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Pt(II)-Catalyzed Hydroxylation of Terminal Aliphatic C(sp³)–H Bonds with Molecular Oxygen

Michiel Janssen,^[a] and Dirk E. De Vos*^[a]

Abstract: The practical application of Shilov-type Pt catalysis to the selective hydroxylation of terminal aliphatic C-H bonds remains a formidable challenge, due to difficulties in replacing Pt(IV) with a more economically viable oxidant, particularly O2. We report the potential of employing FeCl₂ as a suitable redox mediator to overcome the kinetic hurdles related to the direct use of O_2 in the Pt reoxidation. For the selective conversion of butyric acid to γ-hydroxybutyric acid (GHB), a significantly enhanced catalyst activity and stability (TON > 30) were achieved under 20 bar O2 in comparison to current state-of-the-art systems (TON < 10). In this regard, essential reaction parameters affecting the overall activity were identified, along with specific additives to attain catalyst stability at longer reaction times. Deactivation via reduction to Pt(0) was prevented by the addition of monodentate pyridine derivatives, such as 2-fluoropyridine, but also by introducing varying partial pressures of N₂ in the gaseous atmosphere. Finally, stability tests revealed the involvement of Pt(II) and FeCl₂ in catalyzing the non-selective overoxidation of GHB. In situ esterification with boric acid proved to be a suitable strategy to maintain enhanced selectivities at much higher conversions (TON > 60). Altogether, we provide a useful catalytic system for the selective hydroxylation of primary aliphatic C-H bonds with O₂.

Introduction

The oxidation of saturated aliphatic C-H bonds is a powerful tool to obtain useful oxygenated functionalities in otherwise inert organic compounds, thereby uncovering their potential as valuable starting materials.^[1-2] An attractive route comprises the site-selective hydroxylation of terminal C-H bonds, not only because it involves favorable thermodynamics and a high atom economy, but also because the resulting primary alcohol is of prime importance in industrial applications.^[3-5] Nevertheless, this reaction still represents a tremendous challenge in modern organic chemistry, due to the chemical inertness of saturated hydrocarbons. Prevailing systems therefore use harsh radicalmediated pathways that are incompatible with both chemo- and regioselective transformations. More specifically, as the reactivity in such pathways is dictated by the homolytic C-H bond dissociation energy, which decreases in the order of primary > secondary > tertiary C-H bonds, terminal functionalization of the aliphatic chain is less favored. In addition, more advanced oxidation levels are commonly observed, owing to the higher reactivity of the alcohol product relative to the alkane substrate.[6-7]

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To favor the formation of the (primary) alcohol product, fundamentally different activation modes are needed.^[8] A considerable amount of research has been devoted to using electrophilic late transition metals in a variety of protic solvents.^[9-10] This particular interest in electrophilic C-H activation is based on earlier observations of the Pt(II)-mediated H/D exchange of arenes in acidic aqueous solutions.[11] In fact, by incorporating Pt(IV) as a stoichiometric oxidant, Shilov and coworkers successfully extended the intermolecular C-H activation step to true functionalization (Scheme 1).^[12-13] More importantly, the intrinsic value of this Shilov system originates from its unique selectivity pattern. Using Pt(II) significantly reduces the extent of overoxidation and, as a result, directs the oxidative transformation towards selective hydroxylation. In a similar way, Pt discriminates between non-equivalent C-H bonds in a very different manner than radicals do, giving rise to an enhanced reactivity of terminal C-H bonds.^[9,14] Moreover, a complete reversal in regioselectivity was reported for the remote oxidation of mono-functionalized organic compounds, which was attributed to a "chelate effect".[15a,c] In particular, Sen and co-workers observed the following order of reactivity: α -C–H << β -C–H < γ -C–H < δ -C–H for alcohols and α -C–H << β -C–H < γ -C–H ≥ δ -C–H for carboxylic, sulfonic and phosphonic acids.^[15] Based on these trends, it was suggested that a metallocyclic intermediate forms upon coordination of the functional group to the electrophilic Pt(II) center, in which the C-H bond reactivity is determined by the ring strain.[15c]

Nonetheless, the inherently low turnover numbers (TON, < 1) and turnover frequencies (TOF, < 0.004 h⁻¹), in combination with the need for stoichiometric quantities of an expensive Pt(IV) salt,^[15a,c] render this system impractical in large-scale applications.^[3] Fortunately, earlier mechanistic studies confirmed that the oxidation step (Scheme 1) does not proceed via an alkyl transfer, but instead requires an inner-sphere two-electron transfer from Pt(II)–R to Pt(IV).^[1] Accordingly, these findings revealed the possibility of replacing Pt(IV) with a more economical



Scheme 1. Catalytic cycle for the Shilov system with a) Pt(IV) and b) molecular oxygen (O₂) as terminal oxidant.^[1]

Supporting information for this article is given via a link at the end of the document.

and readily available oxidant. While equivalent amounts of CuCl₂ have hitherto been applied with moderate success,^[16-17] using dioxygen (O₂) would offer major opportunities from an industrial and ecological perspective.^[18] However, applying O₂ as sole terminal oxidant is known to impose a kinetic limitation on the overall reaction, causing rapid deactivation of the Pt catalyst via reduction to metallic platinum.^[1,10,19] To ensure a more efficient electron transfer chain between Pt(II) and O₂, together with a faster reoxidation of possibly formed Pt(0), the addition of a redox mediator was originally proposed by Gol'dshlger *et al.*^[20] Although Cu(II)^[20-21], Fe(III)^[22] and certain heteropolyacids^[23-25], e.g. H₅PV₂Mo₁₀O₄₀^[25], have proven to be reasonably efficient in activating O₂, proper systems that combine a sufficiently active and stable catalyst with high alcohol and terminal selectivity remain elusive.

