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Mechanism of Ni-Catalyzed Oxidations of Unactivated C(sp³)–H Bonds

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ABSTRACT: The Ni-catalyzed oxidation of unactivated alkanes, including the oxidation of polyethylenes, by *meta*-chloroperbenzoic acid (*m*CPBA) occur with high turnover numbers under mild conditions, but the mechanism of such transformations has been a subject of debate. Putative, high-valent nickel-oxo or nickel-oxyl intermediates have been proposed to cleave the C-H bond, but several studies on such complexes have not provided strong evidence to support such reactivity toward unactivated $C(sp^3)$ -H bonds. We report mechanistic investigations of Ni-catalyzed oxidations of unactivated C-H bonds by *m*CPBA. The lack of an effect of ligands, the formation of carbon-centered radicals with long lifetimes, and the decomposition of *m*CPBA in the presence of Ni complexes suggest that the reaction occurs



Article

through free alkyl radicals. Selectivity on model substrates and deuterium-labeling experiments imply that the *m*-chlorobenzoyloxy radical derived from *m*CPBA cleaves C–H bonds in the alkane to form an alkyl radical, which subsequently reacts with *m*CPBA to afford the alcohol product and regenerate the aroyloxy radical. This free-radical chain mechanism shows that Ni does not cleave the $C(sp^3)$ –H bonds as previously proposed; rather, it catalyzes the decomposition of *m*CPBA to form the aroyloxy radical.

INTRODUCTION

Oxidation of aliphatic C-H bonds is an important chemical transformation that is widely practiced in nature and in synthetic chemistry. In most living organisms, cytochrome P450 enzymes catalyze the hydroxylation of saturated C-H bonds,¹ and, in methanotrophic bacteria, methane monooxygenases (MMOs) catalyze the hydroxylation of methane to produce methanol.² In synthetic chemistry, the oxidation of feedstock alkanes is a promising way to make valuable products, such as alcohols and ketones, from inexpensive starting materials. However, a highyielding, selective oxidation of unactivated aliphatic C-H bonds is challenging because the large bond dissociation energies (BDEs) near 100 kcal/mol^{3,4} and high highest occupied molecular orbital (HOMO)-lowest unoccupied molecular orbital (LUMO) gaps make them inert to many chemical reactions and because the ubiquity of $C(sp^3)$ -H bonds in organic molecules makes it necessary to distinguish between similar, but inequivalent sites. In addition, oxidized products, such as alcohols and alkyl halides, are generally more reactive than the starting unfunctionalized alkanes, so overoxidation may occur, leading to undesired byproducts.³

Despite these challenges, many methods have been developed in the past century for the oxidation of aliphatic C–H bonds. Several organic reagents, such as ozone,⁶ dioxiranes,^{7,8} and aromatic peracids,^{9,10} were found to oxidize saturated hydrocarbons with high selectivity for tertiary C–H bonds. The oxidation of aliphatic C–H bonds catalyzed by transition-metal complexes also has been developed extensively. As early as the 1890s, Fenton reported the iron(II)-catalyzed oxidation of tartaric acid by hydrogen peroxide.¹¹ Later, the Gif-Barton system,¹² which utilizes iron catalysts and tBuOOH or H_2O_2 as oxidants, the Pt(II) catalytic system by Shilov and Periana,^{3,13,14} and the Ru porphyrin system by Groves and others^{15–17} were developed to achieve the oxidation of alkanes with high turnover numbers (TONs). More recently, white reported a selective oxidation of aliphatic C–H bonds in complex molecules with H_2O_2 and iron catalysts containing nitrogen-based ligands.^{18,19}

Compared to these methods that involve group 8 transitionmetal catalysts, Ni-catalyzed oxidations of alkanes are less explored but have been reported to occur with high TONs. Itoh and others have reported the hydroxylation of cyclohexane and adamantane with *m*CPBA and nickel catalysts containing tetradentate, nitrogen-based ligands, such as tris(2pyridylmethyl)amine (TPA).^{20–22} Our group achieved selective hydroxylation of polyethylenes with *m*CPBA and Ni catalysts containing phenanthroline-based (Phen-based) ligands.²³ This oxidation occurred with loadings of nickel as low as 0.1 mol %, required mild conditions (50 °C under air), and afforded the



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mono-oxidized product (alcohol rather than ketone or ester) with hundreds of TONs (Figure 1A).



