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# Predictable selectivity in remote C-H Oxidation of steroids: analysis of substrate binding mode

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**Abstract:** Predictability is a key requirement to encompass late-stage C-H functionalization in synthetic routes. However, prediction (and control) of reaction selectivity is usually challenging, especially for complex substrate structures and elusive transformations such as remote C($sp^3$)-H oxidation, as it requires to distinguish a specific C-H bond from many others with similar reactivity. Herein, we develop a strategy for predictable, remote C-H oxidation that entails substrate binding to a supramolecular Mn or Fe catalyst followed by elucidation of the conformation of the host-guest adduct via NMR analysis. These analyses indicate which remote C-H bonds are suitably oriented for the oxidation before carrying out the reaction, enabling prediction of site-selectivity. We applied this strategy to late-stage C($sp^3$)-H oxidation of aminosteroids at C15 (or C16) positions, with a selectivity tunable by modification of catalyst chirality and metal.

The precise conformation adopted by the substrate in the active site is key to the exceptional selectivity of C-H oxidizing enzymes. Upon binding, the substrate is preorganized to expose only targeted position(s) to the active unit, resulting in their selective oxidation in front of far more reactive functions. On these bases, elucidating how a substrate is bound and oriented inside the active site (analysis of its binding mode) can enable prediction of reaction selectivity, and even be a guide for its rational modification. An elegant example of the above strategy begun with the co-crystallization of PikC (a *S. Venezuelae* cytochrome P450) with its natural macrolide substrate bound to the active site (Figure 1A).[1,2] The X-ray structure showed the substrate binding mode, clarified which C-H bonds are located close to the metal catalyst and allowed prediction and rationalization of the hydroxylation selectivity.[1,2] Moreover, it provided the basis to modify the enzyme structure in order to host and predictably hydroxylate exogenous substrates.[2,3]

***Prediction of selectivity via elucidation of substrate orientation***

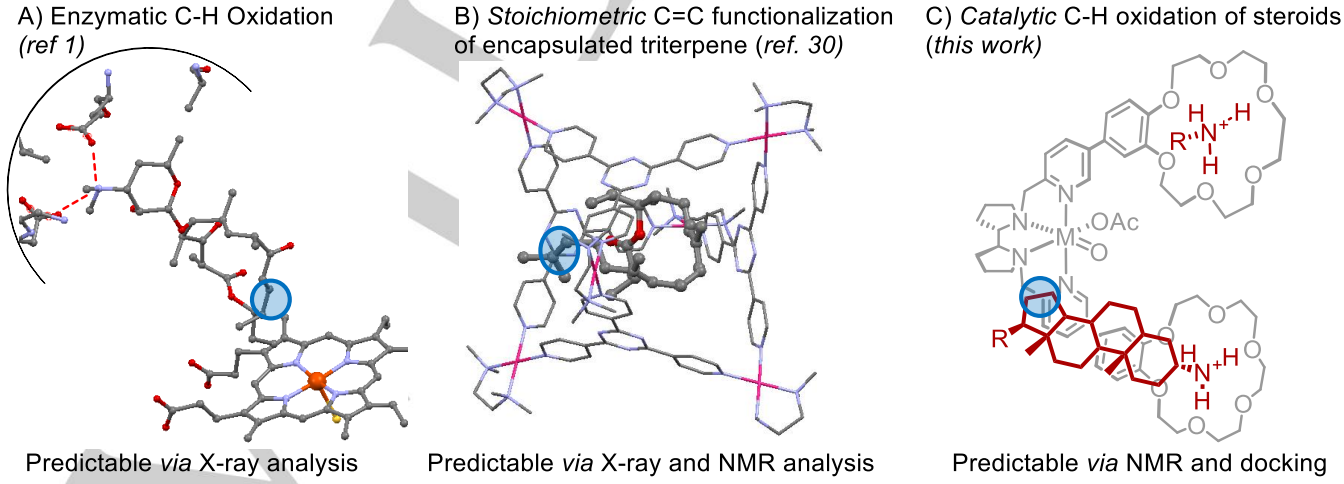


**Figure 1.** : Prediction of selectivity via elucidation of substrate orientation bound to the catalytic moiety in enzymatic PiKC C-H hydroxylation (A),[1] stoichiometric oxyfunctionalization of a triterpene (B)[27] and catalytic C-H oxidation of a steroid (C).

