention times and additionally overlap with the signals of the ketone products K8 and K9. This led to the misinterpretation of the products in the HFIP and TFE experiment in the initial publication. Because an excess of H_2O_2 was used, it was assumed that the observed product signals correspond to ketones, and concluded that the selectivity of our supramolecular catalyst was lost in TFE and HFIP. Once we realized this, the product mixtures obtained were further oxidized in a subsequent step with IBX to exclusively obtain the ketone products. And indeed, in both solvents, an increased selectivity of the deactivated C3/C4 positions was observed for the supramolecular catalyst compared to the unfunctionalized one (Table 2, Figure 3c). Although the best selectivity was still obtained in MeCN (Table 2, entry 8), the 21-fold C3/C4 selectivity increase in HFIP for the switch from **Fe(pdp)** to **Fe(pdp)Twe** was exceptional (Table 2, entries 11-12). Furthermore, as expected the activation of H_2O_2 by TFE and HFIP increased the conversion and yield in the oxidation of decylammonium distinctly (Table 2, entries 7-12).

Substrate Scope

Finally, the oxidation of new substrates was investigated (Table 3, Figure 4). It was decided to utilize the standard conditions using **Fe(pdp)/Fe(pdp)Twe** in MeCN, as they delivered the highest selectivities. In particular, we were interested in the oxidation of 3,7-dimethyloctan-1-ammonium (**8**) and 4,8-dimethylnonan-1-ammonium tetrafluoroborate (**9**), substrates with terpene substitution pattern. The substrates can be readily synthesized from 1-bromo-3,7-dimethyloctane in three steps. First, the bromide was reacted in a S_N2 reaction with NaN_3 or NaCN, respectively.[25] Subsequent reduction with $LiAlH_4$ and direct ammonium salt formation of the crude amines with $HBF_4 \cdot OEt_2$ resulted in the desired substrates **8** and **9** (see SI, p.S12-S14). Both substrates possess two tertiary C-H bonds: an intrinsically deactivated one in proximity to the positive charge (C3 and C4, respectively) and a remote one (C7 and C8, respectively). For analysis of the oxidation products, a combination of GC and NMR analysis was used. The conversion and yield were calculated *via* GC using an internal standard. The regioselectivity, however, was determined by 1H NMR analysis of the isolated product mixture by comparison of the methyl groups and the methylene signal α-to the amide (for details, see SI p. S25-S26 and S30-S32).

Regarding substrate **8**, the oxidation with the unfunctionalized **Fe(pdp)** catalyst gave mainly the remote alcohol product **8**-O7 and only minor amounts of the proximal C3 alcohol product **8**-O3 (11% selectivity for C3, Table 3). Notably, no ketone products from the oxidation of less reactive secondary C-H bonds were observed. As expected, the usage of **Fe(pdp)Twe** catalyst promoted the oxidation of the deactivated C3 C-H bond leading to a distinct selectivity increase from 11 to 41%. When switching to the extended substrate **9**, comparable results were observed with a general increase in the formation of the less deactivated tertiary **9**-O4 alcohol compared to **8**-O3. More precisely, the selectivity for C4 was 25% and 57% for **Fe(pdp)** and **Fe(pdp)Twe**, respectively, making it the major product in the oxidation with the supramolecular catalyst. Comparing the two substrates, a similar performance was achieved by **Fe(pdp)Twe** as it increased the selectivity for the deactivated position by about 30 percentage points in each case. Considering the relative selectivity change, more impressive results were obtained with substrate **8**. While for compound **9** a 2.3-fold increase for the oxidation of C4 was observed, the increase for C3 selectivity was 3.7-fold for **8**, despite the stronger deactivation at C3 as compared to C4.

Next, the oxidations of substrates **10** and **11** were investigated. They can be synthesized in one step from the corresponding commercial amines by reaction with $HBF_4 \cdot OEt_2$ (see SI p.S14-S15). Both substrates possess only one tertiary C-H bond (at C3 and C4, respectively), hence we envisioned the intrinsic reactivity for these positions would be higher compared to the substrates **8** and **9**. Interestingly, this was not the case. For **10**, the C3 oxidation selectivity was only 4.9% for the unfunctionalized **Fe(pdp)** catalyst, which could be increased up to 16% with **Fe(pdp)Twe**. The two major products were the ketone products (*rac*-**10**-K5 and **10**-K6) at the remote cyclohexane positions C5/C6 and also minor amounts of *rac*-**10**-K4 ketone were formed (for details, see SI p. S34-S49). Similarly, in the oxidation of **11**, the selectivity for alcohol product **11**-O4 increased from 9.0% to 27% for **Fe(pdp)** and **Fe(pdp)Twe**, respectively. Again, the main products were the ketone products at the remote cyclohexane positions C6/C7 (for details, see SI p.S50-S61). The reason for the low reactivity of the tertiary C3-H and C4-H bonds in **10** and **11** may be due to steric effects. The electronic difference should favor the tertiary bonds over the cyclic secondary C-H bonds despite their proximity to the positive charge. This is supported by the observation, that no ketone products were formed in the case of the linear substrates **8** and **9**.[26] Again, considering the relative

selectivity change, slightly better results were observed for the C3 oxidation in **10** compared to C4 in **11** with a 3.2-fold increase compared to a 3.0-fold increase, respectively.

Overall, it seems that the substrate-tweezer binding slightly favors C3 over C4, as the C3 selectivity is amplified to a stronger extent than the C4 counterpart. This is most evident for substrates **8** and **9** (Figure 4). Thus, we assume that C3 is closer to the oxidation center in the substrate-tweezer complex.

