

C–H Oxidation

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

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 yet been found. Here, we report the 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 few decades, synthetic methodology has progressed enormously. However, the site-selective oxidation of unactivated C(sp³)–H bonds still poses a remarkable challenge.^[1] Although 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.^[2] Arguably, such a method 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 through the use of complex cytochrome P450 enzymes.^[3] The optimized binding pocket of the active site is crucial in orienting a specific C–H bond that is not necessarily the most reactive one towards the oxidant. Mimicking such selective binding modes with synthetic catalysts has been very challenging.^[4]

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One promising approach is the covalent merger of a well-developed oxidation catalyst with a supramolecular binding motif.^[4b–d,5] For example, seminal work by Breslow et al. involved cyclodextrin(CD)-modified metalloporphyrin complexes.^[4b,6] Several covalently modified substrates (to enable binding to the CD moieties of the catalyst) were selectively oxidized using this strategy. Selective oxidation without the covalent attachment of recognition moieties to the substrate has been less successful, although remarkable examples were reported by the groups of Crabtree and Brudvig^[7] as well as of Bach.^[8] The oxidation of unactivated positions remains problematic.^[4d] Longer alkyl chains comprise one of the most challenging substrate classes for selective oxidation, as the methylene C–H bonds differ little in their reactivity.^[9] For example, the oxidation of a decyl ammonium substrate (Figure 1) with the White–Chen^[1a,2d,10] catalyst **1** yields mixtures of ketone products with a preference for oxidation at carbon atoms C6 and higher.^[11] Remarkably, the Costas group recently reported a novel method for the selective oxidation of alkyl ammonium substrates preferably at positions C8/C9 (Figure 1).^[11] The catalyst utilized in their work features

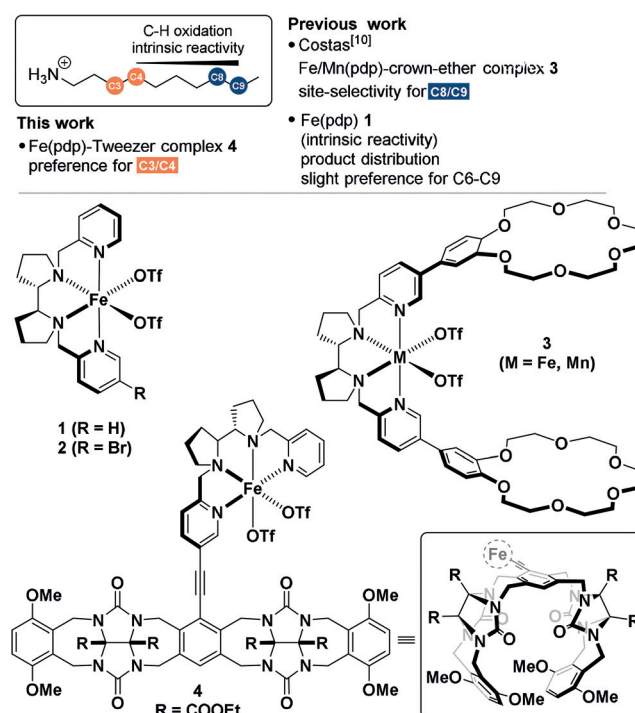


Figure 1. C–H Oxidation catalysts with different selectivities for alkyl ammonium chains.

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a catalytic center (Mn- or Fe-*N,N'*-bis(2-pyridylmethyl)-2,2'-bipyridine (Mn-/Fe(pdp)) attached to two 18-benzocrown-6 ether (BC) receptors (**3**) that are able to bind primary aliphatic ammonium ions.^[11]

Our recent interest in molecular tweezers,^[12] combined with their ability to bind alkyl ammonium ions 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.^[13] Specifically, we decided to utilize a framework similar to the glycoluril-based tweezer **8b** (Scheme 1) originally developed by Isaacs and co-workers.^[14] We speculated that it may bind alkylammonium cations more rigidly than the flexible crown ethers in catalyst **3**, thereby 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 has been documented,^[14] this project depended on binding in acetonitrile, the standard solvent for oxidations with catalyst **1** and its derivatives.^[2e,10,11,15] The binding constant of decyl ammonium tetrafluoroborate (C10-NH₃⁺) with **8b** (R = COOEt) in acetonitrile was determined by 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 those used by Costas (1.0 equiv substrate, 74 mM in MeCN, 5 mol% Fe-Twe **8b**; see below),^[11] >93% of tweezer **8b** would be occupied with substrate.