Figure 1. (A) Ni-Catalyzed hydroxylation of cyclohexane, adamantane, and polyethylenes by *m*CPBA. (B) Previously proposed pathway for Ni-catalyzed oxidation of aliphatic C–H bonds. (C) This work: free-radical chain mechanism of Ni-catalyzed oxidation of $C(sp^3)$ –H bonds by *m*CPBA.

The Ni-catalyzed oxidation of saturated hydrocarbons by *m*CPBA has been proposed to occur by forming a transient Nioxyl or Ni-oxo intermediate²⁴ (hereafter called a Ni-oxygen species) that cleaves the C–H bond (Figure 1B).^{20,25,26} Hikichi reported the isolation and characterization of a Ni complex of *m*CPBA containing a trispyrazolylborate-based (Tp-based) ligand.²⁷ Several other Ni-oxygen species containing macrocyclic, nitrogen-based ligands also have been characterized spectroscopically.^{26,28–34} These nickel intermediates oxidize activated C-H bonds (BDE < 90 kcal/mol) in substrates such as 9,10-dihydroanthracene (DHA) and xanthene, 27,28,33 but the reactivity of such intermediates with unactivated C-H bonds (BDE \approx 100 kcal/mol) has not been convincingly established.³⁵ This trend in reactivity is inconsistent with the results of the catalytic reactions, in which the strong C-H bonds in cyclohexane and polyethylenes undergo hydroxylation under mild conditions. Studies that address this issue of the reactivity of Ni-oxo or Ni-oxyl complexes with C-H bonds and mechanisms of Ni-catalyzed oxidation reactions are crucial to understanding the role of Ni in the catalytic system and to improving the efficiency and selectivity of these reactions further.

In this work, we report mechanistic investigations of the Nicatalyzed oxidation of unactivated aliphatic C–H bonds. We provide evidence that, contrary to the previously proposed reaction pathways, Ni complexes are not involved in the cleavage of C–H bonds; rather, they catalyze the decomposition of *m*CPBA to generate an aroyloxy radical that cleaves the C–H bond via hydrogen atom abstraction (HAA). The resulting alkyl radical then reacts with *m*CPBA to form the hydroxylated product and regenerates the aroyloxy radical. Thus, the catalytic reaction proceeds via a free-radical chain mechanism (Figure 1C) in which the rate of initiation is determined by the concentration and identity of the nickel complex, but the nickel complex does not control the regioselectivity of the oxidations.

RESULTS AND DISCUSSIONS

1. Effect of Ligands on Selectivity. To understand the role of Ni complexes in the catalytic reaction, we studied the effect of varying the ligands on the selectivity of oxidation. If a transient

Ni-oxygen intermediate cleaved the C–H bonds in hydrocarbons, the identity of the ancillary ligands that possess varied electronic and steric properties should affect the selectivity of the catalytic reaction. Therefore, Ni complexes (1a-1h, Figure 2)that contain a series of nitrogen-based, bidentate or tetradentate ligands (L1-L8) were synthesized and used for the catalytic oxidation of cyclohexane (2) and adamantane (3).

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Figure 2. Structures of ligands L1–L8 and Ni catalysts 1a–1h.

The results of the oxidation of cyclohexane (2) catalyzed by this series of nickel complexes are shown in Table 1A. Cyclohexanol (4a) was formed as the major product together with small amounts of cyclohexanone (4b), ε -caprolactone (4c), and chlorocyclohexane (4d). The formation of 4c can be attributed to the uncatalyzed Baeyer–Villiger oxidation of 4b. The ratio of alcohol to ketone and lactone, that is, A/(K + E), defined as the ratio of the yield of 4a to the combined yields of 4b and 4c, reflects the selectivity for mono-oxidation.