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Analogous rational prediction of selectivity is attractive also in artificial catalysis, and especially in late-stage C($sp^3$)-H functionalization, where a specific site has to be reliably singled out from many others with comparable reactivities.[4–8] Predictability is possible only if substrate orientation is well-defined and known, and is thus limited to proximal sites via intramolecular processes[9,10] or activated C-H bonds in intermolecular reactions[4–8] (although the latter may be challenging to discern a priori). Predictable remote (or intermolecular) functionalization demands a supramolecular, biomimetic strategy, where binding of a substrate to a receptor controls its orientation.[11–14] This pioneering approach has already unlocked elusive transformations, such as remote[15–19] or enantioselective C($sp^3$)-H oxidations,[20,21] *meta*[22,23] and *ortho*[24] C-H borylations or selective olefin hydroformylation.[25–27] The selectivity in these systems can be rationalized and somehow predicted by computational methods, design of catalyst and substrate structure and analysis of product distribution. However, in spite of its potential, prediction of site-selectivity via experimental elucidation of the substrate-catalyst relative orientation remains highly underexplored. Proof-of-concept has been recently provided for stoichiometric monofunctionalization of 1,ω-dihaloalkanes inside a cavitand[28,29] or of a triterpene encapsulated into a metal-organic cage (Figure 1B).[30] In the latter case, site-selectivity can be predicted *via* crystal structure and NMR analysis of the adduct. To the best of our knowledge, application of this strategy to catalytic processes and C-H functionalization is unprecedented.

Herein, we combined analysis of substrate binding mode and recognition-driven oxidation to achieve predictable, remote C($sp^3$)-H oxidation of amino-steroids, a class of compounds with promising antiviral and angiogenetic activity.[31–33] We used supramolecular catalysts ($^{CR}$pdp)Mn and Fe (Figure 1C and 2), that were previously shown to promote remote and substrate-selective oxidation of protonated linear alkyl amines.[18,34] These catalysts rely on crown ether receptors to bind primary ammonium ions and expose $C_8$ and $C_9$ C-H bonds[18] to the oxidizing species, a high-valent metal-oxo intermediate generated by $H_2O_2$ activation at a Fe or Mn center and competent for C($sp^3$)-H hydroxylation (Figure 2).[35–38] In order to investigate the orientation of the bound substrate via $^1$H-NMR analysis we prepared complex (*R,R*)-($^{CR}$pdp)Zn which features the same topology of the corresponding Fe and Mn complexes (Figure S1) but contains a diamagnetic metal center.

$^1$H-NMR monitoring of the binding of aminosteroid **1** to (*R,R*)-($^{CR}$pdp)Zn suggests a 2:1 stoichiometry (Figures S2-S5), akin to that previously observed for linear ammonium ions, [18,39] with each crown ether hosting one guest to form a symmetric adduct (Figure 3A and S2, S3). Further evidence for such 2:1 stoichiometry comes from the loss and subsequent recovery of the fine structure of the benzocrown NMR signals along the titration, consistent with initial 1:1 adducts with lower symmetry (loss of signal definition) that eventually form symmetric 2:1 structures after the equivalence (Figure S4).[40] The signals of **1** experience a generalized upfield shift upon binding (~0.1 ppm) due to partial transfer of the positive charge from the guest to the host (Figure 3B). They remain defined up to a 2:1 stoichiometry, after which their upfield shift and fine structure are eroded (Figure S5), consistent with a rapid exchange between bound and unbound **1** that occurs on NMR timescale and allows catalytic turnover. Interestingly, not all the signals of **1** are shifted with the same intensity. In particular, some C-H bonds in the α face ($C_9$, $C_{7\alpha}$, $C_5$, $C_{14}$) experience an upfield shift (0.5-1 ppm) far higher than the average, while the ones of the lateral chain remain untouched (Figure 3B; see SI for full signal assignment and differences in chemical shift). NOESY experiments showed proximity between these C-H bonds and the benzocrown ring, as well as between the D-ring and the pyridine moiety (Figure 3C).