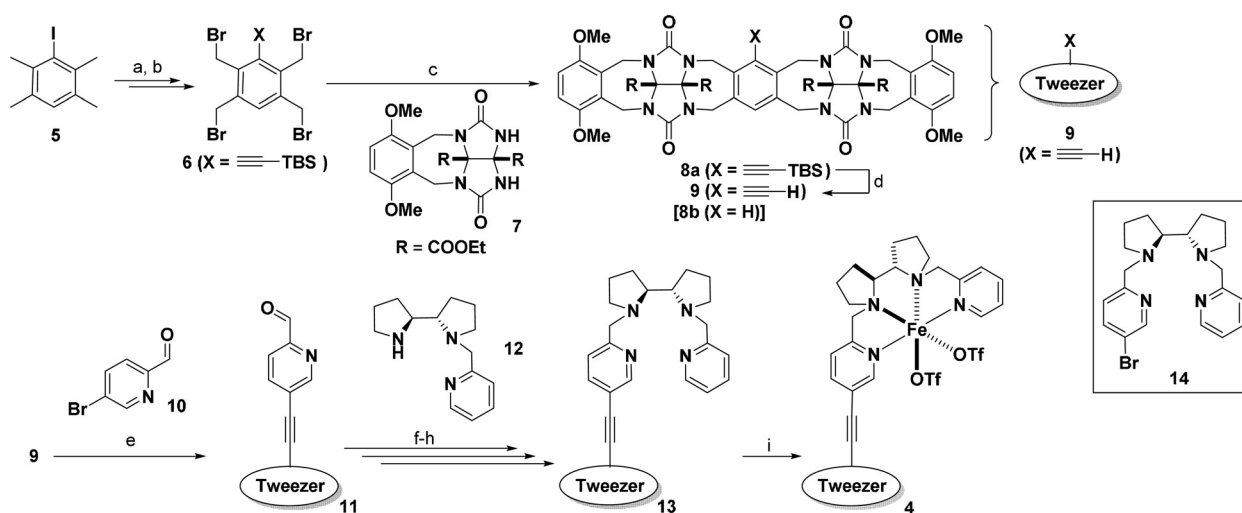
Encouraged by these initial results, we decided to explore a synthetic route towards the tweezer catalyst **4**, which comprises the well-explored catalytic moiety Fe(pdp)^[1a,10] linked to the tweezer binding motif by an alkyne residue. Initially, we envisioned a convergent approach based on the

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 through alkylation with two equivalents of **7**^[14] to produce tweezer **8a**. Cleavage of the TBS group using TBAF resulted in tweezer **9**, which subsequently was coupled with 5-bromo-2-pyridinecarboxaldehyde (**10**). Surprisingly, reductive amination with **12** resulted in low yields under a variety of conditions. Therefore, the desired ligand **13** was constructed by alkylation (after reduction of the aldehyde and Appel-like bromination). The final complex **4** was obtained by coordination of **13** with Fe(OTf)₂(MeCN)₂.^[11] Catalyst **2** (Figure 1) was also synthesized as a reference oxidation catalyst lacking the tweezer binding motif but carrying a substituent at the pyridine 5-position (see the Supporting Information).

Surprisingly, the determination of the binding constant of decyl ammonium tetrafluoroborate with Fe-Twe **4** showed a 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 the Supporting Information, p. S94–99).

