Low Temperature, High Conversion, Liquid-Phase Benzylic Oxidation with Dioxygen by Metal/NHPI-Catalyzed Co-Oxidation with Benzaldehyde

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A new liquid-phase catalytic oxidation system for the low temperature, high conversion benzylic mono-oxyfunctionalization of 10,11-dihydrocarbamazepine (**1**) into oxcarbazepine (**4**) with dioxygen has been developed. The method is based on a co-oxidation of **1** with benzaldehyde in the presence of a four-component catalyst system consisting of $Co(OAc)_2$, $Ni(OAc)_2$, $Cr(NO_3)_3$, and *N*-hydroxyphthalimide (NHPI). The influence of the catalyst system on the formation and decomposition of the crucial hydroperoxide intermediate **2** has been investigated. Based on these results, the role of each of the components in the catalyst system is discussed. The scope of this method for the oxidation of other substrates has been studied, and the results are compared with those obtained by Co/NHPI catalyzed oxidation of these substrates.

Introduction

Methods for carrying out benzylic oxidation in the liquid phase on an industrial scale can be separated into catalytic oxidations based on dioxygen as the oxidant and stoichiometric oxidations based on metal-based oxidants, most often chromates or permanganates. The former usually require high temperatures (150−200 °C) and are of prime importance in the manufacture of bulk chemicals.[1−3] The latter stoichiometric oxidations are carried out at much lower temperature (<100 °C) and are typically used for the manufacture of fine chemicals.[4] Despite their obvious disadvantages over the catalytic oxidations from an economic and environmental point of view, industrial use of these stoichiometric oxidations is often enforced because known catalytic methods fail for the manufacture of fine chemicals, either because the catalytic O_2 oxidations do not proceed, or because the high temperature required for these catalytic oxidations is incompatible with the usually considerable molecular complexity of fine chemicals. In our search for an efficient route for the direct oxidation of 10,11-dihydrocarbamazepine (**1**) to the anti-epileptic compound oxcarbazepine (**4**), we required an industrially viable method based on an inexpensive, "green" oxidant for the monooxidation of the benzylic CH_2CH_2 group in **1** that proceeds with high conversion and runs at low temperature (<30 °C).

A highly efficient method for low temperature, high conversion C−H bond oxyfunctionalization based on a polyoxometalate catalyst and ozone as terminal oxidant has been reported recently.[5] Other recent work by Ishii and Einhorn has shown that the requirements can also be fulfilled under catalytic conditions with O_2 as the terminal oxidant in the presence of *N*-hydroxyphthalimide (NHPI) as a catalyst, the two methods differing in that the Ishii process employs metal/NHPI catalyst systems,[6−12] whereas the Einhorn system is based on metal-free co-oxidations in the presence of acetaldehyde with only NHPI as catalyst.[13−16] However, these two methods turned out to be unsuitable for the oxidation of **1** to **4**. After extensive research, a method with characteristics of both the Ishii and Einhorn method turned out to afford reasonable yields of **4** while running at room temperature. According to the new method, **1** is subjected to a co-oxidation with PhCH(O) using a catalyst system containing both NHPI as well as metal catalysts. Results of investigations to determine the scope of this new catalytic oxidation system with respect to the oxidation of substrates other than **1** are also presented, together with a mechanistic rationalization of some of the experimental observations.

Results

The oxidation of **1** was generally carried out by stirring a solution of **1** and NHPI in the presence of metal co-catalysts and/or an aldehyde additive at or near room temperature under an atmosphere of O_2 (1 bar). Details of the

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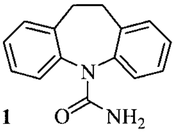
systems studied are provided below. Analysis of the reaction mixtures obtained after catalytic oxidation of **1** with O_2 by electrospray HPLC-MS (positive ion mode) revealed the presence of five products derived from **1** with molecular masses of 252, 254, 266, 270, and 282, respectively.



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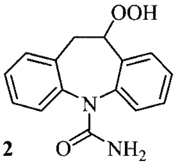

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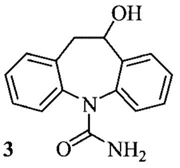

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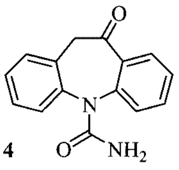

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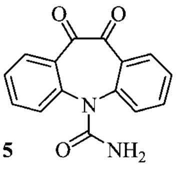

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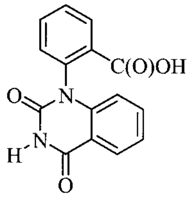

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The compound with M = 252, which was isolated, was identified as the target product **4** by comparison with an authentic commercial sample. The compound with M = 254 shows, besides the $[M + H]^+$ $m/z = 255$ peak, a peak with $m/z = 237$. This peak is assigned to the $[M + H - H_2O]^+$ ion. Accordingly, the structural formula assigned to the product with M = 254 corresponds to that of the benzylic alcohol **3**. The compound with M = 270 also shows an $m/z = 237$ peak, which in this case is assigned to the $[M + H - H_2O_2]^+$ ion formed by elimination of hydrogen peroxide from the protonated benzylic hydroperoxide **2**. The structural formula assigned to the M = 266 compound corresponds to that of dione **5**. In accordance with this structure, no lower molecular weight ions resulting from elimination of water or hydrogen peroxide were observed for this product. These four products, i.e., **2**, **3**, **4**, and **5**, are the expected products formed in a radical-chain oxidation of **1** with O_2. The compound with M = 282 shows an $[M + H]^+$ peak at $m/z = 283$ in the positive ion mode and an intense $[M - H]^-$ peak at $m/z = 281$ in the negative ion mode, pointing to the presence of an acidic proton in the compound. The presence of an acidic group is further supported by the observation of a diadduct containing two sodium atoms ($m/z = 609$) in the positive ion mode besides the usua $[M + Na]^+$ peak (at $m/z = 305$). This $m/z = 609$ value results from a proton/sodium exchange to afford a diadduct $[\{M + Na\}\{M - H + Na\}]^+$. Based on the this evidence, the molecular structure tentatively assigned to the M = 282 by-product corresponds to that of **6**. The formation of **6** will be rationalized shortly. Compared to the main product **4**, the by-products **2**, **3**, **5**, and **6** are usually formed only in (very) small amounts. Because of this, and because of the instability of hydroperoxide **2**, these by-products have not been isolated. In the following, data concerning the yields of the former three by-products are semi-quantitative estimations based on HPLC response factors of **2**, **3**, and **5** that are made equal to that of **1**. These data serve for relative comparisons of the amounts of these compounds formed in the various experiments.