In this work, we successfully illustrate the ability of FeCl₂ to generate a highly active and durable Pt catalyst for the regioselective hydroxylation of butyric acid to γ -hydroxybutyric acid (GHB) with O₂. Moreover, a more profound understanding is provided concerning those experimental parameters that determine the overall activity of the catalytic system, together with the specific role of nitrogen-containing additives in prolonging the catalyst stability. Ultimately, a reaction network is proposed for the overoxidation of GHB, and suitable strategies are evaluated to counteract these non-selective side reactions.

Results and Discussion

Pt-related characteristics of remote aliphatic C-H oxidation

Although water is one of the few reaction media that is fully stable under oxidative conditions, its use in C-H activation processes was initially considered ineffective. It was believed that the preferential solvation of the metal center with water would hinder coordination of the aliphatic substrate and elicit hydrolysis of the resulting metal-alkyl species.^[9] Nevertheless, by implementing a simple Pt(II) catalyst, Shilov and co-workers^[12] were the first to demonstrate the potential of using acid aqueous media in the field of selective C-H functionalization. To illustrate this unique property of Pt(II), the activity of K₂PtCl₄ was compared to that of a Pd- and Ni-based catalyst, by measuring the conversion of butyric acid in an acidified aqueous solution (0.33 M H₂SO₄) upon reaction for 6 h at 150 °C under 20 bar O2 (Table 1). Butyric acid was selected as cheap and abundant substrate, since selective hydroxylation at -CH₃ is a promising route towards GHB and γ -butyrolactone (GBL), both of which are extensively used in industry, for example as major industrial solvent, for medical purposes (e.g. treatment of narcolepsy) and as precursor in the chemical synthesis of pyrrolidones and biodegradable polyhydroxyalkanoates.^[26] Moreover, its molecular structure promotes a chelating effect; a six-membered ring with minimal ring strain can form upon coordination of the carboxylic acid group to Pt(II), favoring remote C-H activation (Scheme 2).^[15a,c] By analogy with the work of Lin et al., [21] CuCl₂ was included as cocatalyst to ensure proper comparison of the catalyst activity.

As expected, substantial conversion of butyric acid (75%) was only observed in the presence of K_2PtCl_4 (Table 1), thereby

confirming the specific role of Pt(II) in activating terminal aliphatic C–H bonds in protic aqueous solutions. The selectivity towards GHB was however limited to 25% due to extensive overoxidation. Accordingly, a comprehensive qualitative analysis via 1D and 2D NMR revealed the formation of succinic acid in combination with multiple lower degradation products, such as acetic acid, glycolic acid and formic acid (see Supporting Information, Figures S1-4). Moreover, a certain amount of gaseous compounds, primarily CO₂ and to a minor extent CO and CH₄, was detected by quantitative infrared spectroscopy. These results contrast with those reported by Lin *et al.*,^[21] who stated that no C–C cleavage occurred during the oxidative transformation of short-chain carboxylic, sulfonic and phosphonic acids under similar or even more severe reaction conditions (150 °C, 90 bar O₂).

Co-catalyst screening

Transition metal salts have proven successful as redox mediator in accelerating the Pt reoxidation by $O_2.^{[20-22]}$ Nevertheless, only moderately active systems are available since research has hitherto been restricted to the use of CuCl₂^[20-21] and FeCl₃^[22]. A more comprehensive screening of other transition metal salts was therefore performed based on the redox potential of the metal cation.^[27] Notably, a suitable redox mediator has to be able to oxidize the Pt(II)–R complex, but in turn has to be reoxidized by O_2 as well. As a result, Cu, Re, Mo, Fe, V and Mn were evaluated in the transformation of butyric acid under 20 bar O_2 . As illustrated in Figure 1, no clear correlation was found between the overall carbon yield and redox potential of the corresponding metal cation. However, replacing CuCl₂ with FeCl₂ led to a significantly increased catalytic activity, yielding 25% of GHB within 1 h with a

Table 1. Carbon yields in the transition metal-catalyzed hydroxylation of butyric acid with $O_2{}^{\rm [a]}$

Catalyst	V (0/)	S (%) -	Carbon yield (%) ^[b]						
Catalyst	X (%)		GHB	BHB	AHB	SA	DP ^[c]		
-	0.7	0	0	0	0.1	0	0.6		
K_2PtCl_4	75.4	25	19.0	1.5	1.2	1.3	52.4		
PdCl ₂	17.5	17	3	0.2	0.2	0.4	13.7		
NiCl ₂	2.5	0	0	0	0	0	2.5		

[a] Conditions: butyric acid (0.67 M), catalyst (1 mol%), H₂SO₄ (0.33 M), CuCl₂:2H₂O (5 mol%), H₂O (1.5 mL), 6 h, 150 °C, 20 bar O₂. Abbreviations: GHB, γ -hydroxybutyric acid; BHB, β -hydroxybutyric acid; AHB, α -hydroxybutyric acid; SA, succinic acid; DP, degradation products. [b] Number of mmoles of C in the respective product divided by the total mmoles of C initially supplied in butyric acid; i.e. 4 mmol). [c] Lower degradation products include lactic acid, acetone, acetic acid, glycolic acid, acetaldehyde, formic acid, methanol and gaseous compounds.

$\begin{array}{c} \mathbf{Pt}^{H} \\ H \rightarrow 0 \\ 0 \\ 0 \\ \end{array} \\ H \rightarrow 0 \\ H \end{array} \xrightarrow{-H^{+}} \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{+} \\ 0 \\ \end{array} \\ \begin{array}{c} H^{+} \\ H^{$

Scheme 2. Chelate effect upon coordination of butyric acid to Pt(II).^[15c]

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selectivity of 76%, which amounted to a TON of 33. In addition, only minor amounts of β -hydroxybutyric acid (BHB) and α -hydroxybutyric acid (AHB) were observed, corresponding to a remarkable regioselectivity of 93% within the aliphatic chain. The proposed combination of K₂PtCl₄ and FeCl₂/O₂ thus clearly outperforms current state-of-the-art systems in the regioselective C–H hydroxylation of butyric acid to GHB (Table 2).