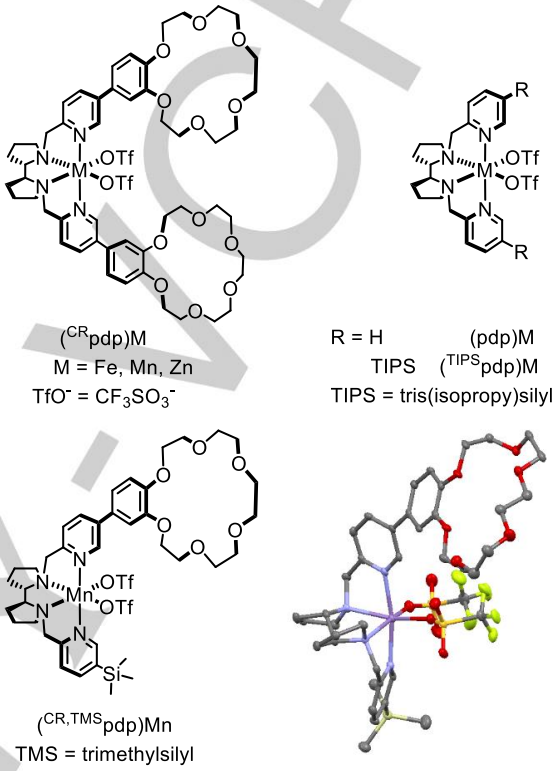


**Figure 2.** Structures of the complexes used in this work. ORTEP Plot (50% probability) of the crystal structure of (*S,S*)-($^{CR,TMS}$pdp)Mn (hydrogen atoms omitted for clarity).

Both the shifts and the NOESY correlations are lost upon addition of Ba(OTf)$_2$, which displaces the ammoniums from the crown ethers (Figure S10). All these observations suggest that **1**$_2$·(*R,R*)-($^{CR}$pdp)Zn adopts the geometry depicted in Figure 3B, with the α-face oriented towards the aromatic rings, the B ring on top of the benzocrown and the D-ring above the pyridine. Such analysis places the D-ring C-H bonds, and in particular $C_{15}$, close to the metal center, suggesting their selective hydroxylation. Oxidation of proximal $C_{16}$-H bond cannot be fully excluded, and other factors, such as catalyst chirality or the relative reactivity of these C-H bonds, may play a role in modulating this preference. Since these sites are located 8 or 9 carbons away from the anchoring α -$C_3$-$NH_3^+$ function, such prediction would be fully in line with the C8 and C9 selectivity previously observed with alkyl chains.[18] The same prediction can be reinforced by simple and rough docking of the crystal structures to provide a rapid yet surprisingly accurate way to confirm the predicted selectivity (Figure S12).

$C_{15}$ oxidation is very attractive, since $C_{15}$ oxygenated steroids are known to inhibit natural sterol biosynthesis[41,42] and some of these derivatives have found application as anti-hypertensive and anti cholesterol drugs.[41] However, D-ring oxidation is elusive, and the only reported methodology requires several steps, the key one

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being Breslow's templated, stoichiometric remote functionalization.[43–49]