Einhorn- and Ishii-Type (Co-)Oxidations

An Einhorn-type co-oxidation of **1** and acetaldehyde (5 equiv.) catalyzed by NHPI (20 mol %)[13] on a 1 mmol scale in a flask equipped with a balloon filled with O_2 gave a promising result in one run (47% yield at 83% conversion) when MeCN was used as the solvent and MeCH(O) was added slowly over 6 h. This experiment, however, as well as other experiments with acetaldehyde, proved to be poorly reproducible, with yields varying from 3−47% and conversions ranging from 23−83%.[17] Even poorer results were obtained with other aldehydes [PhCH(O), octanal] and/or other solvents (MeCN/AcOH, CH_2Cl_2, $CHCl_3$, EtOAc, MTBE, cyclohexanone).

An Ishii-type oxidation of **1** with O_2 catalyzed by $Co(OAc)_2$ (0.5−3 mol %) and NHPI (20−40 mol %)[6] in various solvents (AcOH, PhCN, MeCN, PhMe) and at various temperatures (22, 40, 75 °C) gave conversions ranging from zero to, at most, 53%, generally with low yields of **4** (0−20%).

Metal/NHPI Catalyzed Co-Oxidation with PhCH(O)

The results of O_2 co-oxidations of **1** and PhCH(O) in the presence of metal/NHPI catalyst systems are listed in Table 1 (entries 1−11). These reactions were carried out at 22 °C in AcOH on a 1 mmol scale, using 1 mol % metal catalyst, 38 mol % NHPI and 1.2 equiv. of PhCH(O). A greater than 20% yield of **4** at reasonably high conversions was only obtained with $Cr(NO_3)_3$, $Ni(OAc)_2$, and $Ni(acac)_2$. *At this point it should be noted that unless specified otherwise, the* $Ni(OAc)_2$ *used is 98% pure. This nickel acetate turned out to be contaminated with approximately 116 ppm of cobalt. The effect of Co on the course of the oxidation will be outlined later on.* Formation of **5** was markedly enhanced by Mn, whereas high levels of **2** were observed for Fe, Cu, Ce, and all Ni-based catalysts. The latter catalysts, as well as Mn and Co, also induced formation of considerable amounts of **3**. Remarkably, very low amounts of **2**, **3**, and **5** were formed in the presence of $Cr(NO_3)_3$ as catalyst. In two consecutive experiments, no oxidation was observed in the presence of $Cr(acac)_3$. With respect to the Ni-catalyzed oxidations, the presence of each of the three components $Ni(OAc)_2$, NHPI, and PhCH(O) turned out to be essential. Yields dropped to less than 4% with a concomitant large drop in conversion when one of these three components was omitted.

Additional Catalysts in Ni/NHPI- or Cr/NHPI-Catalyzed Co-Oxidation with PhCH(O)

Table 1 (entries 12−26) lists the results of attempts to enhance the yield of **4** in Ni/NHPI-catalyzed co-oxidations by stimulating the conversion of **2** and **3** into **4** by addition of metal co-catalysts along with $Ni(OAc)_2$ and NHPI. Generally, (potentially) redox-active co-catalysts were added in small amounts (approx. 0.25 mol %) relative to Ni (1

Table 1. Co-oxidation of **1** with PhCH(O) catalyzed by NHPI and metal catalysts[a]

Entry	Metal cat[b]	Metal co-cat[b]	Conv (%)[c]	**2**[c,d] (%)	**3**[c,d] (%)	**4**[c] (%)	**5**[c,d] (%)
1	$V(acac)_3$	–	19	0	2	4	1
2	$Cr(acac)_3$	–	0	0	0	0	0
3	$Cr(NO_3)_3$	–	47	0	1	21	5
4	$Mn(OAc)_2$	–	56	2	10	8	8
5	$Fe(OAc)_2$	–	13	13	0	2	0
6	$Co(OAc)_2$	–	56	1	9	19	3
7	$Ni(OAc)_2$[e]	–	63	10	9	27	1
8	$Ni(acac)_2$	–	61	11	5	20	1
9	$NiCl_2$	–	55	21	3	13	1
10	$Cu(OAc)_2$	–	34	15	2	12	1
11	$Ce(OAc)_3$	–	19	14	1	3	0
12	$Ni(OAc)_2$ [e]	$LiBF_4$[f]	38	5	2	14	0
13	$Ni(OAc)_2$ [e]	Cs_2CO_3[g]	47	21	3	17	1
14	$Ni(OAc)_2$ [e]	$Ti(O\textit{i}Pr)_4$ [f]	4	0	0	3	0
15	$Ni(OAc)_2$ [e]	$Zr(O\textit{t}Bu)_4$ [f]	29	16	2	7	0
16	$Ni(OAc)_2$ [e]	$V(acac)_3$	44	2	6	18	1
17	$Ni(OAc)_2$ [e]	$Cr(acac)_3$	63	1	0	44	1
18	$Ni(OAc)_2$ [e]	$Cr(NO_3)_3$	65	2	0	45	1
19	$Ni(OAc)_2$ [e]	MoO_3 [f]	62	14	6	23	2
20	$Ni(OAc)_2$ [e]	$Mn(OAc)_2$	51	10	4	18	4
21	$Ni(OAc)_2$ [e]	$Fe(OAc)_2$	40	15	4	21	1
22	$Ni(OAc)_2$ [e]	$RuCl_3$	59	10	9	19	2
23	$Ni(OAc)_2$ [e]	$Co(OAc)_2$	49	3	4	22	3
24	$Ni(OAc)_2$ [e]	$Pd(OAc)_2$	57	12	8	21	1
25	$Ni(OAc)_2$ [e]	$Cu(OAc)_2$	50	22	3	21	1
26	$Ni(OAc)_2$ [e]	$La(Otf)_3$ [f]	32	21	2	6	0
27	$Co(OAc)_2$	$Cr(NO_3)_3$	57	1	10	19	4
28	$Mn(OAc)_2$	$Cr(NO_3)_3$	55	5	8	11	6
29	$Ni(OAc)_2$ [e]	$Cr(NO_3)_3$	65	2	0	45	1
30	$Pd(OAc)_2$	$Cr(NO_3)_3$	46	0	0	24	3
31	$Cu(OAc)_2$	$Cr(NO_3)_3$	59	4	0	39	2
32	$Ce(OAc)_2$	$Cr(NO_3)_3$	62	3	2	25	2