Initially, decyl ammonium tetrafluoroborate was chosen as a model substrate and investigated in the oxidation reactions with Fe-Br **2** (intrinsic reactivity) and Fe-Twe **4** (Figure 2). As expected,^[11] the nondirected 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 barely detectable because of deactivation by the nearby ammonium moiety.^[16] The main products were K6–K9 in nearly equal amounts. Employing catalyst Fe-Twe **4** also led



Scheme 1. Synthesis of the Fe(pdp)-functionalized tweezer Fe-Twe **4**. a) TBS-acetylene, PdCl₂(PPh₃)₂, CuI, Et₃NH, 50°C, 16 h, 97%. b) NBS, AIBN, CCl₄, 95°C, 72 h, 58%. c) **7**, KOtBu, **6**, DMSO, rt, 16 h, 44%. d) TBAF, THF, 0°C, 2 h, 80%. e) **10**, PdCl₂(PPh₃)₂, CuI, PPh₃, THF, microwaves, 120°C, 90 min, 76%. f) NaCNBH₃, TFA, MeOH, CH₂Cl₂, rt, 4 h, 96%. g) PBr₃, CH₂Cl₂, 0°C→rt, 16 h, 75%. h) **11**, K₂CO₃, TBAB, MeCN, 90°C, 16 h, 97%. i) Fe(OTf)₂(MeCN)₂, MeCN, rt, 2.5 h, 58%. AIBN: azobis(isobutyronitrile), TBS: *tert*-butyldimethylsilyl, TBAB: tetra-*n*-butylammonium bromide, TBAF: tetra-*n*-butylammonium fluoride, TFA: trifluoroacetic acid, NBS: *N*-bromosuccinimide.

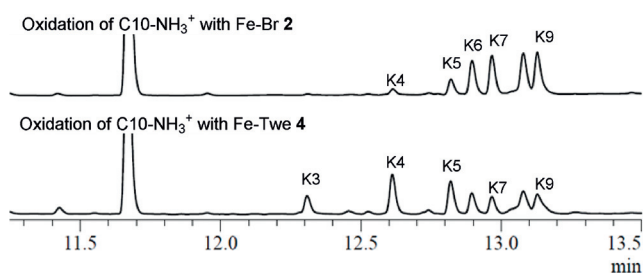


Figure 2. GC Chromatograms of the oxidation of C10-NH₃⁺ with Fe-Br **2** (top) and Fe-Twe **4** (bottom).

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. entry 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 obtained with Fe-Br **2**, thus 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 through methylation of the amine residue. The oxidation of C10-NMeH₂⁺ already delivered reduced selectivities (entry 5 vs. entry 6) while the use of dimethylated C10-NMe₂H⁺ as the substrate resulted in an almost complete loss of the selectivity. These results strongly indicate that the substrate binds to the tweezer through hydrogen bonds. The yields in these two cases (entries 6 and 8) were only slightly reduced in comparison to entry 2, which suggests that oxidation without specific binding to the tweezer takes place as a background reaction. This is

also indicated by the oxidation of cyclohexane by both catalysts (see the Supporting Information, p. S37). In a competition experiment, decyl ammonium and cyclohexane were subjected to oxidation reactions with Fe-Br **2** and Fe-Twe **4** in equal amounts, which resulted in only a slightly increased selectivity for decyl ammonium with Fe-Twe **4**. The background reaction was much less pronounced with **3**,^[11] presumably because of 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**. NH₄PF₆, NaOTf, and methyl viologen dichloride hydrate were explored as inhibitors. The yields of the oxidation products, as well as the selectivity for C3 and C4 decreased. However, these results are difficult to interpret, since the inhibitor also inhibits the oxidation of the regular catalyst Fe-Br **2**, which is devoid of a tweezer moiety. However, the reduced selectivity with these experiments also indicates some background oxidation with regular “solution” selectivity at C6–C9.