At this point, we tested our predictions in the oxidation of **1** with catalytically active Mn and Fe catalysts (Figure 4 and Table 1). Non-directed oxidation with (pdp)Fe and Mn complexes afford a mixture of 6 products (see SI), the main one being **1a** (Figure 4 and Table 1, entries 1-4, 12-14% yield), irrespective of the catalyst chirality or the nature of the metal center (Fe or Mn). **1a** derives from hydroxylation of the most accessible tertiary $C_{25}$-H bond on the lateral chain, which is the preferential reaction site in related transformations with dioxiranes or radical reactants.[47] Bulkier ($^{TIPS}$pdp) catalysts increase the selectivity for the sterically accessible $C_{25}$-H oxidation up to 60% (entries 5-6), but yields are generally low (23-35%), testifying the low propensity of **1** to undergo oxidation.

To our delight, supramolecular catalysts completely suppressed oxidation at $C_{25}$ and furnished ketones **1b** and **1c** as the main products (entries 7-13 and S4-S6), with a selectivity for $C_{15}$ and $C_{16}$ sites fully in line with our predictions. Catalyst chirality and the nature of the metal center[50] now exert a great impact over selectivity, likely as a result of the limited flexibility of the bound substrate, and modulate the $C_{15}$/$C_{16}$ preference. Under catalytic conditions (Table 1), (*S,S*)-($^{CR}$pdp)Mn delivered oxidation on $C_{16}$ (with alcohol as the main product) in 13% yield and 86% selectivity (entry 7-8), (*R,R*)-($^{CR}$pdp)Mn and (*S,S*)-($^{CR}$pdp)Fe yield 1:1 mixture of **1b**:**1c** (entries 9-10), while (*R,R*)-($^{CR}$pdp)Fe inverts this preference and mainly furnishes **1c** (14%, 82% selectivity,