Our data show that the identity of the ligand affects the rate of the oxidation process. Reactions in the presence of complexes 1a-1e, which contain sterically unhindered ligands L1-L5, reached full conversion of *m*CPBA within 1-1.5 h (Table 1A, entries 1-5), whereas those in the presence of 1f and 1g, which contain sterically encumbered ligands L6 and L7, required 2 and 3 h to reach greater than 90% conversion, respectively (Table 1A, entries 6 and 7). The conversion of the reaction with complex 1h, which contains the most sterically hindered ligand L8, in which two methyl groups flank the phenanthroline moiety, was low even after 4 h of heating (Table 1A, entry 8). Time courses further confirmed that the rates of the reactions in the presence of complex 1a were significantly higher than those in the presence of Ni complexes containing sterically hindered ligands, such as 1h (see the Supporting Information).

However, the data in Table 1 also show the lack of a pronounced effect of the ligand on the yield of oxidized products or on the A/(K + E) ratio. All reactions in the presence of complexes **1a–1g** gave product **4a** in 31%–39% yield and products **4b**, **4c** in 10%–11% combined yield; the A/(K + E) ratios of these reactions range from 3.1 to 3.5, which is well within experimental error. The oxidation of cyclohexane in the

Table 1. Results of the Oxidation of (A) Cyclohexane and (B) Adamantane in the Presence of Different Catalysts

(A)

``	, 	. 01	mCPBA	OH	0 II	0	CI
) <u> </u>	CM:MeCN (3:	31)	+	+	
	2		50 °C	4a	4b	4c	4d
entry	cata- lyst	time $(h)^a$	4a (%)	4b (%)	4c (%)	4d (%)	A/(K+E)
1	1a	1	33.8±6.0	10.9±0.3	0.0±0.0	12.8±3.2	3.1±0.6
2	1b	1	38.1±2.5	$10.3{\pm}1.0$	1.1 ± 1.0	11.4±2.9	3.3±0.6
3	1c	1	39.1±2.1	10.4 ± 0.6	1.0 ± 1.0	12.4±3.0	3.4±0.5
4	1d	1.5	31.1±1.7	6.3±0.5	3.3±0.2	8.3±0.8	3.2±0.3
5	1e	1.5	32.9±2.3	8.3±1.4	2.1±1.3	13.0±3.8	3.2±0.9
6	1f	2	34.6±1.9	5.2 ± 0.7	4.8 ± 0.7	9.5±1.5	3.5 ± 0.5
7	1g	3	33.7±2.1	4.7±1.4	5.4±0.8	10.6 ± 0.5	3.3±0.7
8	1h	4^b	$10.0{\pm}2.3$	2.3 ± 0.4	5.1±0.3	5.8±1.1	_c
9	$NiCl_2$	4	30.7±1.0	8.3±1.6	4.4±1.8	9.7±0.8	2.4±0.6
10	$CoCl_2$	1.5	24.7±5.1	$10.7{\pm}0.4$	0.0 ± 0.0	9.1±1.0	2.3 ± 0.5
11	none	4^b	1.3±2.2	0.9±1.5	0.6±1.1	$0.0{\pm}0.0$	
(B)	,	<i>n</i> CPBA	он ⊥	_	ОН _ //	o L	,CI
Æ	0.1 m	ol % cat	alyst	+ 17	+	+ 10+	·P
3	/	50 °C	5a	5b	5c	5d	5e
entry	cata- lyst	time (h) ^a	5a (%)	5b+5c (%)	5d (%)	5e (%)	3°/2°
1	1 a	1	36.7±6.4	3.1±0.7	2.7±0.4	3.9±3.6	5.6±3.1
2	1b	1	30.6±3.8	2.6±0.2	2.8±0.5	2.7±2.3	6.3±2.8
3	1c	1	30.6±5.7	2.4±0.3	2.4±0.2	2.4±2.1	6.9±3.3
4	1d	1.5	24.9±2.1	2.5±0.7	4.0±0.7	4.0±0.6	4.4±0.7
5	1e	1.5	30.0±1.2	2.5±0.1	4.8±0.1	4.9±0.6	4.7±0.4
6	1f	2	38.5±6.0	3.0±0.3	3.5±0.9	4.1±0.4	5.9±0.9
7	1g	3	29.0±1.2	2.6±0.5	5.2±0.6	5.0±0.7	4.5±0.5
8	1h	4^b	20.7±2.1	1.4±0.2	4.0±0.4	2.6±0.3	6.2±0.8
9	NiCl ₂	4	28.2±1.8	2.4±0.1	4.4±0.3	3.5±0.1	5.5±0.3
10	CoCl ₂	1.5	27.9±0.7	2.8±0.1	2.0±0.5	2.1±1.8	6.1±2.3
11	none	4^b	8.8±5.0	0.6±1.1	0.4±0.7	0.2±0.3	_c
12	$1\mathbf{a}^{d}$	1	6.5	5.0	53.8	13.4	