Subsequently, we studied the oxidation of several aliphatic ammonium salts with different chain lengths (Table 1 and Figure 3). For all oxidation reactions with Fe-Twe **4**, a pronounced selectivity increase for the C3 and C4 positions was observed compared to the nondirected oxidations. In fact, with most substrates, ketones K3 or K4 were the favored products in the 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 the Supporting Information, p. S39–42). The only exception is the oxidation of C7-NH₃⁺, in which almost all the positions are deactivated.^[16] Moreover, substrates with longer alkyl chains mostly resulted in higher yields compared to the short ones, a trend also observed with **3**.^[11] In terms of the selectivity, two different binding motifs can, in principle, be envisioned for catalyst **4** (Figure 3b): 1) The binding of the aliphatic chain inside the cavity of the

Table 1: Oxidation of aliphatic ammonium salts by catalysts Fe-Br **2** and Fe-Twe **4**.^[a]

Entry	Substrate	Catalyst	Conv. [%]	Total yield ^[b] [%]	Yield K3/K4 [%]	Yield K3–K5 [%]	Selectivity ^[c] K3/K4 [%]	Selectivity ^[c] K3–K5 [%]
1 vs. 2 ^[d]	C10-NH ₃ ⁺	Fe-Br 2 vs. Fe-Twe 4	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 ₃ ⁺	Fe-Br 2 vs. Fe-Br 2 + 8b	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 ₂ ⁺	Fe-Br 2 vs. Fe-Twe 4	57 vs. 43	27 vs. 18	1.9 vs. 2.9	5.5 vs. 5.6	7.1 vs. 16	20 vs. 32
7 ^[e] vs. 8 ^[e]	C10-NMe ₂ H ⁺	“	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 ₃ ⁺	“	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 ₃ ⁺	“	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 ₃ ⁺	“	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 ₃ ⁺	“	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 ₃ ⁺	“	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 ₃ ⁺	“	77 vs. 68	33 vs. 18	0.7 vs. 3.8	2.1 vs. 6.1	2.1 vs. 21	8.8 vs. 34

[a] General reaction conditions:^[11] substrate (18.5 μmol, 1.0 equiv), catalyst (925 nmol, 5 mol %), AcOH (148 μmol, 8.0 equiv), H₂O₂ (278 μmol, 15 equiv, addition by a syringe pump over 90 min), MeCN, 0 °C. After 15 min, internal standard (biphenyl, 9.25 μmol, 0.5 equiv), NEt₃ (100 μL), and Ac₂O (150 μL) added, 0 °C. After 1 h, washed with H₂O, 2 M H₂SO₄, NaHCO₃, H₂O, 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. [d] 5 mol % of tweezer **8b** was added additionally. [e] Different work-up, see the Supporting Information.