While the lower efficiency of $FeCI_3$ compared to $CuCI_2$ has already been reported,^[22] the above-mentioned effect of $FeCI_2$ has not yet been seen before. The difference between $FeCI_2$ and

FeCl₃ is striking, as the oxidizing species Fe(III) could be assumed to be similar in both cases. In order to rationalize this dissimilarity, one must note that the tendency of Fe(III) to interact with one or more Cl⁻ ions is quite high and even increases with temperature;^[30] conversely, FeCl₃ is not expected to dissociate to free Fe(III), but will occur as stable FeCl₃, [FeCl₂]⁺ and/or [FeCl]²⁺ during reaction. Also for the association of Fe(III) with sulfate, a very high equilibrium constant has been reported,^[31] suggesting that any free Fe(III) would be converted to FeH(SO₄)₂ or [Fe(SO₄)₂]⁻ in the reaction conditions, comprising 0.33 M H₂SO₄.



Figure 1. Influence of different transition metal salts on the Pt-catalyzed hydroxylation of butyric acid with O₂, with illustration of their corresponding standard redox potential (25 °C, 1 atm, pH 0) in V.^[27] Conditions: butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0.33 M), co-catalyst (5 mol%), H₂O (1.5 mL), 1-6 h, 150 °C, 20 bar O₂.

Table 2. Comparison of the proposed catalytic system with relevant state-of-the-art systems for the regioselective C-H hydroxylation of butyric acid to γ -hydroxybutyric acid.

Catalyst	Oxidant	T (°C)	TON	TOF (h ⁻¹)	S (%)	PS (%) ^[f]	Ref.
K ₂ PtCl4 ^[a]	FeCl ₂ / O ₂	150	33	33	76	93	This work
K ₂ PtCl ₄ ^[b]	K ₂ PtCl ₆	80-90	0.24	0.0034	92	92	[15a]
K ₂ PtCl4 ^[C]	K ₂ PtCl ₆	110-120	0.52	0.0036	92	92	[15c]
CuCl _{2^[d]}	H_2O_2 (<i>in situ</i> formed by reaction of Pd(0) with CO and O ₂)	75	5.7	0.32	78	8.9	[28]
Tridentate NHC-amidate- alkoxide Pd(II) complex ^[e]	H₂O₂ / AgBF₄	60	No data	No data	14	14	[29]

[a] Butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0.33 M), FeCl₂·4H₂O (5 mol%), H₂O (1.5 mL), 1 h, 150 °C, 20 bar O₂.

[b] Butyric acid (0.23 M), K₂PtCl₄ (17 mol%), K₂PtCl₆ (33 mol%), D₂O (3 mL), 144 h, 80-90 °C, O₂ atmosphere.^[15a]

[c] Butyric acid (0.23 M), K₂PtCl₄ (17 mol%), K₂PtCl₆ (33 mol%), D₂O (1 mL), 72 h, 110-120 °C, O₂ atmosphere.^[15c]

[d] Butyric acid (0.55 M), Pd(5%)-C (3 mg), CuCl₂ (10 mol%), H₂O (0.5 mL), CF₃COOH (1.5 mL), 18 h, 75 °C, CO/N₂/O₂ (14/55/7 bar).^[28]

[e] Butyric acid (0.46 M), Pd(II) complex (3 mol%), AgBF₄ (7 mol%), H₂O₂ (30 wt% in H₂O, 40 µL), CD₃CN (0.5 mL), 16 h, 60 °C.^[29]

[f] Positional selectivity of GHB within hydroxybutyric acid fraction.

On the other hand, association constants of Fe(II) with both SO42and Cl⁻ are small,^[30-31] meaning that when FeCl₂ is used, there is initially a lot of free Fe(II) in solution. After oxidation of Fe(II) to Fe(III), the latter may partially associate with available Cl⁻ ions to form stable complexes in solution. Furthermore, with CuCl₂ as alternative redox-active reagent, high chloride concentrations have proven to be beneficial for the conversion, which has been explained in terms of a chlorine bridge formation between Pt(II) and Cu(II).^[22] However, with FeCl₂, a decrease in conversion occurred when 5 mol% of an alkali metal halide, such as NaCl, was added to the reaction mixture (Figure S5). Consequently, too high chloride concentrations might prevent the formation of a bridged Fe-Cl-Pt intermediate by saturating the Fe co-catalyst or even the Pt catalyst. Moreover, halides typically increase the oxidation potential of the metal, which could slow down reoxidation of Fe(II) to its trivalent state.[30] Additionally, the previously observed difference between FeCl₂ and FeCl₃ more or less disappeared upon replacing Cl⁻ with weakly coordinating anions, such as triflate or perchlorate (Table S1).^[32] These findings confirm that the dissimilarity is largely due to the presence of Cl⁻ and its coordination to Fe. In contrast, sulfate does not seem to hinder Fe in functioning as a redox mediator. Altogether, FeCl₂ remained the best option in terms of catalyst activity and stability, as well as product selectivity (Table S1), and it was therefore used for further investigation.

Next, time profiles were constructed at 150 °C under 20 bar O₂ to develop a better understanding of the time-dependent changes in carbon yield and selectivity to GHB in the presence of FeCl₂ (Figure 2). First, the more rapid increase in total carbon yield at short reaction times once again revealed that the Pt-based catalytic system exhibits a higher activity when FeCl₂, instead of CuCl₂, is applied as co-catalyst, suggesting that the oxidation of Pt(II)-R to Pt(IV)-R (Scheme 1) is likely the rate-determining step in the overall reaction. Moreover, a superior stability of the Pt catalyst was observed with FeCl₂, as evidenced by the slower formation of metallic platinum on the bottom of the glass vial during reaction (Figure 2a, *). FeCl₂ therefore appears to be more efficient than CuCl₂ in reoxidizing Pt(0) back to its catalytically active Pt(II) analogue, in a manner similar to that applied for the oxidation of Pd(0) to Pd(II) in the Wacker process.[33] More importantly, when using FeCl₂, elevated selectivities were consistently observed for GHB over the full course of reaction (Figure 2b), presumably because of a reduced degree of nonselective side reactions. By combining these findings, a carbon yield of 37.5% was achieved with sufficiently high selectivity (71%) and within 2 h. Hence, FeCl₂ is ideally suited to function as redox mediator between the Pt(II)-R complex and O₂.