Conditions: 0.125 mmol *m*CPBA, 7.5 equiv of **2** or 2 equiv of **3**, 0.1 mol % catalyst, DCM/MeCN (3:1, 0.125 M), 50 °C under air. All yields were based on *m*CPBA and reported as the arithmetic mean of three repeated experiments. ^{*a*}Time required to reach greater than 90% conversion of *m*CPBA unless noted otherwise. ^{*b*}Low conversion of *m*CPBA even after 4 h of reaction. ^{*c*}Conversion too low to determine. ^{*d*}In the presence of CCl₄ (1 equiv).

presence of ligandless NiCl₂ (Table 1A, entry 9) formed product 4a in 31% yield and products 4b and 4c in 13% combined yield, corresponding to an A/(K + E) ratio of 2.4 ± 0.6. This ratio is comparable to those of reactions catalyzed by ligated Ni complexes 1a–1g. Similar results were observed for the oxidation of 2 catalyzed by CoCl₂, although the cobalt-catalyzed reaction was faster than the nickel-catalyzed one and reached full conversion within 1.5 h (Table 1A, entry 10). The negligible effect of ligands on both product distribution and selectivity for mono-oxidation, along with the similar yield of products and selectivity of the catalytic reactions conducted without ligands, is inconsistent with the previously proposed pathway in which a Ni-oxygen species cleaves the C–H bond.

Although the chemoselectivity for the formation of alcohol, ketone, and lactone products 4a-4c provided preliminary evidence that a ligated nickel complex is not involved in the cleavage of C-H bonds, the ketone and ester are likely to be secondary products. Therefore, the distribution of these products could be envisioned to depend on several factors besides the identity of the species that cleaves the C-H bond. A more rigorous test would involve the measurement of the initial products. In addition, measuring the selectivity for tertiary versus secondary (or primary) C-H bonds in a model alkane is important to identify the species that cleaves the C-H bond and to understand the mechanism of Ni-catalyzed oxidations of hydrocarbons. Thus, we also measured the regioselectivity for the oxidation of adamantane.

The results of the oxidations of adamantane (3) catalyzed by a series of nickel complexes are shown in Table 1B. 1-Adamantanol (5a) was the major product; 2-adamantanol (5b), 2-adamantanone (5c), and 1- and 2-chloroadamantane (5d and 5e) were the minor products. Like the reactions of cyclohexane, the rates of the reactions of adamantane depended on the ligand bound to nickel. Reactions catalyzed by Ni complexes 1a-1e reached greater than 90% conversion of *m*CPBA within 1-1.5 h (Table 1B, entries 1-5), whereas those catalyzed by 1f and 1g, which contain sterically encumbered ligands L6 and L7, required 2 and 3 h to reach similar levels of conversion (Table 1B, entries 6 and 7). The reaction in the presence of complex 1h, which contains the most sterically hindered ligand L8, did not reach 90% conversion, even after 4 h of heating (Table 1B, entry 8).

Despite the different rates of reactions catalyzed by these complexes, all of the reactions catalyzed by complexes 1a-1g furnished product 5a in 24.9%-38.5% yield, the combination of products 5b and 5c in 2.4%-3.1% yield, product 5d in 2.4%-5.2% yield, and product **5e** in 2.4%–5.0% yield. The ratio of the combination of products from functionalization at the tertiary positions (5a and 5d) to the combination of those at the secondary position (5b, 5c, and 5e), which is denoted $3^{\circ}/2^{\circ}$, reflects the regioselectivity of this reaction. These $3^{\circ}/2^{\circ}$ ratios were between 4.4 and 6.9 and well within the experimental error of each other. In addition, the oxidation of adamantane catalyzed by ligandless NiCl₂ and CoCl₂ furnished the combination of products 5a and 5d in 32.6% and 29.9% yield and the combination of products 5b, 5c and 5e in 5.9% and 4.9% yield, corresponding to $3^{\circ}/2^{\circ}$ ratios of 5.5 and 6.1, respectively, which are indistinguishable from those of reactions catalyzed by the ligated Ni complexes 1a-1g. The lack of dependence of the product distribution and regioselectivity of the oxidation of adamantane on this series of Ni complexes containing different ligands and on ligandless metal chlorides, again, is inconsistent with the hypothesis that a Ni-oxygen species cleaves unactivated C–H bonds in alkanes.