[a] 1 mmol substrate, 0.5 mmol 1,2,4-trichlorobenzene (internal standard), and 1.2 mmol PhCH(O) at 22 °C in 3 mL AcOH under O_2 (1 bar, balloon) with 40 mol % NHPI, 1 mol % metal catalyst, and 0.25 mol % metal co-catalyst unless otherwise indicated. [b] Potential water of crystallisation not indicated. [c] By HPLC after 5 h. [d] Estimated. [e] 98% pure. [f] Approx 3.5 mol %. [g] 1.4 mol %.

mol %) and NHPI (38 mol %), whereas non-redox active Lewis-acid catalysts were mostly used in higher amounts (3.5 mol %). Systems based on either $Cr(NO_3)_3$ or $Cr(acac)_3$ as co-catalyst are clearly much better than systems based on other co-catalysts in terms of yield of **4**, which is twice as high for the Cr-based systems than for the next-best system. The two Cr-based systems also show much lower amounts of **2** and **3**, which suggests that the increase of yield on addition of Cr as co-catalyst to the Ni/NHPI system indeed results from an efficient conversion of **2** and **3** into **4** (cf. entries 7 and 8 with entries 17 and 18). Note that the oxidation is effectively catalyzed by the $Ni(OAc)_2$/$Cr(acac)_3$/NHPI system, whereas no reaction is observed with the $Cr(acac)_3$/NHPI system (see above). The level of **5** was again highest in the presence of Mn. The dependence of conversion and yield of **4** on the amount of Cr at a level of 1 mol % of $Ni(OAc)_2$ is shown in Figure 1, which illustrates that approximately 0.25 mol % of Cr is optimum. The influence of the amount of Ni and NHPI will be dealt with in detail below.

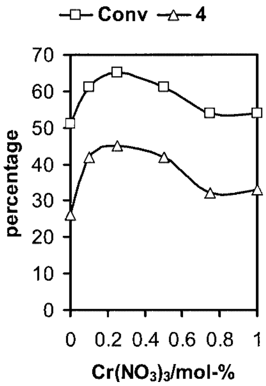


Figure 1. Dependence of the conversion of **1** and yield of **4** after 5 h in the Ni/Cr/NHPI catalyzed co-oxidation of **1** (1 mmol, AcOH, 22 °C, 1 bar O_2) with PhCH(O) (1.2 equiv.) on the amount of Cr in the presence of 1 mol % $Ni(OAc)_2$ (98% pure) and 40 mol % NHPI

The results of experiments aimed at testing the efficiency of various metal catalysts (1 mol %) in combination with NHPI (38 mol %) and $Cr(NO_3)_3$ as co-catalyst (0.25 mol %) are listed in Table 1 (entries 18 and 27–32). The highest yield and conversion is obtained with the Ni/Cr/NHPI system, with Cu/Cr/NHPI performing only slightly less well. In this case, the highest level of **5** was also observed with Mn.

Optimization of the Ni/Cr/NHPI System

A few other aldehydes besides PhCH(O) have been tested as co-substrate for the co-oxidation of **1** catalyzed by Ni/Cr/NHPI (1/0.25/37 mol %). The oxidation did not proceed with *p*-$MeOC_6H_4CH(O)$ or phthalaldehyde. The results obtained with *p*-Me-, *p*-F-, *p*-Cl-, and *o*-Cl-$C_6H_4CH(O)$ differed only slightly from that with PhCH(O), whereas the yield and conversion decreased significantly when octanal was used. The yield and conversion do not increase progressively with the amount of PhCH(O). After a slight increase on doubling the amount of PhCH(O), both conversion and yield drop again. The Ni/Cr/NHPI-catalyzed co-oxidation of **1** with PhCH(O) afforded optimum results at 22 °C, with both yield and conversion being lower at higher or lower temperatures. AcOH turned out to be the best solvent for this reaction, inferior results being obtained with MeCN, PhCN, CH_2Cl_2, and $EtCO_2H$. The conversion and yield also decreased when 90:10 or 95:5 (v/v) AcOH/H_2O was used as the reaction medium instead of pure AcOH. Typical time course profiles of a 1 mmol scale Ni/Cr/NHPI-catalyzed reaction with 1.1 equiv. of PhCH(O) are shown in Figure 2 (right), which illustrates that an optimum yield of **4** is obtained after about 5 h. Comparison with the time course profiles of Ni/NHPI- and Cr/NHPI-catalyzed oxidations (left and middle) demonstrates once more the efficiency of the Ni/Cr/NHPI system. The figure also illustrates the much higher level of peroxide **2** in the Ni/NHPI-catalyzed reaction than in the two other reactions, in which Cr is present as co-catalyst.

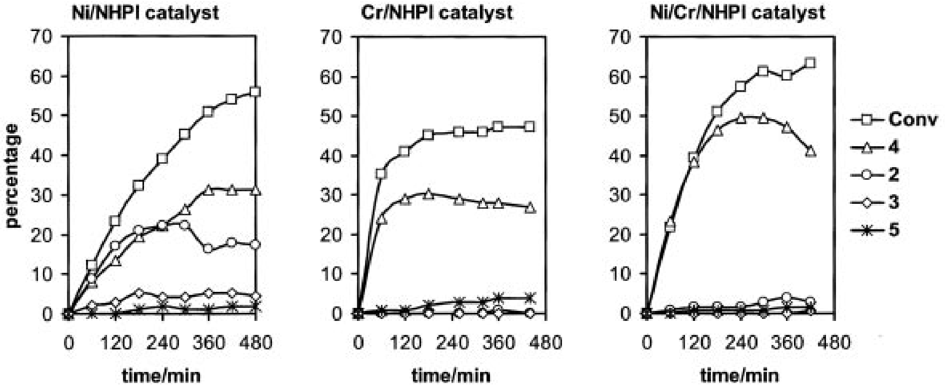


Figure 2. Time course profiles for the co-oxidation of **1** (1 mmol, AcOH, 22 °C, 1 bar O_2) with PhCH(O) (1.1 equiv.) catalyzed by: *left:* $Ni(OAc)_2$/NHPI (1/37 mol %/mol %); *middle:* $Cr(NO_3)_3$/NHPI (1/37 mol %/mol %); *right:* $Ni(OAc)_2/Cr(NO_3)_3$/NHPI (1/0.25/37 mol %/mol %/mol %).; 98% pure $Ni(OAc)_2$ was used

The influence of the amount of NHPI on the Ni/Cr/NHPI-catalyzed co-oxidation of **1** and PhCH(O) (1.1 equiv.) is shown in Figure 3. After an initial sharp increase of yield and conversion, an optimum is obtained in the presence of about 40 mol % NHPI, followed by a slow decrease on further increasing the amount of NHPI.