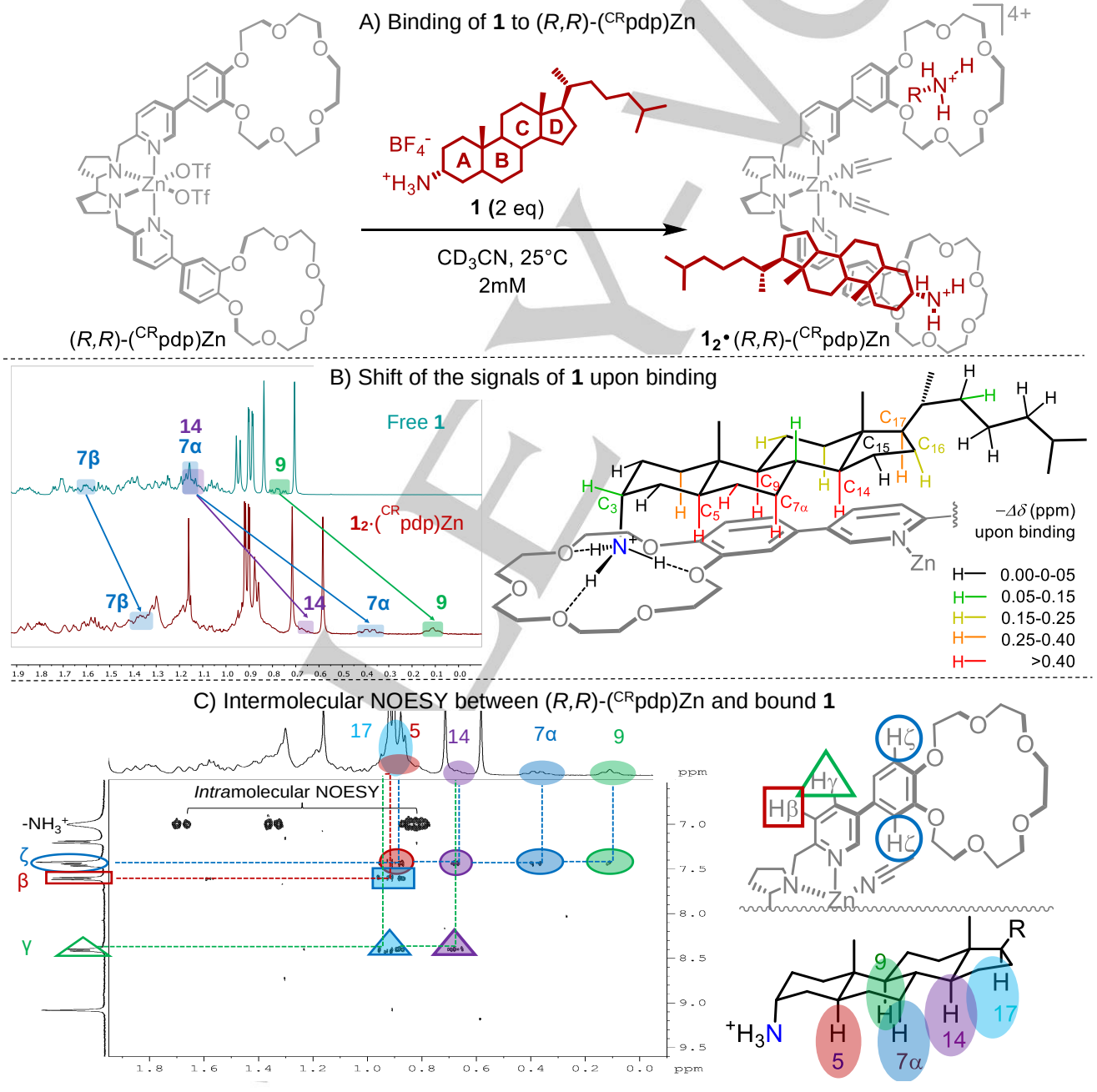


**Figure 3.** Analysis of the binding mode of **1** to (*R,R*)-($^{CR}$pdp)Zn (A). B) Upfield shift of the signals of **1** upon binding (full assignation, spectra and shifts shown in the SI). C) Intermolecular NOESY correlations between **1** and (*R,R*)-($^{CR}$pdp)Zn (full spectrum in the SI).

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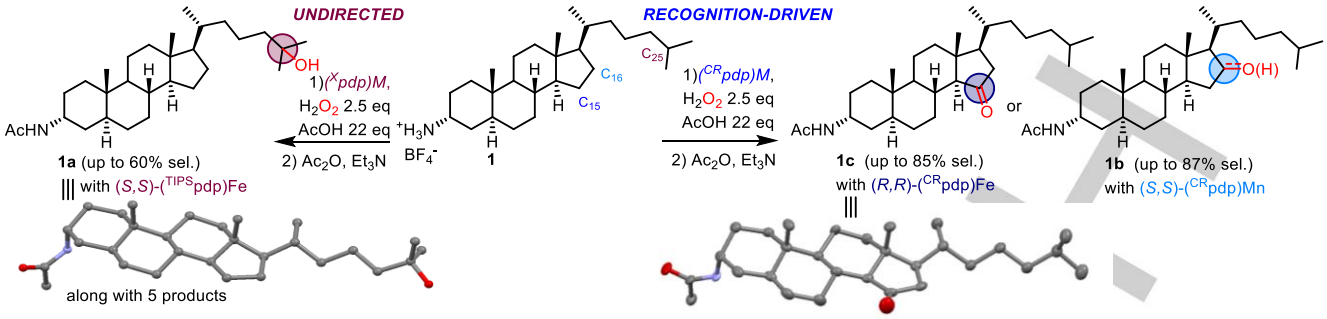


**Figure 4.** Oxidation of **1** with the structures of the oxidation products.[51] Selectivity calculated as product yield/total yield.