2. Formation of Carbon-Centered Radicals with Long Lifetimes. Determining whether carbon-centered radicals are formed and, if so, estimating the lifetime of these radicals is crucial to understanding the mechanism of oxidations of C–H bonds. The formation of chlorinated products 5d and 5e in high yields in a Ni-catalyzed oxidation of adamantane with 1 equiv of CCl_4 (Table 1B, entry 12) strongly suggests the formation of

carbon-centered radicals and subsequent trapping by CCl₄. Substrates that react as radical clocks are often employed to study the lifetime of carbon-centered radicals and the rate of the formation of C–O bonds during the oxidation of C–H bonds.³⁶ For example, several radical clocks based on cyclopropanes were used to study the mechanism of the hydroxylation of saturated C–H bonds catalyzed by P450 enzymes.¹ In this work, we used the well-known *cis*- and *trans*-1,2-dimethylcyclohexane (*cis*- and *trans*-6) as radical clocks³⁷ to investigate the lifetime of carbon-centered radicals formed in the Ni-catalyzed oxidation reaction.

The Ni-catalyzed oxidation of *cis*-**6**, which occurred predominantly at the tertiary position, generated the tertiary alkyl radical 7, which is known to epimerize rapidly (first-order rate constant $k \approx 10^9 \text{ s}^{-1}$),³⁶ and afforded tertiary alcohols **8a** and **8b** as major products (Table 2A). The fraction of the *cis*

Table 2. Results of the Ni-Catalyzed Oxidation^a of (A) cis-6 and (B) trans-6



^{*a*}Conditions: 0.125 mmol of *m*CPBA, 7.5 equiv of *cis*- or *trans*-6, 0.1 mol % [Ni], DCM/MeCN (3:1, 0.125 M), 50 °C under air, 1–4 h. All yields were based on *m*CPBA and reported as the arithmetic mean of three repeated experiments.

product (ratio of the yield of **8a** to the combined yield of **8a** and **8b**) reflects the rate of the epimerization of 7 versus that of the formation of a C–O bond. If the formation of the C–O bond occurs much faster than the epimerization, then the *cis* product **8a** would be formed predominantly. When the step that forms the C–O bond occurs more slowly than the epimerization of 7, the products **8a** and **8b** have been observed in similar amounts, corresponding to a *cis*-fraction close to 50%.^{36,38} As shown in

Table 2A, the oxidation of *cis*-6 in the presence of a series of Ni complexes, including the ligandless $NiCl_2$, formed the tertiary alcohols with a *cis*-fraction ranging from 42.6% to 48.9%. These results indicate that the lifetime of the carbon-centered radical formed in these reactions is long enough that complete epimerization occurs before the formation of the C–O bond.

The *cis* fraction from the Ni-catalyzed oxidation of *trans-6*, summarized in Table 2B, ranged from 36.9% to 41.7%. The lower fraction of the *cis* product from reactions catalyzed by 1e-1g and NiCl₂, which are slower than the reactions catalyzed by 1a-1c (Table 2B, entries 4–7), is likely due to a competing background, uncatalyzed hydroxylation by *m*CPBA. Uncatalyzed oxidation of alkanes by *m*CPBA is known to occur with retention of configuration.⁹ These results are also consistent with the Ni-catalyzed reactions occuring through a long-lived alkyl radical before the step that forms the C–O bond.