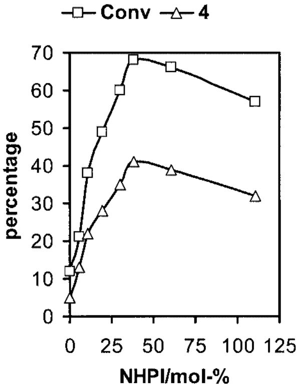


Figure 3. Dependence of the conversion of **1** and yield of **4** after 5 h in the Ni/Cr/NHPI-catalyzed co-oxidation of **1** (1 mmol, AcOH, 22 °C, 1 bar O_2) with PhCH(O) (1.2 equiv.) on the amount of NHPI in the presence of 1 mol % $Ni(OAc)_2$ (98% pure) and 0.25 mol % $Cr(NO_3)_3$

Bubble-Column Experiments; Gradual PhCH(O) Addition

Time course measurements of two Ni/Cr/NHPI-catalyzed oxidations in 10 mmol scale bubble-column experiments, one in which 1.3 equivalents of PhCH(O) was added in one portion, and one in which the same amount of PhCH(O) was added over five hours, revealed that gradual PhCH(O) addition improves yield and conversion. The induction period that is otherwise observed during gradual PhCH(O) addition experiments was minimized by first adding 0.1−0.3 equivalents of PhCH(O) in one portion, followed by gradual addition of the remaining equivalent of PhCH(O) over five hours. The results of several slow PhCH(O) addition bubble column experiments carried out on a 10, 25, or 33 mmol scale are collected in Table 2. This table shows that a 50−53% yield of **4** is obtained under various conditions with different amounts of NHPI and PhCH(O).

Influence of Purity and Amount of $Ni(OAc)_2$: The Role of Co

The course of the Ni/Cr/NHPI-catalyzed co-oxidation of **1** and PhCH(O) depends on the purity of the $Ni(OAc)_2$ catalyst. When "100% pure" $Ni(OAc)_2$ was used instead of the 98% pure quality used in all the experiments described above, the reaction started only after a considerable induction period and both conversion and yield were lower than those obtained with the impure $Ni(OAc)_2$. Subsequent elemental analysis revealed that the 98% $Ni(OAc)_2$ contained about 116 ppm of Co, whereas less than 5 ppm of Co was present in the "100% pure" $Ni(OAc)_2$. The effect of traces of Co on the Ni/Cr/NHPI-catalyzed oxidation was studied in a series of 10 mmol bubble column experiments in which increasing amounts of $Co(OAc)_2$ were added while keeping the concentration of 100% pure $Ni(OAc)_2$, $Cr(NO_3)_3$ and NHPI at a constant level of 1 mol %, 0.25 mol %, and 40 mol %, respectively. The amount of added Co was varied from 0 to 0.0021 mol % around the standard value (approx. 0.0005 mol %) that was added when using 1 mol % of 98% pure $Ni(OAc)_2$. The conversion, yield, and amount of **2** as a function of the Co content after five hours [sample taken immediately after all PhCH(O) had been added] and seven hours [sampling 2 hours after complete PhCH(O) addition] is shown in Figure 4.

This figure illustrates that: (i) the conversion increases first rapidly, then slowly with the amount of Co; (ii) the yield reaches a maximum at a Co level close to that obtained by using 1 mol % 98% $Ni(OAc)_2$; (iii) the level of **2** remains constant up to the Co level at which the yield reaches its optimum, and increases in a fairly linear way above this Co level; (iv) the increase in the level of **2** is approximately equal to the decrease in the yield of **4** after passing the maximum.

Co/Ni/Cr/NHPI-catalyzed bubble column oxidations based on varying amounts of 100% pure $Ni(OAc)_2$ and a constant amount of 0.0004 mol % $Co(OAc)_2$ showed that

Table 2. Effect of the PhCH(O) addition rate on the Ni/Cr/NHPI catalyzed co-oxidation[a]

Entry	**1**/NHPI/PhCH(O) (mmol/mmol/mmol+mmol)[b]	Cr co-cat	Dosing time (h)	Reaction time (h)	Conv (%)[c]	**4** (%)[c]
1	10.0/4.00/12.1+0	$Cr(NO_3)_3$ [d]	0	7	62	39
2	10.0/4.00/3.0+10.1	$Cr(NO_3)_3$ [d]	5	7	72	53
3	10.0/4.10/0+12.1	$Cr(NO_3)_3$ [d]	5	7	66	53
4	25.0/10.0/2.5+40.1	$Cr(acac)_3$	5	7	72	51
5	10.0/6.1/0+30.3	$Cr(acac)_3$	6	7	77	51
6	33.3/20.0/0+100.0	$Cr(acac)_3$	6	7	79	50

[a] x mmol scale reactions in $3x$ mL of AcOH under O_2 (1 bar, 80 mL/min) at 22 °C with 1 mol % 98% pure $Ni(OAc)_2$ and 0.25 mol % of Cr co-catalyst. [b] Amount of PhCH(O) ($x + y$) means flask charged with x mmol at the start and y mmol added subsequently during the dosing time. [c] By HPLC. [d] $Cr(NO_3)_3 \cdot 9H_2O$.