**Table 1.** Oxidation of **1**.[a]

| Entry | Catalyst | Conv/tot yield (%) | **1a** (sel) | **1b** (sel) | **1c** (sel) |
|---|---|---|---|---|---|
| 1 | (*S,S*)-(pdp)Mn | 26/23 | 12 | 7 | 4 |
| 2 | (*R,R*)-(pdp)Mn | 61/31 | 14 | 9 | 6 |
| 3 | (*S,S*)-(pdp)Fe | 56/28 | 12 | 8 | 8 |
| 4 | (*R,R*)-(pdp)Fe | 63/27 | 12 | 7 | 8 |
| 5 | (*S,S*)-($^{TIPS}$pdp)Mn | 62/35 | 21 (60) | 8 | 4 |
| 6 | (*S,S*)-($^{TIPS}$pdp)Fe | 34/32 | 14 | 9 | 7 |
| 7[b] | (*S,S*)-($^{CR}$pdp)Mn | 16/15 | tr. | 13[c] (87) | 2 |
| 8 | (*S,S*)-($^{CR}$mcp)Mn | 40/16 | tr. | 10[c] | 3 |
| 9 | (*R,R*)-($^{CR}$pdp)Mn | 32/21 | tr. | 10[c] | 11 |
| 10 | (*S,S*)-($^{CR}$pdp)Fe | 27/18 | tr. | 6 | 6 |
| 11 | (*R,R*)-($^{CR}$pdp)Fe | 28/17 | tr. | 3 | 14 (82) |
| 12[d] | " | 82/48 | tr. | 6 | 41[e] (85) |
| 13 | (*S,S*)-($^{CR,TMS}$pdp)Mn | 45/15 | <1 | 8[c] | 3 |

[a] Reaction conditions: cat 1 µmol, 1 mol% (5 mol% for Fe complexes), **1** 0.1 mmol (1 eq, 2.5 mM in $CH_3CN$), $H_2O_2$ 2.5 eq (added over 30 min. by syringe pump), AcOH 22 eq (11 eq for Fe complexes). Workup described in the SI. All reactions have been carried out in triplicate, analysed by GC (error ±5%) and referred to an internal standard. Total yield includes unidentified, detected products. Further optimizations are reported in the SI. [b] cat 5mol%, propanoic acid (22 eq), -40°C (optimization in Table S6). [c] The main product of the mixture is the alcohol in $C_{16}$, which has the same retention time (see SI). [d]Cat (5 mol%), $H_2O_2$ (2.5 eq) and AcOH (22 eq) added three times.[36] [e] 37% isolated yield.

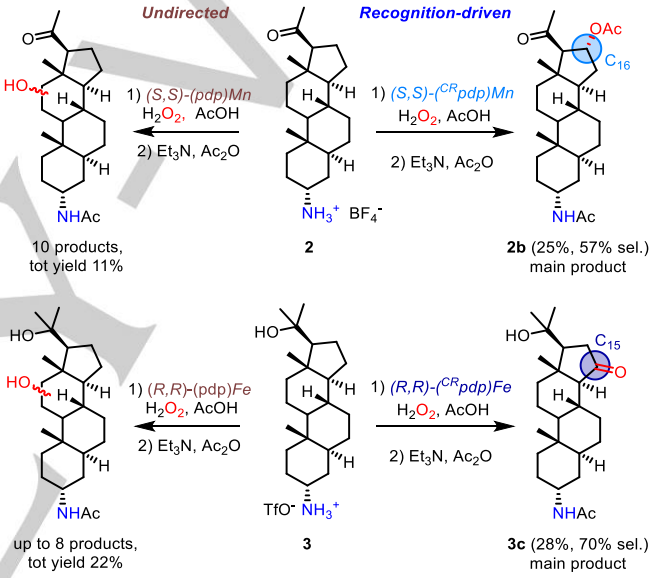


**Figure 5.** Oxidation of **2** and **3**.

entry 11). In the latter case, yield of **1c** can be improved up to 41% without erosion of selectivity (entry 12), providing the first catalytic, direct $C_{15}$ functionalization of steroids. The enhancement in selectivity going from linear amines to aminosteroid **1** (from 61-81% combined $C_8$+$C_9$ selectivity up to 85% $C_{15}$ selectivity) is likely due to the increased rigidity of the latter. A catalyst bearing a single receptor, (*S,S*)-($^{CR,TMS}$pdpMn) (Figure 2[52] and entry 13), affords essentially the same selectivity of (*S,S*)-($^{CR}$pdp)Mn, indicating that only even a single receptor can effectively control substrate orientation. Control experiments run under stoichiometric conditions similar to those of the binding experiments (**1**:cat ratio 2:1, Table S4) show a similar change in selectivity, albeit to a lower extent.[53]