3. Ni-Catalyzed Decomposition of *m*CPBA and a Callback to Fenton Chemistry. Our attempts to isolate Nioxygen intermediates or Ni-*m*CPBA adducts ligated by phenanthrolines have simply led to the decomposition of *m*CPBA. In the absence of alkanes, *m*CPBA was consumed completely to form *meta*-chlorobenzoic acid (*m*CBA) in 72% yield and chlorobenzene (9) in 15% yield in the presence of Ni complex 1a under standard conditions (Figure 3A). Chlor-



Figure 3. (A) Results of Ni-catalyzed decomposition of mCPBA in the absence of alkanes. (B) Formation of chlorobenzene in Ni-catalyzed oxidation of **2** by mCPBA.

obenzene, which was formed in ~51% yield in the catalytic oxidation of cyclohexane (Figure 3B), would arise from the decarboxylation of the *meta*-chlorobenzoyloxy radical (10). Moreover, our data show that the rate of decomposition of *m*CPBA is dependent on the identity of the ligand in the Ni catalyst. Time courses indicate that the rate of decomposition in the presence of complex 1a is significantly higher than that in the presence of complex 1h, which contains sterically hindered ligands (see the Supporting Information).

This Ni-catalyzed decomposition of an aromatic peracid that involves free-radical intermediates is reminiscent of the classic Fenton chemistry (Scheme 1),^{39,40} in which an iron(II) cation catalyzes the decomposition of hydrogen peroxide to generate the hydroxyl radical (11) (eq 1–1). If an alkane is present in the reaction system, the highly reactive radical 11 abstracts a hydrogen atom from a C–H bond to form water and an alkyl radical, which can subsequently form alcohol (eq 1–2). If no alkane is present, H₂O₂ will decompose to release O₂ and water through either a radical chain (eqs 1–3 and 1–4) or a nonchain pathway (eqs 1–1, 1–3, and 1–5). The decomposition of *m*CPBA in the presence of Ni complexes, the lack of an effect of the ligands on the selectivity of catalytic reactions, and the

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Scheme 1. Mechanism of Fenton Reactions of H_2O_2

$$Fe(II) + H_2O_2 \longrightarrow Fe(III) + HO' + HO^{\ominus}$$
(1-1)

$$HO' + R - H \longrightarrow H_2O + R' \xrightarrow{[O]} R - OH$$
(1-2)

$$HO' + H_2O_2 \longrightarrow H_2O + HOO'$$
(1-3)

 $HOO' + H_2O_2 \longrightarrow H_2O + O_2 + HO'$ (1-4)

 $Fe(III) + HOO' \longrightarrow Fe(II) + O_2 + H^{\textcircled{0}}$ (1-5)

formation of long-lived carbon-centered radicals led us to propose an alternative reaction pathway in which the Ni species does not cleave the C–H bond; instead, it reacts with *m*CPBA to generate free radicals that abstract a hydrogen atom from the $C(sp^3)$ –H bond. However, because the nickel-catalyzed reaction occurs with *m*CPBA instead of H₂O₂, the identity of the species that cleaves the C–H bond in such a scenario was unclear.

4. Identity of the Free Radical Responsible for C–H Bond Cleavage. To identify the radical that cleaves the C–H bond during the reactions with *m*CPBA containing catalytic amounts of nickel complex, we conducted the reactions of *m*CPBA and Ni complexes with deuterium-labeled cyclohexane $(2-d_{12})$ and adamantane (3) and compared the selectivity of these reactions to the known selectivities for the reactions involving abstraction of the hydrogen atom in a C–H bond by various radicals. Figure 4A shows four *m*CPBA-derived free radicals that might be formed in the reaction system containing nickel: the 3-chlorobenzoyloxy radical (10), the hydroxyl radical (11), the 3-chlorophenyl radical (12), which can be formed by decarboxylation of 10, and the 3-chlorobenzoylperoxy radical (13).

The selectivity of hydroxyl radical (11) for the oxidation of adamantane is low. The $3^{\circ}/2^{\circ}$ ratios from oxidations of 3 that involve cleavage of C–H bonds by radical 11 range from 0.4 to 1.3 (Figure 4B, entries 1–3).⁴¹ These values are much smaller than those of Ni-catalyzed oxidation of 3 by *m*CPBA, which range from 4.4 to 6.9. Thus, hydroxyl radical 11 is unlikely to be the species that cleaves the C–H bond in this reaction.