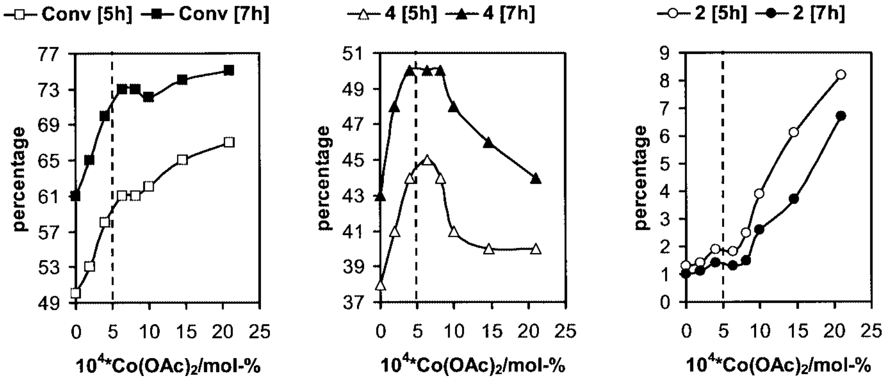


Figure 4. Dependence of conversion, yield of **4**, and estimated yield of **2** after 5 h and 7 h on the cobalt concentration for the Co/Ni/Cr/NHPI-catalyzed co-oxidation of **1** (10 mmol, AcOH, 22 °C, 1 bar O_2) and PhCH(O) (1.35 equiv.) in the presence of 1 mol % of $Ni(OAc)_2$, 0.25 mol % of $Cr(acac)_3$, and 40 mol % of NHPI; 0.28 equivalents of PhCH(O) added in one portion, remainder added over 5 h. For these experiments, 100% pure $Ni(OAc)_2$ (<5 ppm Co) was used. The vertical dotted line refers to the standard amount of Co added in other experiments through addition of 1 mol % of 98% pure $Ni(OAc)_2$ containing 116 ppm of Co.

both conversion and yield are almost insensitive to the amount of Ni, and only below about 0.1 mol % Ni do the conversion and yield decrease sharply (Figure 5). Accordingly, addition of 0.0004 mol % Co allows the amount of Ni [in the form of 100% pure $Ni(OAc)_2$] to be reduced by a factor of ten compared to the amount of 1 mol % commonly used in the experiments based on 98% pure $Ni(OAc)_2$ without deliberate addition of Co.

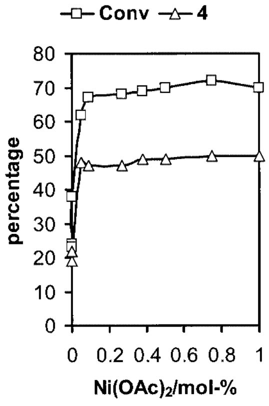


Figure 5. Dependence of the conversion of **1** and yield of **4** after 7 h in the Co/Ni/Cr/NHPI-catalyzed co-oxidation of **1** (10 mmol, AcOH, 22 °C, 1 bar O_2) with PhCH(O) (1.35 equiv.) on the amount of Ni in the presence of 0.0004 mol % Co, 0.25 mol % $Cr(NO_3)_3$, and 40 mol % NHPI; 0.29 equiv; PhCH(O) added in one portion, remainder added during 5 h; for these experiments, 100% pure $Ni(OAc)_2$ (<5 ppm Co) was used

Oxidation of Other Substrates

Besides **1**, several other substrates have been subjected to co-oxidation with PhCH(O) catalyzed by the four component Co/Ni/Cr/NHPI catalyst system. In addition, their oxidation under Ishii conditions (Co/NHPI catalyst system) has been carried out (Table 3). At room temperature after 7 h, the co-oxidation method affords higher yields (>60%) than the Ishii system[18] in the case of ethylbenzene (**7**; entry 1), indane (**9**; entry 2), diphenylmethane (**14**; entry 4), bis(4-fluorophenyl)methane (**16**; entry 5), and 3-phenyl-1-propanol (**31**; entry 12). As expected, the corresponding benzylic oxidation products are formed in all cases, except for the latter substrate, for which oxidation of the alcohol rather than the benzylic function dominated.[19] The co-oxidation afforded only modest yields (20−45%) — although still much higher than the Ishii system — in the room temperature oxidation of bibenzyl (**20**; entry 7), 4-*tert*-butyltoluene (**23**; entry 8), 4-methoxytoluene (**25**; entry 9), 2-octanol (**27**; entry 10), and 2-phenylethanol (**29**; entry 11). Efficient oxidation of **23** and **25** to **24** and **26**, respectively,

Table 3. Oxidation of various substrates by Co/NHPI catalysis and by Co/Ni/Cr/NHPI catalysis in the presence of PhCH(O)

Entry	Substrate	Product(s)	Co/NHPI-catalyzed oxidn[a,b]			Co/Ni/Cr/NHPI-catalyzed co-oxidn with PhCH(O)[a,c]		
			Temp °C	Conv %[d]	Yield %[d]	Temp °C	Conv %[d]	Yield %[d]
1	Ethylbenzene (**7**)	Acetophenone (**8**)[e]	22	9	1	22[f]	81	68
2	Indane (**9**)	1-Indanone (**10**)[e]	22	68	22	22[f]	99	75
3	5-Methoxyindane (**11**)	5-Methoxy-1-indanone (**12**)[e]	22	94	30	22[f]	77	14
		6-Methoxy-1-indanone (**13**)[e]			8			5
4	Diphenylmethane (**14**)	Benzophenone (**15**)[e]	22	6	6	22[f]	74	72
5	Bis(4-fluorophenyl)methane (**16**)	4,4′-Difluorobenzophenone (**17**)[g]	22	0	0	22[f]	81	77
			60[h]	59	38	30[f]	96	89
6	Xanthene (**18**)	Xanthone (**19**)[e]	22	99	49	22[f]	30	11
7	Dibenzyl (**20**)	Deoxybenzoin (**21**)[e]	22	1	0	22[f]	79	44
		Benzil (**22**)[e]			1			6
8	4-*tert*-Butyltoluene (**23**)	4-*tert*-Butylbenzoic acid (**24**)[g]	22	0	0	22[i]	55	32
			60[h]	94	82	30[f]	78	57
9	4-Methoxytoluene (**25**)	4-Methoxybenzoic acid (**26**)[g]	22	0	0	22[i]	61	20
			60[h]	92	73			
10	2-Octanol (**27**)	2-Octanone (**28**)[e]	22	5	5	22[i]	52	45
11	2-Phenylethanol (**29**)	Phenylacetic acid (**30**)[g]	22	38	9	22[i]	75	33
			60[h]	56	8			
12	3-Phenyl-1-propanol (**31**)	3-Phenylpropanoic acid (**32**)[e]	22	3	1	22[i]	97	68