Experimental study of the catalyst activity and stability

In an attempt to better understand and optimize the catalytic system with $FeCl_2$ as co-catalyst, several reaction variables were examined in detail, such as the oxygen pressure, (co-)catalyst loading, etc. To ensure proper comparison of the acquired results in terms of catalyst activity and stability, standard reactions were performed for respectively 1 h and 6 h.

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Parameters influencing the catalyst activity

A substantial raise in the conversion of butyric acid was observed when standard reactions were performed under increasing oxygen pressures, ranging from 5 to 20 bar (Table 3, entries 2-4). This confirms that with O₂ as terminal oxidant, the overall reaction rate is determined by the ease with which the Pt(II)-R complex is oxidized to its Pt(IV)-R analogue. Contrary to our expectations, further increasing the oxygen pressure to 30 bar (entry 5) resulted in a decrease in total activity. Additionally, a similar negative relation was observed between the conversion and co-catalyst loading (entries 2, 7-8). Considering that this adverse impact at higher FeCl₂ concentrations might be due to an elevated amount of chloride in solution (Figure S5), $\ensuremath{\text{FeCl}}_2$ was replaced with Fe(ClO₄)₂ and reactions were performed under identical conditions. Although less pronounced, a reduction in total carbon yield was still observed when an increasing concentration of Fe(ClO₄)₂ was initially included in the substrate solution (Figure S6). A reasonable explanation is that the undesired oxidation of [Pt(II)Cl₄]²⁻ to [Pt(IV)Cl₆]²⁻ is favored at high oxygen pressures or when too much co-catalyst is supplied and, in this way, diminishes the amount of active Pt(II) catalyst during reaction.^[19,22] On top of



Figure 2. Time profiles of (a) carbon yields and (b) selectivities in the Ptcatalyzed hydroxylation of butyric acid with O₂, in the presence of CuCl₂ vs. FeCl₂ as co-catalyst. Conditions: butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0.33 M), CuCl₂·2H₂O/FeCl₂·4H₂O (5 mol%), H₂O (1.5 mL), 150 °C, 20 bar O₂. Abbreviations: GHB, γ -hydroxybutyric acid. * Reaction time at which the formation of metallic platinum was first observed on the bottom of the glass vial after reaction.

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that, only a slight increase in conversion was observed when the catalyst loading was raised, while keeping the catalyst/co-catalyst ratio constant (entries 2, 10-11). After reaction, we however observed the formation of metallic platinum at the bottom of the glass vial. In particular, this deactivation within short reaction times suggests that at higher Pt concentrations (i) disproportionation of Pt(II) to Pt(0) and Pt(IV) [Eq. (1)] occurs more readily or (ii) Pt(II) also partially functions as terminal oxidant in the oxidation of Pt(II)–R [Eq. (2)]:^[3]

$$2 [Pt(II)Cl_4]^{2-} \rightarrow Pt(0) + [Pt(IV)Cl_6]^{2-} + 2 Cl^{-}$$
(1)

 $[Pt(II)CI_{3}R]^{2-} + [Pt(II)CI_{4}]^{2-} \rightarrow [Pt(IV)CI_{5}R]^{2-} + Pt(0) + 2 CI^{-} (2)$

Both reactions decrease the amount of Pt(II) that is available for the C–H activation of butyric acid, limiting the effect of higher catalyst loadings.

Furthermore, standard reactions were performed with different concentrations of butyric and sulfuric acid. As is evident from the data in Table 3, entries 2 and 12-14, a fourfold reduction in substrate concentration corresponded to a strong decrease in

conversion. This outcome can be rationalized in terms of the coordination equilibrium of butyric acid to Pt(II); if the equilibrium is not very much to the right, dilution of butyric acid will diminish the fraction of Pt(II) that holds a butyrate ligand. As the solubility of O2 is often relatively low in aqueous solutions,[34] this result can also be understood by considering that higher concentrations of an organic compound could increase the O₂ solubility, and as a result, enhance the rate of the overall reaction. Next, the total carbon yield gradually declined upon lowering the sulfuric acid concentration from 0.33 M to 0 M (entries 2, 15-17). A logical explanation is that the driving force for the reoxidation of Fe(II) by O2 increases with decreasing pH, since the oxidative half reaction of Fe(III)/Fe(II) involves no protons, whereas a linear inverse correlation exists between the redox potential of O₂/H₂O and the pH following a Nernst-type equation.^[27] In addition, alternative inorganic and organic acids were evaluated under standard conditions (Figure S7). For instance, conversion was completely lost when H₂SO₄ was replaced with HCl, which is in agreement with previous findings concerning (co-)catalyst deactivation at high chloride concentrations (Figure S5). In contrast, no apparent

Table 3. Experimental study of parameters influencing the catalyst activity in the Pt-catalyzed hydroxylation of butyric acid with