If 3-chlorophenyl radical (12) were the major species that cleaves the C-H bond in Ni-catalyzed oxidations of alkanes, then the oxidation of deuterated cyclohexane $(2-d_{12})$ would afford deuterated cyclohexanol $(4\mathbf{a} \cdot d_{11})$ and deuterated cyclohexanone $(4b-d_{10})$ as the major products, along with a stoichiometric amount of deuterated chlorobenzene $(9-d_1)$. However, ²H NMR spectra of the reaction of $2 - d_{12}$ with *m*CPBA and a catalytic amount of Ni complex 1a showed that this reaction formed $4a-d_{11}$ and $4b-d_{10}$ in 26% and 8% yields, respectively, but produced 9- d_1 in only 2% yield (Figure 4D). This result indicates that aryl radical 12 cannot be the major intermediate that cleaves C-H bonds in hydrocarbons. The large amount of byproduct 9 observed in the catalytic oxidations of 2 and 3 (Figure 3B) was most likely formed by hydrogen atom transfer (HAT) from solvent molecules, such as dichloromethane (DCM), to 12. This hypothesis is supported by the detection of 1,1,2,2-tetrachloroethane in the reaction mixture, which is the homocoupling product of dichloromethyl radicals $(CHCl_2)$ that would form by hydrogen atom transfer from DCM to 12. We also conducted the Ni-catalyzed oxidation of cyclohexane by mCPBA with DCM- d_2 as the solvent and



Entry	[0]	radical	3*/2*
1	O ₂ -H ₂ O ₂ -"Bu ₄ NVO ₃ - PCA	11	0.4
2	O_2 - H_2O_2 - $h\nu$	11	0.5
3	O_2 - H_2O_2 - $Fe(ClO_4)_3$	11	1.3
4	benzil-O2-hv in DCE ^a	13'	11.2-12.1
5	Ni-mCPBA ^b	TBD	4.4-6.9

^aDCE instead of DCM/MeCN was used to reduce evaporation of solvent while the solution was sparged with O₂. ^bSimilar selectivity in DCE and DCM/MeCN.



Figure 4. (A) Free radicals derived from *m*CPBA that might cleave C– H bonds in the catalytic reaction. (B) Tertiary to secondary selectivity of free radicals for the oxidation of **3.** (C) Photomediated formation of benzoylperoxy radical from benzil under an atmosphere of O_2 . (D) Results of Ni-catalyzed oxidation of **2**- d_{12} .

observed that 87% of the chlorobenzene that formed contained the deuterium label (see the Supporting Information). These results further support our hypothesis that chlorobenzene (9) is formed primarily by hydrogen atom transfer from solvent molecules to radical 12.

The benzoylperoxy radical (13') can be generated by the photomediated homolysis of benzil under an atmosphere of O_2 (Figure 4C).^{42,43} To measure the selectivity of radical 13' for the oxidation of adamantane (3), we conducted the photochemical oxidation of 3 with benzil and O_2 in 1,2-dichloroethane (DCE). The 3°/2° ratios derived from the products of these reactions range from 11.2 to 12.1 (Figure 4B, entry 4), which is higher than those from Ni-catalyzed oxidations of 3 conducted in the same solvent (Figure 4B, entry 5). Given the similar structures of radicals 13 and 13', it is likely that the 3°/2° selectivity for the oxidation of 3 by these two radicals is similar. Therefore, the 3-chlorobenzoylperoxy radical (13) is unlikely to be the species that cleaves C–H bonds in Ni-catalyzed oxidations of alkanes.

Thus, the aroyloxy radical **10** is the most likely radical to cleave the C–H bond. The BDE of the O–H bond in *m*CBA was reported to be 107.3 kcal/mol,⁴ which is higher than those of unactivated C–H bonds in alkanes and makes HAT from

alkanes to radical **10** thermodynamically favorable. The secondorder rate constant for the abstraction of a hydrogen atom from **2** by 4-methoxybenzoyloxy radical (**14**) was measured to be on the order of $10^5 \text{ M}^{-1} \text{ s}^{-1}$, whereas the first-order rate constant for decarboxylation of **14** was measured to be 10^4-10^5 s^{-1} .⁴⁴ Given the similarity between the structures of *m*-chloro- and *p*methoxy-substituted benzoyloxy radicals **10** and **14**, it is likely that the rate constants for abstraction of a hydrogen atom from an unactivated $C(\text{sp}^3)$ -H bond by these two radicals are similar and that the rate of abstraction of a hydrogen atom by **10** would be similar to that of the decarboxylation. This prediction based on the literature values fits with the observed oxidation process and formation of chlorobenzene.