Table 3. Oxidation of **7** and new substrates (**8-11**) with **Fe(pdp)** and **Fe(pdp)Twe**.[a]

Substrate[a]	Fe(pdp)		Fe(pdp)Twe	
	Total Yield[b] [%]	🟠 Selectivity[c] [%]	Total Yield[b] [%]	🟠 Selectivity[c] [%]
7	31	6.4	14	27
8	34	11	16	41
9	24	25	15	57
10	28	4.9	11	16
11	36	9.0	14	27

[a] General reaction conditions: substrate (1.0 equiv.), Fe (3 mol%), AcOH (8.0 equiv.), H$_2$O$_2$ (2.5 equiv., addition *via* a syringe pump over 16 min), MeCN, 0 °C. After 45 min, internal standard (biphenyl, 9.25 µmol, 0.5 equiv.), NEt$_3$, Ac$_2$O, 0 °C. After 1 h, work up, see SI p. S19-S20. [b] Total yield refers to the mixture of all isomers. [c] Selectivity refers to the yield of selected ketones/total yield.
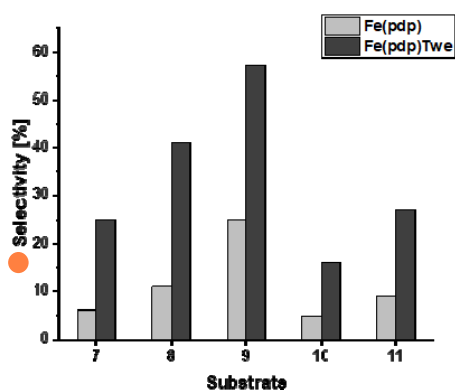

Figure 4. Oxidation selectivity of **Fe(pdp)** and **Fe(pdp)Twe** for C3 and/or C4.

Conclusion

In summary, we synthesized four new supramolecular oxidation catalysts that are based on well-established Fe/Mn oxidation catalysts linked to a molecular glycoluril-based tweezer. The **Fe(pdp)Twe$_2$**, unfortunately, did not improve yield and even showed a slightly lower C3/C4 selectivity. These results indicate that the rotational freedom of the alkyne linkage, as well as the low binding constant of decyl ammonium tetrafluoroborate (**7**) in MeCN (determined for **Fe(pdp)Twe** as K_a = 29.5±1.9 M^{-1}, K_d = 34.0 ± 2.2 mM)[16], remain limitations of this supramolecular catalyst class.

The two Mn tweezer catalysts (**Mn(mcp)Twe** and **Mn(pdp)Twe**) resulted in a distinct increase in conversion and yield. They both showed a significant increase in C3/C4 selectivity compared to the unfunctionalized catalysts, however not as marked as with the **Fe(pdp)Twe** catalyst. Moreover, in both cases, C5 oxidation was substantially amplified.

The oxidation of four additional substrates with the **Fe(pdp)Twe** catalyst was investigated. In the case of substrate **9**, it was possible to observe the deactivated C4 oxidation product as the major product. Moreover, the relative increase in selectivity for the strongly deactivated C3 positions in compound **8** was exceptional. These results highlight the potential of supramolecular catalysts for the oxidation of deactivated C-H bonds that are very difficult to oxidize with alternative means. However, further improvements in the design and efficiency of these systems are required to enable more general applicability.

Experimental Section

General small-scale Fe oxidation reactions: Substrate (18.5 µmol, 1.0 equiv.) and Fe catalyst (555 nmol, 3 mol%) were dissolved in 200 µL solvent in a 1 mL screw vial. After the addition of AcOH (8.5 µL, 148 µmol, 8.0 equiv.), the mixture was cooled to 0 °C. Next, a solution of commercially available aq. H$_2$O$_2$ (50% w/w, Sigma Aldrich, 51.4 µL, 46.2 µmol, 2.5 equiv.) diluted in solvent (~ 0.9 M) was slowly added over 16 min by a syringe pump. After the addition, the mixture was left to stir for another 45 min. The workup was performed according to SI, p. S19-S20.
General small-scale Mn oxidation reactions: Substrate (18.5 µmol, 1.0 equiv.) and Mn catalyst (185 nmol, 1 mol%) were dissolved in 200 µL solvent in a 1 mL screw vial. After the addition of AcOH (23.3 µL, 407 µmol, 22.0 equiv.), the mixture was cooled to 0 °C. Next, a solution of commercially available aq. H$_2$O$_2$ (50% w/w, Sigma Aldrich, 51.4 µL, 46.2 µmol, 2.5 equiv.) diluted in solvent (~ 0.9 M) was slowly added over 16 min by a syringe pump. After the addition, the mixture was left to stir for another 45 min. The workup was performed according to SI, p. S19-S20.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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Entry for the Table of Contents

C-H Oxidation: Supramolecular catalysts with preferential oxidation of deactivated C3/C4 positions

Fe(pdp)Twe₂
Fe(pdp)Twe
Mn(pdp)Twe
Fe(mcp)Twe
Mn(mcp)Twe

● = deactivated   ● = intrinsic reactivty
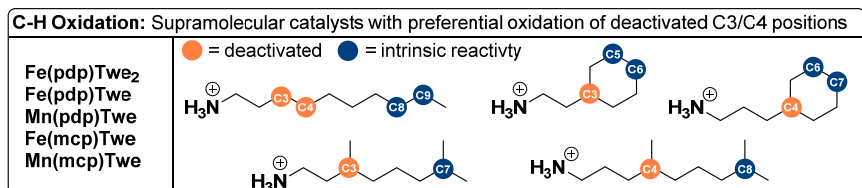
New supramolecular tweezer catalysts capable of oxidizing strongly deactivated C3/C4 positions of aliphatic ammonium salts were synthesized. The best performing catalyst **Fe(pdp)Twe** was explored in the oxidation of new substrates.

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