	[Butyric acid]	[H ₂ SO ₄]	K₂PtCl₄	FeCl ₂	P ₀₂	N (01)	0 (0()		Carbon yield (%) ^[b]			
	(M)	(M)	(mol%)	(mol%)	(bar)	X (%)	S (%)	GHB	BHB	AHB	SA	DP ^[c]
1	0.67	0.33	1	-	20	3.2	44	1.4	0.3	0.2	0	1.3
2	0.67	0.33	1	5	20	33.3	76	25.2	1.4	0.5	0.5	5.7
3	0.67	0.33	1	5	5	5.6	66	3.7	0.3	0.9	0.1	0.6
4	0.67	0.33	1	5	10	12.1	74	8.9	0.5	0.9	0.2	1.6
5	0.67	0.33	1	5	30	14.7	73	10.7	0.6	0.8	0.2	2.4
6	0.67	0.33	1	1	20	33.6	67	22.5	1.6	1.7	0.8	7.0
7	0.67	0.33	1	10	20	13.3	68	9.0	0.5	1.1	0.1	2.6
8	0.67	0.33	1	20	20	6.2	53	3.3	0.4	0.8	0.1	1.6
9	0.67	0.33	0.5	2.5	20	6.9	72	5.0	0.3	0.2	0	1.4
10	0.67	0.33	2	10	20	37.5	74	27.6	1.4	1.2	0.6	6.7
11	0.67	0.33	5	25	20	43.2	72	31.2	2.6	1.2	1.2	7.0
12	0.167	0.33	1	5	20	15.2	54	8.2	0.4	4.4	0.1	2.1
13	0.33	0.33	1	5	20	14.5	64	9.3	0.4	2.2	0.1	2.5
14	0.5	0.33	1	5	20	19.7	70	13.8	0.5	1.3	0.3	3.8
15	0.67	0	1	5	20	21.2	74	15.6	1.0	0.8	0.4	3.4
16	0.67	0.067	1	5	20	22.1	78	17.3	0.7	0.4	0.4	3.3
17	0.67	0.2	1	5	20	29.8	76	22.7	0.9	0.6	0.5	5.1

[a] Conditions: butyric acid (0-0.67 M), K₂PtCl₄ (0.5-5 mol%), H₂SO₄ (0-0.33 M), FeCl₂:4H₂O (1-25 mol%), H₂O (1.5 mL), 1 h, 150 °C, 5-30 bar O₂. Abbreviations: GHB, γ -hydroxybutyric acid; BHB, β -hydroxybutyric acid; AHB, α -hydroxybutyric acid; SA, succinic acid; DP, degradation products. [b] Number of mmoles of C in the respective product divided by the total mmoles of C initially supplied in butyric acid (i.e. 4 mmol). [c] Lower degradation products include lactic acid, acetone, acetic acid, glycolic acid, acetaldehyde, formic acid, methanol and gaseous compounds.

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shift in total carbon yield was noted when similar reactions were performed in the presence of CH_3SO_3H , CF_3SO_3H or CF_3COOH , while the use of solid acids, such as zeolite H-Beta or Amberlyst- $15^{\ensuremath{\circledast}}$, led to a decline in conversion.

Improvement of the catalyst stability

Although a highly active system was achieved by selecting a suitable redox mediator, catalyst deactivation via reduction to metallic platinum still occurred over time; in optimal conditions, the formation of a black precipitate was observed from a reaction time of 4 h on (Figure 2a). For the purpose of prolonging the catalyst stability, the influence of adding small amounts of suitable ligands was examined in the Pt-catalyzed hydroxylation of butyric acid. In particular, previous studies, e.g. on the Periana-Catalytica system for methane oxidation with SO₃,^[35-36] have revealed the potential of using bidentate *N*-heteroaromatic ligands in stabilizing related Pt(II) complexes, based on the strong σ -donor and π -acceptor interactions of these ligands with electron rich low oxidation state metals.^[37]

As shown in Table 4, no metallic platinum was detected in the reaction vial after 6 h when 1 mol% of 2,2'-bipyridine was initially added to the substrate solution (entry 2). A similar improvement of the catalyst stability was however achieved with 1 mol% of pyridine (entry 3), demonstrating that a monodentate ligand gives comparable stabilization as a bidentate, chelating ligand. Moreover, a negative impact on the activity was observed for both ligands, which proved to be more severe for 2,2'-bipyridine. Consequently, an inverse relation appears to exist between the ligand's affinity for Pt(II) and the activity of the resulting catalyst complex. Strikingly, this adverse relationship was alleviated when a strongly electron-withdrawing group, such as a F-atom (entry 7), was incorporated in the 2-pyridyl position. By analogy to the work of Izawa and Stahl,^[38] these findings can be understood by

considering that a higher basicity of the pyridine nitrogen simultaneously results in a stronger σ -bond interaction and a lower electrophilicity of Pt(II). Since the electrophilic nature of Pt is essential for catalyst activity, ligands that are more basic tend to lower the catalyst's activity. Accordingly, the reduced basicity of 2-F-pyridine compared to pyridine allowed to stabilize the Pt catalyst without significantly altering the activity of the latter. On top of that, a similar result was obtained with 2-OH-pyridine (entry 8). Although a OH-group is intrinsically less electron withdrawing than a F-atom, the tautomerization of 2-OH-pyridine to 2-pyridone in water reduces the basicity of this additive.^[39-41] Ultimately, it is also notable that with suitable ligands, such as 2-OH- or 2-F-pyridine, higher GHB selectivities are maintained up to high butyric acid conversions than in the absence of these ligands.