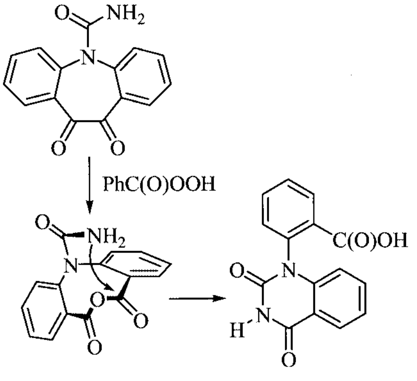
[a] 10 mmol substrate and 5 mmol 1,2,4-trichlorobenzene (internal standard) in 30 mL AcOH under O_2 (1 bar, 80 mL/min). [b] 0.5 mol % $Co(OAc)_2$ and 10 mol % NHPI. [c] 0.0006 mol % $Co(OAc)_2$, 0.1 mol % 100% pure $Ni(OAc)_2$, 0.25 mol % $Cr(acac)_3$, and 40 mol % NHPI. [d] After 7 h; determined by GC or HPLC. [e] GC analysis. [f] 3 mmol PhCH(O) added in one portion, 11 mmol PhCH(O) added subsequently over 5 h. [g] HPLC analysis. [h] 1 mmol substrate and 0.5 mmol 1,2,4-trichlorobenzene (internal standard) in 3 mL AcOH under O_2 (1 bar, balloon). [i] 14 mmol PhCH(O) added in one portion.

can be achieved with the Ishii method, however, by simply increasing the temperature from 22 °C to 60 °C (entries 8; 9).[20] Because the co-oxidation method requires a considerably more complex workup procedure in order to separate the $PhCO_2H$ by-product from the target substituted benzoic acid products, the Ishii method is preferred for the oxidation of substituted toluenes. At room temperature, the Ishii method is also superior in the case of easily oxidized substrates such as 5-methoxyindane (**11**; entry 3) and xanthene (**18**; entry 6). For **16** (entry 5), a slight increase in temperature to 30 °C resulted in very good yields with the co-oxidation method, whereas the Ishii method still gives a modest yield at 60 °C. It can be concluded that the (near) room temperature co-oxidation method is useful for the oxidation of unreactive substrates when this conversion does not tolerate elevated temperatures because of a decrease in selectivity.

Discussion

By-Product Formation

The reaction probably follows a free-radical chain mechanism in which the oxidation is initiated by benzylic C−H abstraction from **1** by chain-propagating radicals. Strong evidence for this is the presence of sometimes substantial amounts of benzylic hydroperoxide **2** in the reaction mixture.[21] The concomitant formation of **3** and **4** is also characteristic of such a free-radical chain oxidation, and dione **5** is an expected secondary oxidation product of **4**. The high levels of **5** observed in oxidations with Mn-containing catalyst systems are in accordance with the well-known efficiency of Mn to catalyze oxidation of methylene groups adjacent to carbonyl groups.[22] The tentative formation of **6** can be rationalized by a Baeyer−Villiger oxidation of **5** with perbenzoic acid, which is formed from PhCH(O) and O_2. The resulting anhydride subsequently undergoes an intramolecular aminolysis by the pendant amide group. This intramolecular aminolysis is expected to occur very easily because of the non-planar nature of the eight-membered ring, which brings the pendant amide group into a position close to the anhydride unit [Equation (1)].



(1)

Optimum Catalyst System Composition and Mode of Operation

Under optimum conditions, **1** is oxidized in acetic acid in the presence of PhCH(O) and a four-component catalyst system comprising NHPI, Ni, Cr, and Co in amounts of

40, 0.1−1.0 (not critical, Figure 5), 0.25, and 0.0007 mol %, respectively. The undoubtedly very complex reaction network involved in the oxidation precludes a detailed discussion of the mechanism without further in-depth studies. Nevertheless, some conclusions concerning the mechanism can be drawn on the basis of experimental observations and literature information.

Role of PhCH(O): (Gradual) addition of PhCH(O) as a co-substrate during oxidation of **1** allows the reaction to proceed up to high conversion at room temperature. This is expected because of the much higher oxidizability of PhCH(O) ($k_p/[2k_t]^{0.5} \times 10^3 = 290$ $\text{M}^{-0.5}\text{s}^{-0.5}$)[23] relative to an alkylaromatic like ethylbenzene ($k_p/[2k_t]^{0.5} \times 10^3 = 0.21$ $\text{M}^{-0.5}\text{s}^{-0.5}$),[23] for which the oxidizability is probably rather close to that of **1**.[24,25]

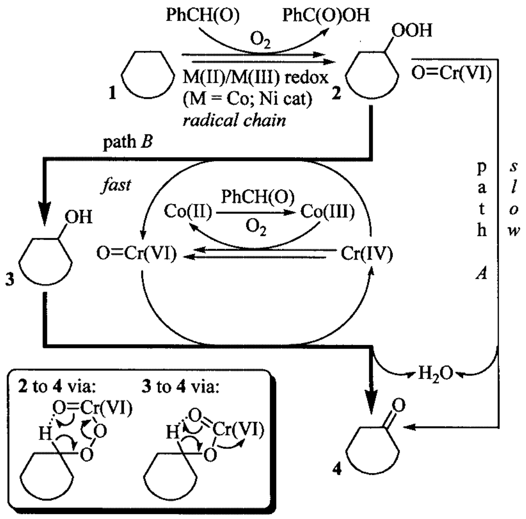
Role of NHPI: From the work of Ishii,[6,7,11] it can be concluded that the NHPI-derived *N*-oxyl radical PINO, which is formed during homolytic oxidation processes, is involved in C−H abstraction steps. The optimal amount of NHPI in the Co/Ni/Cr/NHPI-catalyzed co-oxidation (40 mol %) is higher than the amount commonly applied by Ishii in Co/NHPI-catalyzed oxidations (10 mol %), but within the same order of magnitude.[26]