To test the generality of our strategy, we extended our study to other aminosteroid substrates with the same androstane skeleton, bearing an α-$C_3$-$NH_3^+$anchoring group (Figure 5, compounds **2** and **3**). We were pleased to observe that the selectivity for remote D-ring oxidation, rationally tunable by manipulation of catalyst chirality and nature, is retained also with these substrates. **2b** is the main product (25% yield, 57% sel.) in the oxidation of **2** with (*S,S*)-($^{CR}$pdp)Mn, and derives from oxidation of $C_{16}$.[54] **3c** is the main product (28% yield, 70% sel.) in the oxidation of **3** catalyzed by (*R,R*)-($^{CR}$pdp)Fe, with the same $C_{15}$ selectivity observed for **1**. Also in these cases, undirected oxidations furnished mixtures of products with low yield (Tables S7-S8).

In summary, we have designed a supramolecular strategy for predictable, late-stage C-H oxidation at remote sites. This strategy relies on a biomimetic Mn or Fe catalyst equipped with crown ether receptors to bind and orient ammonium substrates. Orientation of the bound substrate inside the catalytic moiety can be inferred by NMR analysis, enabling prediction of the oxidation

site. The potential of this method was tested in the late-stage oxidation of aminosteroids to disclose a selectivity which is fully in line with predictions. Remarkably, this strategy enables elusive D-ring oxygenation in three steroidal substrates, and represents one of the very few methodologies for remote steroid functionalization.

## Acknowledgements

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**Keywords:** Molecular Recognition • Supramolecular Catalysis • Oxidation • Predictability • Hydrogen Bonds

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[40] Although formation of diastereomeric adducts can be possible via binding of **1** to different faces of the crown ether receptor, we observed a single isomer, with the substrate bound opposite to the hindered diamine backbone. The different atropoisomers of the catalyst (differing for the relative orientation of the benzocrown and pyridine rings) interconvert rapidly on the NMR timescale via rotation around the aryl-aryl bond.

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[50] The origin of the difference in selectivity between Fe and Mn ($^{CR}$pdp) catalysts with the same chirality is not clear at the present stage.
[51] X-Ray structures of **1a** and **1c** can be found at CCDC with numbers 1999035 and 1999034, respectively
[52] CCDC number 1999033.
[53] The erosion of selectivity in stoichiometric oxidations (cat:**1**: $H_2O_2$ 1:2:2.5) might be due to the greater relevance of the initial one-electron oxidation of the metal by $H_2O_2$ leading to homolytic cleavage of the peroxide bond and free radical induced unselective oxidation.
[54] Acetylation of $C_{16}$ alcohol is more efficient in **2b** than in **1b** likely as a result of the lower steric hindrance of the former, making acetylated α-$C_{16}$-alcohol **2b** the main product in the oxidation of **2**.

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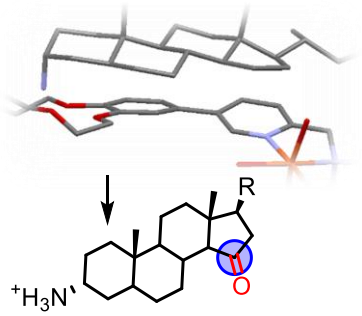


Analysis of substrate binding mode to a supramolecular catalyst enables rational prediction of site-selectivity in late-stage C($sp^3$)-H oxidation of aminosteroids.

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