Notably, analogous results were achieved by introducing varying partial pressures of N_2 (5-10 bar) in the gaseous atmosphere, while keeping the O₂ partial pressure constant at 20 bar: no metallic platinum was visible after reaction of butyric acid for 6 h. Additionally, too high N₂ partial pressures curiously resulted in a reduced catalyst activity, as evidenced by the significant drop in conversion (Figure 3), which led us to believe that N₂ in some way affects the catalytic system. In fact, this specific role of N₂ was confirmed by the observation that no stabilizing effect was found when identical reactions were performed with different partial pressures of He (Table S2, entries 5-6). Furthermore, replacing FeCl₂ with CuCl₂ also led to a complete loss of the beneficial effects (Table S2, entries 7-10), which suggested that the activity of Fe, and not Pt, is positively altered by N₂. As the role of Fe is to reoxidize Pt(0) to Pt(II), the Pt-mediated hydroxylation of butyric acid was studied using FeCl₂, but with initial addition of Pt(0), instead of K₂PtCl₄, to the reaction mixture and with variation of the atmospheric composition. After

Table 4. Effect of *N*-heteroaromatic ligands on the Pt-catalyzed hydroxylation of butyric acid with O2.^[a]

	Linond	Motallia platinum ^[b]	V (0/)	C (0()	Carbon yield (%) ^[c]					
	Ligand		× (%)	5 (%)	GHB	BHB	AHB	SA	DP ^[d]	
1	-	V	85.5	32	27.6	1.4	0.8	1.9	53.8	
2	2,2'-Bipyridine	N	9.4	3	0.3	0.2	0	0	8.9	
3	Pyridine	N	32.4	50	16.3	0.7	1.0	0.3	14.1	
4	2-Phenylpyridine	N	7.4	26	1.9	0.2	0	0	5.3	
5	2-Chloropyridine	N	29.9	57	16.9	2.2	2.0	0	8.8	
6	2-Trifluoromethylpyridine	N	49.8	49	24.5	1.3	2.0	0.8	21.2	
7	2-Fluoropyridine	N	82.8	40	33.0	1.4	1.1	2.1	45.2	
8	2-Hydroxypyridine	N	77.3	45	34.6	1.5	0.8	1.5	38.9	

[a] Conditions: butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0.33 M), FeCl₂'4H₂O (5 mol%), ligand (1 mol%), H₂O (1.5 mL), 6 h, 150 °C, 20 bar O₂. Abbreviations: GHB, γ -hydroxybutyric acid; BHB, β -hydroxybutyric acid; AHB, α -hydroxybutyric acid; SA, succinic acid; DP, degradation products. [b] Visual observation of metallic platinum at the bottom of the glass vial after reaction? = Yes, = No. [c] Number of mmoles of C in the respective product divided by the total mmoles of C initially supplied in butyric acid (i.e. 4 mmol). [d] Lower degradation products include lactic acid, acetone, acetic acid, glycolic acid, acetaldehyde, formic acid, methanol and gaseous compounds.

6 h, much higher butyric acid conversions were observed when the gaseous atmosphere was complemented with 5 bar N₂ (Figure 4), giving evidence that the specific combination of Fe salts and N₂ is more effective in activating Pt(0). Since N₂ in itself is considered to be rather inert, evidence was sought for the presence of more reactive nitrogen oxides (NOx). Quantitative infrared spectroscopy of the vapor phase was therefore conducted; the IR data clearly revealed characteristic bands corresponding to the N-O stretch vibration of nitrogen monoxide (Figure S8). In summary, a reasonable explanation for the stabilizing effect of N₂ is that minor amounts of NO, or other Noxides, are formed in situ under the oxidative conditions and as such, or upon activation by Fe,^[42] facilitate the reoxidation of Pt(0) during reaction. Furthermore, higher concentrations of these N-oxides are likely to be formed at elevated partial pressures of N₂, which, by analogy to the reoxidation of Pt(0), could favor the



Figure 3. Pt-catalyzed hydroxylation of butyric acid under 20 bar O₂ and varying partial pressures of N₂. Conditions: butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0.33 M), FeCl₂·4H₂O (5 mol%), H₂O (1.5 mL), 6 h, 150 °C, 20 barO₂/2-20 bar N₂.



Figure 4. Influence of introducing N₂ in the gaseous atmosphere on the rate of Pt(0) reoxidation. Conditions: butyric acid (0.67 M), Pt(0) (1 mol%), H₂SO₄ (0.33 M), FeCl₂·4H₂O (5 mol%), H₂O (1.5 mL), 1-6 h, 150 °C, 20 bar O₂/5 bar N₂.

undesired oxidation of $[Pt(II)Cl_4]^{2-}$ to $[Pt(IV)Cl_6]^{2-}$, thereby reducing the amount of active catalyst in solution and limiting the conversion.

While the formation of metallic platinum has generally been accepted as a measure of Pt(II) deactivation in Shilov chemistry, supporting evidence for the enhanced catalyst stability was obtained by means of determining the Pt(II) activity after including a second part of substrate. For this, time-dependent changes in the yield of GHB were evaluated after adding 1 mmol of butyric acid to substrate mixtures already subjected to a reaction for 6 h with and without either of the two nitrogen-containing additives. As indicated in Figure S9, a substantial reduction in yield occurred after 10 h under standard reaction conditions; conversely, a continuous formation of GHB up to 12 h was observed (i) in the presence of 2-F-pyridine (1 mol%) as well as (ii) after introducing N₂ (5 bar) in the gaseous atmosphere. Accordingly, the prolonged catalyst activity under optimized conditions could be attributed to a superior stability of the Pt catalyst.

Selectivity enhancing strategies

Thus far, high selectivities for GHB (≥ 70%) were only maintained at relatively low conversion (≤ 50%, Figure 2). As previously mentioned, multiple by-products, including succinic acid, as well as lower degradation and gaseous compounds, were identified after conducting a qualitative 1D and 2D NMR analysis of the product mixture, in combination with infrared spectroscopy of the vapor phase. Consequently, developing a more comprehensive understanding of how these undesirable products are formed during reaction is essential to enhance the preferential formation of GHB at elevated conversions. For instance, the gradually decreasing carbon yield of GHB at longer reaction times (Figure 2a) points to the occurrence of consecutive overoxidation reactions. To study this stability issue and to evaluate the catalytic activity of certain compounds towards these non-selective side reactions, GHB was first synthesized according to the procedure described by Ferris and Went;^[43] the purity of the resulting sample was determined by ¹H NMR (Figure S10). Next, 1 mmol of GHB was added to distinct solutions containing (a) no catalyst or cocatalyst, (b) FeCl₂, (c) Pt(0), (d) K₂PtCl₄ and (e) K₂PtCl₄ as well as FeCl₂. For each of the resulting mixtures, a kinetic profile was recorded at short reaction times and under standard reaction conditions (0.33 M H₂SO₄, 150 °C, 20 bar O₂).