Role of Ni and Co: An intriguing feature of the current co-oxidation process is that both Co and Ni have to be present for optimum results and that the amount of Ni under optimum conditions (0.1−1.0 mol %) exceeds that of Co (approx. 0.0007 mol %) by a factor of 140−1400. Whereas the very low amount of Co that is required to eliminate the induction period underlines the role of Co as a highly efficient radical-chain initiator,[27,28] the necessity of having substantial amounts of Ni in the catalyst system for optimum results is less easy to understand. Co and Ni are both known to be catalysts for PhCH(O) oxidation with O_2, but they differ in that Co is mainly present in the form of Co^{III} whereas for Ni the lower, divalent oxidation state prevails because oxidation of Ni^{II} to Ni^{III} by intermediate perbenzoic acid is slow compared to the rapid reduction of Ni^{III} by PhCH(O).[29] The large amount of **2** in co-oxidations by a Cr-free catalyst system comprising only (Co-containing) Ni as the metallic catalyst (Table 1, entries 7−9) is in accordance with the slow decomposition of perbenzoic acid by Ni^{II} since the latter is expected to react even slower with alkyl hydroperoxides, which are much weaker oxidants than peracids. Thus, the role of Ni in the radical chain co-oxidation process is to drive the reaction to high conversion by generating chain propagating benzoyloxy and benzoylperoxy radicals via a $\text{Ni}^{\text{II}}/\text{Ni}^{\text{III}}$ redox cycle that involves decomposition of perbenzoic acid by Ni^{II} and oxidation of PhCH(O) by Ni^{III} while leaving **2** intact, the latter being efficiently transformed into **4** by the Cr-catalyst (see below). It is the slow rate of (unselective) radical decomposition of alkyl hydroperoxides under the influence of Ni that makes Ni distinct from Co, which, because of its efficiency in radical decomposition of hydroperoxides, can only be applied in very small amounts in order to avoid loss in selectivity as a result of build up of high levels of **3** formed alongside **4** in the Co-catalyzed radical decomposition of **2** (see Table 1, entry 6). Because of its inefficiency in generating radicals from peroxides, efficient chain initiation by Ni requires relatively high amounts, and an effective elimination of the induction period is only achieved in the presence of trace amounts of Co. Without Ni, radical chain initiation at this very low Co level is too slow (Figure 5).

Role of Cr: Addition of Cr results in a strong decrease in the concentration of **2** and **3** and a concomitant increase of conversion and yield of **4**. This ketone-enhancing effect of Cr during radical-chain oxidations with O_2 is well-known and is ascribed to the ability of Cr to catalyze the dehydration of alkyl hydroperoxides, thus directing the hydroperoxide decomposition towards the carbonyl compound rather than to the alcohol. This dehydration is commonly believed to proceed according to a heterolytic mechanism via a catalytically active Cr^{VI} species.[22,30,31] These Cr^{VI} species also stimulate carbonyl formation via alcohol oxidation with concomitant formation of Cr^{IV}, which is reoxidized to Cr^{VI} during the co-oxidation process.[22,32−34] The non-radical-chain nature of these two reactions involving Cr implies that fairly high Cr concentrations (about 0.25 mol %) have to be used. Additional aspects concerning the transformation of **2** to **4** are discussed below.

Mechanism of Hydroperoxide Transformation

Whereas the conversion increases progressively with the Co content, the yield of **4** reaches a maximum value at about 0.0005 mol % Co. Surprisingly, despite the high peroxide decomposition activity of Co, the level of **2** also increases with the Co content when the latter exceeds the value required for obtaining a maximum yield of **4**. The decrease in yield of **4** after passing the maximum value is approximately equal to the increase in the level of **2** (Figure 4). This indicates that the loss in yield above the optimum Co concentration is a result of a less-efficient transformation of **2** into **4**. We propose that Co interferes in the catalytic cycle of hydroperoxide **2** decomposition mediated by Cr by modifying the $\text{Cr}^{\text{IV}}/\text{Cr}^{\text{VI}}$ species ratio (Scheme 1). The transformation of **2** into **4** proceeds either by dehydration under the influence of a Cr^{VI} catalyst (path *A*),[22,30,31] or by oxidation of Cr^{IV} to Cr^{VI} by **2**[35] and consecutive fast oxidation of the resulting alcohol **3** by Cr^{VI} to **4** (path *B*).[22] Because of the intrinsic instability of the Cr^{IV} oxidation state, we propose that oxidation of Cr^{IV} to Cr^{VI} by **2** (path *B*) is very fast compared to the Cr^{VI}-mediated dehydration of **2** (path *A*). Any interference in the Cr-mediated catalytic cycle of the transformation of **2** into **4** that causes a lowering of the concentration of Cr^{IV} results in a reduced rate of decomposition of **2** because the fast path *B* is replaced by the slower path *A*, and, consequently, higher levels of **2** are expected in the reaction mixture. The build-up of **2** above a certain Co concentration is thought to be caused by an enhanced oxidation of Cr^{IV} to less active Cr^{VI} through a twofold oxidation by Co^{III},[36,37] which is continuously regenerated from Co^{II} via a virtually instantaneous oxidation by the intermediate perbenzoic acid [formed from PhCH(O) and O_2].[29,38−41]



Scheme 1. Proposed mechanism of chromium-catalyzed hydroperoxide **2** decomposition that explains the observed retardation of conversion of **2** into **4** upon increasing cobalt concentration; path *A*: slow non-redox dehydration by Cr^{VI}; path *B*: fast oxidation of Cr^{IV} to Cr^{VI} by peroxide **2**, followed by Cr^{VI}-mediated oxidation of alcohol **3**; path *B* is slowed down when the Cr^{IV} concentration decreases as a result of oxidation of Cr^{IV} to Cr^{VI} by Co^{III}, which is continuously regenerated from Co^{II} during the PhCH(O) co-oxidation process

Conclusion

Benzylic oxidations can be carried out at low temperature and up to high conversions by Co/Ni/Cr/NHPI-catalyzed co-oxidation with PhCH(O). When the substrate contains both benzylic C−H bonds as well as an alcohol functionality, oxidation of the latter may prevail over benzylic oxyfunctionalization. From a summary of literature data and experimental observations, the following description of the roles of each of the components in the oxidation system is proposed: PhCH(O) drives the oxidation to high conversion at room temp.; NHPI provides a catalytic pathway for C−H abstraction through introduction of a highly efficient *N*-oxyl radical chain carrier in the propagation step; Ni catalyzes radical chain PhCH(O) oxidation without decomposing the intermediate substrate-derived alkyl hydroperoxides; Cr catalyzes conversion of the intermediate alkyl hydroperoxides to afford carbonyl compounds; Co serves as a chain initiator that eliminates the induction period.