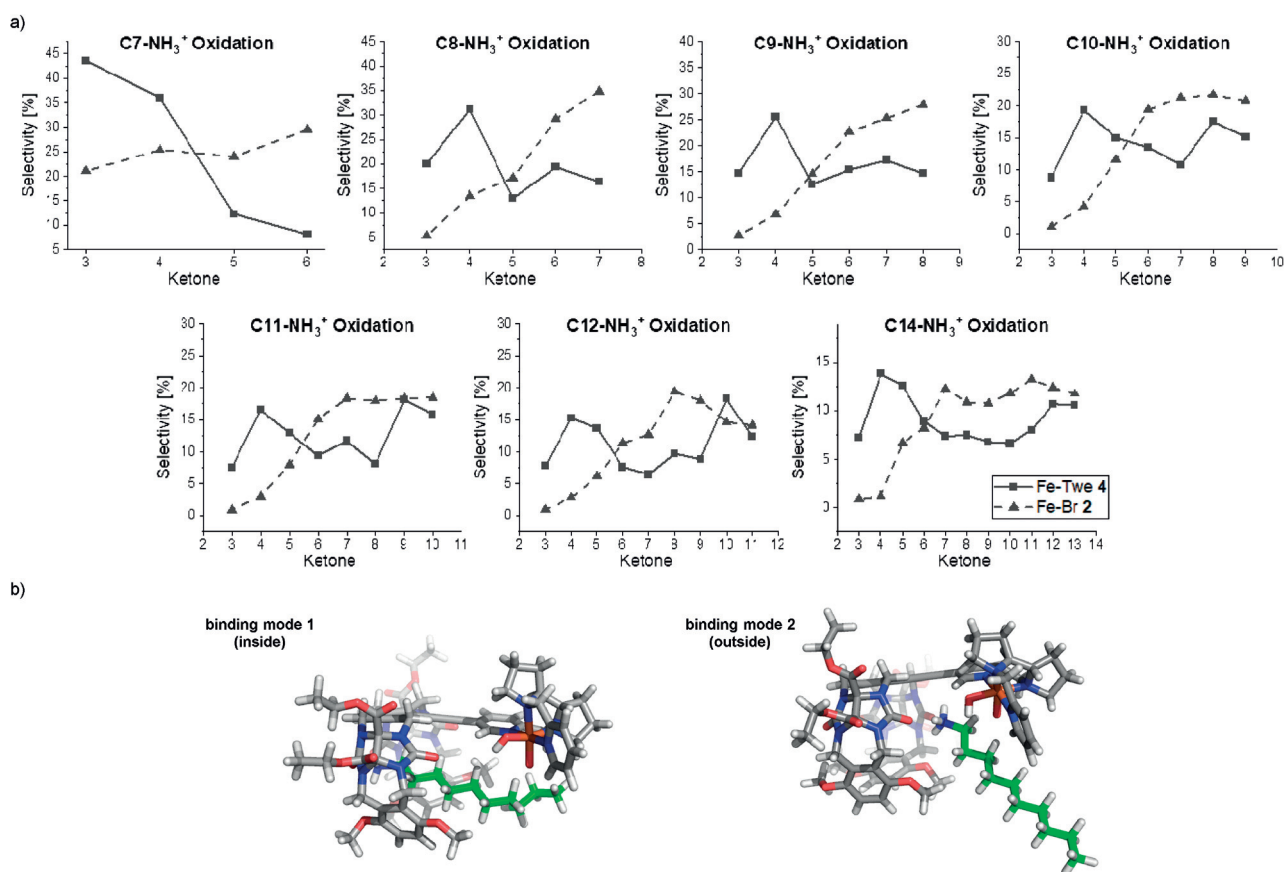


Figure 3. a) Reaction selectivities of the possible ketone products for the oxidation of different aliphatic ammonium ions with Fe-Br 2 and Fe-Twe-4. b) Binding modes 1 and 2 of Fe-4 and decyl ammonium (optimized at the PM3 level).

tweezer. This binding mode is observed in aqueous solution, presumably as a result of the hydrophobic effect.^[14] It would expose positions C6–C8 to the oxidant. 2) Without the hydrophobic effect, sole binding to the polar end groups (urea carbonyl group and methoxy oxygen atom) of the tweezer would be feasible, thereby favoring oxidation of positions C3–C5. The oxidation results obtained clearly suggest that the second binding mode is the predominant one. Molecular modeling studies were performed to investigate the suggested binding modes of the ammonium substrate to the tweezer (see the Supporting Information, p. S101–107). According to the calculations, the two binding modes are relatively close in energy, thus indicating that C6–C9 oxidation not only stems from a background reaction but also from binding mode 1. However, binding mode 2 (the cavity is filled with acetonitrile solvent, not shown in Figure 3) is preferred by approximately 5 kJ mol⁻¹, in accordance with the experimental results. Since binding mode 2 depends on the guest acetonitrile molecule, the observed selectivity for K3–K5 should be solvent-dependent. Indeed, the selectivity is greatly reduced with trifluoroethanol and disappears completely when the larger hexafluoro-2-propanol is used as solvent (see the Supporting information, p. S35–36). These results provide further evidence that the observed oxidation of the unactivated positions C3–C5 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 the aliphatic C–H oxidation of alkyl ammonium salts. The main products formed were ketones at carbon atoms C3 and C4, positions that are intrinsically strongly deactivated and, therefore, not formed to a significant degree with other catalysts. Although the selectivities clearly have to be improved to achieve synthetically useful yields, these results augur well for the selective oxidation of unactivated C–H positions of complex carbon frameworks.

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Conflict of interest

The authors declare no conflict of interest.

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

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