As shown in Figure 5a, GHB remained fully stable in the absence of any (co-)catalyst, as well as upon the addition of FeCl₂ to the substrate solution. Hence, the possibility of a radical-mediated initiation seems excluded. On the other hand, overoxidation of the remote hydroxyl group took place to a considerable extent when K₂PtCl₄ was included instead, as demonstrated by the predominant formation of succinic acid during reaction (Figure 5b). Although this side reaction appears to correspond to the well-known oxidative transformation of alcohols on metallic Pt,^[44] no degradation of GHB occurred over time in the presence of Pt(0). Given these observations, the Pt-mediated degradation can be rationalized by assuming that GHB remains coordinated to the Pt(II) center via its hydroxyl group, rendering the C–H bonds in the α -position susceptible to further oxidation. Moreover, adding FeCl₂ to the catalyst-containing solution gave

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Figure 5. Stability of γ -hydroxybutyric acid (GHB) in the Pt-catalyzed hydroxylation of butyric acid with O₂, illustrated via the time-dependent changes in (a) relative concentration of GHB and (b) carbon yields of the side products formed. Conditions: γ -hydroxybutyric acid (0.67 M), K₂PtCl₄ (0-1 mol%), Pt(0) (0-1 mol%), H₂SO₄ (0.33 M), FeCl₂'4H₂O (0-5 mol%), H₂O (1.5 mL), 0-2 h, 150 °C, 20 bar O₂.

rise to a significantly altered product distribution, while no additional decline in the relative concentration of GHB occurred. More specifically, a reduced amount of succinic acid was invariably detected, together with elevated levels of lower degradation products, in particular acetic acid and glycolic acid. Additionally, comparison of the vapor phase composition via quantitative infrared spectroscopy revealed an increased formation of CO₂, CO, CH₄ and acetaldehyde. This particular change in product distribution suggests that Fe(III)/Fe(II) accelerates the decarboxylation of succinaldehydic acid and succinic acid via one-electron oxidations, along with the oxidative C–C cleavage of both compounds.^[45] In short, K₂PtCl₄ and FeCl₂ not only catalyze the regioselective C–H hydroxylation of butyric acid to GHB, but also appear to facilitate consecutive reactions of the latter, leading to undesirable selectivities at high conversions

To stop the oxidation process at the level of GHB, by preventing further oxidation of the remote hydroxyl mojety. standard reactions were performed with varving amounts of boric acid (H₃BO₃). In fact, H₃BO₃ has been applied for many years in hydrocarbon oxidation processes, e.g. the autoxidation of linear saturated alkanes to secondary alcohols, with the purpose of controlling the chemoselectivity.^[45-47] It is believed that esterification of H₃BO₃ to the corresponding borate ester is able to protect the alcohol product from further oxidation; the electronwithdrawing nature of the boron atom lowers the electron density of the neighboring C-H bonds, causing H-abstraction by radicals to be unfavorable.^[47] We however presumed that this reduced electron richness of the α -C-H bonds might also lower their tendency to coordinate to the electrophilic Pt catalyst and therefore reduce their reactivity towards overoxidation. Consequently, by including 1 equiv. of H₃BO₃, a selectivity of 70% could indeed be maintained at much higher conversion, yielding 47% of GHB within 6 h and a TON of 67 (Figure 6). At the same time, combining this protective effect with the addition of stabilizing agents turned out unsuccessful, since esterification was negatively affected in the presence of pyridine derivatives, such as 2-F- or 2-OH-pyridine (see Supporting Information, Table S3). Nonetheless, limiting the interaction between the desired product and Pt(II) proved to be an appropriate strategy to avoid non-selective consecutive reactions.

As was already evident from Figure 2b, non-selective overoxidation reactions were considerably more prominent when CuCl₂, instead of FeCl₂, was applied as co-catalyst, which translated into lower selectivities over the full course of reaction. Moreover, quantitative infrared spectroscopy revealed a larger amount of gaseous products for the Cu-mediated reaction. To evaluate the applicability of the above-mentioned approach, standard reactions with CuCl₂ were also performed in the presence of 0.5-1 equiv. of H₃BO₃. However, only a negligible increase in selectivity of GHB was observed (Figure S11). On the contrary, the selectivity to GHB for the Cu co-catalyzed reaction surprisingly improved when sulfuric acid was fully omitted from the substrate mixture (Figure S12). Despite the slight decrease in catalyst activity, a selectivity of > 80% was retained within the first 2 h (Figure 7). While FeCl₂ is still the preferred co-catalyst in terms of catalyst activity and stability, this observation is quite remarkable and is most likely related to the speciation of Cu(II) in solution. First, one must note that CuCl₂ is expected to partially dissociate to free Cu(II), as a moderately low equilibrium constant





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has been reported for the interaction of Cu(II) with one or more Clions.^[48] Conversely, Cu(II) has a high tendency to associate with SO₄^{2-,[49]} which indicates that CuCl₂ is partially transformed into CuSO₄ when H₂SO₄ is present. Moreover, stability tests with varying H₂SO₄ concentrations revealed a notable change in the side product distribution; an elevated concentration of the degradation product acetic acid was observed in H₂SO₄-free conditions. In addition, Imamura et al.[50] reported that CuSO4 is more active in the oxidative decomposition of acetic acid than CuCl₂, due to its superior stability in solution at high temperatures. Analogously, a more advanced degree of GHB degradation was observed upon replacing CuSO₄ with CuCl₂ (Figure S13), which led us to believe that in situ formed CuSO4 is responsible for the higher degree of overoxidation. Altogether, these findings provide a possible explanation for the unusual relation between the sulfuric acid concentration and selectivity for GHB in reactions that use Cu as the co-catalyst.