Experimental Section

General Remarks: Substrates **7**, **9**, **11**, **14**, **16**, **18**, **20**, **23**, **25**, **27**, **29**, and **31** as well as products **8**, **10**, **12**, **13**, **15**, **17**, **19**, **21**, **22**, **24**, **26**, **28**, **30** and **32** are commercially available from Aldrich. Substrate **1** is available from DSM Fine Chemicals Austria GmbH. Product **4** was provided by Novartis Pharma AG. $Ni(OAc)_2 \cdot 4H_2O$ (98% pure) was purchased from Aldrich. $Ni(OAc)_2 \cdot 4H_2O$ (100% pure) was purchased from Baker. $Cr(NO_3)_3 \cdot 9H_2O$ (99% pure) was purchased from Baker. $Cr(acac)_3$ (97% pure) was purchased from Acros. All products were identified by comparison with commercial samples. Positive-ion electrospray spectra were obtained at a fragmentor voltage of 50 V and a capillary voltage of 5 kV. Negative-ion electrospray MS were obtained at a fragmentor voltage of −50 V and a capillary voltage of −3 kV. HPLC analyses concerning the oxidation of **1** were performed using a 120-5-C_{18} column (250 mm × 4 mm, eluent: water/MeCN 75:25 v/v). HPLC analyses concerning the oxidation of **16**, **23**, **25**, and **29** were performed using an Inertsil ODS-3 column (150 mm × 4.6 mm, eluent A: 50 mmol/L H_3PO_4; eluent B: 50 mmol/L H_3PO_4/MeCN 25:75 v/v). GC analyses concerning the oxidation of **7**, **9**, **11**, **14**, **18**, **20**, and **27** were performed using a CP sil 5 CB capillary column (25 m × 0.32 mm). GC analyses concerning the oxidation of **31** were performed using a wcot fused-silica FFAB CB capillary column (25 m × 0.32 mm). ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively.

Oxcarbazepine (4) from the Co-Oxidation of 10,11-Dihydrocarbamazepine (1) and PhCH(O): A jacketed cylindrical reaction vessel was charged with $Cr(NO_3)_3 \cdot 9H_2O$ (0.0100 g, 0.025 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.0249 g, 0.100 mmol; purity 98%: contains about 116 ppm Co), 10,11-dihydrocarbamazepine (**1**; 2.38 g, 10.0 mmol), glacial AcOH (30.0 mL), and PhCH(O) (0.32 g, 3.0 mmol). Pure O_2 (80 mL/min) was blown via a frit through the magnetically stirred solution at 22 °C whilst adding PhCH(O) (1.07 g, 10.1 mmol)[42] gradually over the course of 5 h. The supply of O_2 was continued for another 2 h, after which HPLC analysis indicated a 53% yield of **4** and 72% conversion of **1**. Residual peroxides were reduced by addition of 0.17 g of $Na_2S_2O_5$ to the reaction mixture. After concentration under reduced pressure to a viscous mass (8.0 g), EtOH (1.7 mL) was added and the resulting mixture was added slowly to a 4 M aqueous solution of KOH (35 mL), in which **4** is soluble in the form of the potassium enolate. Insoluble residues were separated by filtration, and the filtrate was washed once with THF (17.5 mL). The pH of the aqueous solution was adjusted from 14 to 9 by addition of concentrated H_2SO_4 (5.0 mL). Precipitated **4** was isolated by filtration, washed with water (three times), and dried under reduced pressure. Yield: 0.94 g; purity by HPLC: 90%. The raw material was further purified by dissolution in HCO_2H (5 mL), treatment with active carbon, and precipitation by slow addition of water (1.5 mL) after removal of the active carbon by filtration. The precipitate was dried to constant weight under reduced pressure. Yield: 0.66 g (26%); purity by HPLC: 95%. M.p. 222−226 °C (M.p. commercial sample: 224.3 °C). ES-MS (positive ion mode): $[M + H]^+$ $m/z = 253$. ^1H and ^{13}C NMR spectroscopic data are in accordance with those of the commercial sample, but indicate the presence of some residual HCO_2H. ^1H NMR (CD_3CO_2D): $\delta = 3.91$ (d, $J = 14.8$ Hz, 1 H), 4.52 (d, $J = 14.8$ Hz, 1 H), 7.7−7.3 (m, 7 H), 8.08 (dd, $J = 1.7, 8.1$ Hz, 1 H) ppm. ^{13}C NMR (CD_3CO_2D): $\delta = 49.4$, 128.8, 129.0, 129.8, 130.2, 130.5, 131.1, 131.2, 131.6, 135.1, 135.3, 142.0, 144.0, 159.6, 194.2 ppm.

Oxidations of the other substrates on a 10 mmol scale were carried out similarly. Oxidations on a 1 mmol scale were carried out in round -bottomed flasks equipped with a balloon filled with O_2.

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[27] Ref.[25], p. 40.

[28] As suggested by Ishii (see ref. 11 for a review), formation of the PINO *N*-oxyl radical from NHPI occurs via H-abstraction by a labile cobalt-dioxygen complex formed in situ from Co^{II} and O_2. This could well be the mechanism behind initiation by cobalt, although Co concentrations under Ishii conditions are much larger than under our co-oxidation conditions.

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[36] In *aqueous* solution, generation of Cr^{VI} from Cr^{III} via a Cr^{IV} intermediate by oxidation with Co^{III} is slow (ref. 37 and references therein). However, efficient oxidation of Cr^{IV} by Co^{III} may occur in *acetic acid* solution, since in this solvent $Co(OAc)_2$ is oxidized instantaneously by peracids to afford a highly redox-active μ-oxo-bridged dinuclear species (refs.[38−40]). Through this dinuclear μ-oxo Co^{III} species, the $Cr^{IV} \rightarrow Cr^{VI}$ oxidation via two consecutive one-electron transfers including the difficult $Cr^{IV} \rightarrow Cr^{V}$ [$E° = 1.3V$] oxidation may be replaced by a more favourable direct $Cr^{IV} \rightarrow Cr^{VI}$ two-electron [$E° = 0.9V$] oxidation, see: I. Dellien, F. M. Hall, L. G. Hepler, *Chem. Rev.* **1976**, *76*, 283−310.

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