Figure 7. Time profiles of (a) carbon yields and (b) selectivities in the Ptcatalyzed hydroxylation of butyric acid with O₂ and varying concentrations of sulfuric acid, in the presence of CuCl₂ as co-catalyst. Conditions: butyric acid (0.67 M), K₂PtCl₄ (1 mol%), H₂SO₄ (0-0.33 M), CuCl₂·2H₂O (5 mol%), H₂O (1.5 mL), 150 °C, 20 bar O₂.

Conclusions

By implementing FeCl₂ as appropriate co-catalyst, we have successfully demonstrated the potential of using O₂ as terminal oxidant in realizing a practical Shilov-chemistry inspired Pt-based

system for the selective terminal hydroxylation of cheap and abundant aliphatic compounds. As opposed to current state-ofthe-art systems, a notable increase in catalyst activity was achieved for the conversion of butyric acid, together with the selective formation of GHB. Accordingly, the intrinsic activity of the proposed system was studied in detail by carefully exploring the different reaction parameters. In addition, introducing catalytic amounts of ortho-functionalized pyridine derivatives proved to be an effective way to improve the catalyst stability. A similar outcome was achieved by introducing N_2 in the gaseous atmosphere, which was explained in terms of the role played by *in situ* formed *N*-oxides. Finally, insights into the potential overoxidation pathways of GHB revealed the need for suitable protecting agents, such as boric acid, which allowed to attain elevated selectivities (70%) at much higher conversion (> 60%).

Experimental Section

Catalytic reaction

In a typical reaction, a glass reaction vial (5.5 mL) was loaded with the substrate (0.67 M), a noble metal catalyst (1 mol%), a co-catalyst (5 mol%), an acid (0.33 M), deionized water (1.5 mL) and a magnetic stirring bar. After partially closing the vial with a teflon stopper, it was positioned into a stainless steel reactor (11 mL). The reactor was sealed, after which its atmosphere was purged for 5 s with pure O2 and pressurized with 20 bar O2. Next, while stirring at 500 rpm, the reaction was initiated by heating the reactor to 150 °C and time recording was started when this temperature was reached. After 6 h, heating was discontinued and the reaction was quenched by cooling of the reactor on ice. Ultimately, the residual solution was separated and analyzed as such by proton nuclear magnetic resonance (¹H NMR) spectroscopy. Due to difficulties related to the paramagnetism of iron (Fe) in NMR measurements, Fe-containing mixtures were first basified by adding 1.5 mL of a concentrated solution of NaOH (2 M). This change in pH caused a complete precipitation of the iron species present in solution. Afterwards, the precipitate was removed by centrifugation (10 min, 3200 rpm) and the supernatant was analyzed in a similar fashion.

Product analysis and identification

To quantify the product yields, reaction mixtures were analyzed by ¹H NMR spectroscopy. Samples were first prepared by transferring 100 µL of the product solution to 500 µL of D₂O, containing an external standard (benzyl alcohol, 0.133 M), after which corresponding ¹H NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer equipped with a BBO 5 mm atma probe and a sample case. During measurements, the broad water signal was suppressed by applying a zgpr pulse program, p1 9.75 $\mu s;$ ns 32; d1 25 s; aq 2.55 s; plw1 15 W; plw9 5.7 $^{\cdot}$ 10 $^{-5}$ W; o1P, on the resonance signal of water, determined and selected automatically. In addition, ¹³C NMR and two distinct methods of 2D NMR were combined to elucidate the identity of all products observed in the ¹H NMR spectrum of a standard reaction mixture. ¹³C NMR was carried out according to the following pulse program: p1 7.65 µs, ns 1024, d1 2s, plw1 120 W, plw2 15 W, plw12 0.19 W, plw13 0.09 W; ¹H-¹³C NMR over 1 bond (HSQC) according to the following pulse program: p1 9.75 µs, p2 19.50 µs, p3 7.50 μs, p4 15 μs, ns 128, d1 1.41 s, plw1 15 W, plw2 120 W, plw12 1.05 W; and ¹H-¹³C NMR over 2 or 3 bonds (HMBC) according to the following pulse program: p1 9.75 µs, p2 19.50 µs, p3 7.50 µs, ns 40, d1 1.41 s, plw1 15 W, plw2 120 W. Furthermore, to account for the non-selective C-C cleavage of primary reaction products towards lower degradation byproducts, yields were calculated as follows: the amount of mmoles for each

compound was determined by comparing the normalized peak area with the one obtained for benzyl alcohol, from which corresponding carbon yields were obtained by dividing the number of mmoles of C in the respective product by the total mmoles of C initially supplied in the substrate (i.e. 4 mmol). Finally, quantitative Fourier Transform Infrared (FTIR) spectroscopy was conducted, using a Gasmet DX4000 FTIR gas analyzer, to evaluate the presence of gaseous products in the vapor phase. Prior to each measurement, part of the vapor phase was transferred from the reactor into a plastic syringe (5 mL) and injected as such into a N₂ stream (160 mL/min). Next, volume concentrations of the various compounds were measured at the detector level and were processed using the Calcmet Standard software version 12.161.

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Keywords: C–H activation • Hydroxylation • Molecular oxygen • Primary C–H bonds • Shilov-type Pt catalysis

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- ✓ Economically viable and readily available oxidant
- ✓ Highly active and durable Pt-based system (TON > 60, TOF > 10 h⁻¹)
- ✓ Site-selective hydroxylation of terminal C–H bonds

H2O H2O H2O H2O H2O H2O H2O H2O H2O H2O	Michiel Janssen, Dirk E. De Vos* Page No. – Page No. Pt(II)-Catalyzed Hydroxylation of Terminal Aliphatic C(sp ³)–H Bonds with Molecular Oxygen