However, reliable data on the selectivity of aroyloxy radical **10** for the abstraction of hydrogen atoms from alkanes were needed to assess more precisely whether this radical cleaves the C–H bonds in Ni-catalyzed oxidations. Thus, we generated radical **10** in situ via the thermal decomposition of bis(3-chlorobenzoyl)-peroxide (**15**), measured its selectivity for hydrogen-atom abstraction of a model alkane, 2,2,4,4-tetramethylpentane (**16**), and compared the selectivity of the metal-free bromination of **16** by peroxide **15** to that of Ni-catalyzed reactions (Figure 5). All



Figure 5. Bromination of alkane **16** by (A) peroxide **15**, (B) *m*CPBA and Ni complex **1a**, and (C) peracid **18** and Ni complex **1a**. Conditions: (A) 0.0625 mmol of **15**, 10 equiv of **16**, 4 equiv of CBr₄, DCM (0.0625 M), 80 °C under N₂; (B) 0.125 mmol of *m*CPBA, 5 equiv of **16**, 2 equiv of CBr₄, 0.1 mol % **1a**, DCM (0.125 M), 50 °C under N₂. (C) 0.125 mmol of **18**, 5 equiv of **16**, 2 equiv of CBr₄, 1 mol % **1a**, DCM (0.125 M), 50 °C under N₂. ^{*b*}Average of three repeated experiments. ^{*b*}Average of three repeated experiments.

reactions were conducted in the presence of CBr_4 , which is wellknown to trap carbon-centered radicals rapidly. In this case, the distribution of products **17a** and **17b** from bromination at the secondary and primary C–H bonds accurately reflects the selectivity in the hydrogen-atom transfer step. The model substrate **16** was chosen because radicals derived from CBr_4 , such as CBr_3 , do not cleave the strong primary and secondary C–H bonds in alkane **16** and, therefore, do not interfere with the measurement of the selectivity of hydrogen-atom abstraction by aroyloxy radical **10**. The tertiary C–H bonds in adamantane, however, can be cleaved by these radicals derived from CBr_4 , so adamantane is not a suitable substrate for this experiment (see the Supporting Information).

The reaction of peroxide **15** with alkane **16** in the presence of 2 equiv of CBr₄ furnished **17a** in 10.4% yield and **17b** in 5.5% yield, corresponding to a $2^{\circ}/1^{\circ}$ ratio of 1.9 ± 0.4 (Figure 6A).



Figure 6. Illustration of the GC experiment for the detection of alkyl hydroperoxide intermediates designed by Shul'pin.

The Ni-catalyzed bromination of **16** by *m*CPBA formed **17a** in 35.2% yield and **17b** in 17.9% yield, corresponding to a $2^{\circ}/1^{\circ}$ ratio of 2.0 \pm 0.2 (Figure 6B). The similarity between the selectivity of the bromination reactions with diaroyl peroxide **15** and the process with the nickel complex and *m*CPBA strongly suggests that radical **10** is the species that cleaves the C–H bond in the catalytic system.

To assess further our proposal that the aroyloxy radical derived from the aromatic peracid is the species that cleaves the C–H bond in the catalytic reaction, we conducted reactions with a different peracid. We envisioned that the selectivity for the Ni-catalyzed bromination of **16** would be different for reactions with aromatic peracids bearing different substituents than the chloride in *m*CPBA. Indeed, the Ni-catalyzed bromination of **16** by 3,5-bis(trifluoromethyl)perbenzoic acid (**18**) furnished **17a** in 14.7% yield and **17b** in 13.4% yield, corresponding to a $2^{\circ}/1^{\circ}$ ratio of 1.1 ± 0.1 (Figure 6C). This ratio is lower than those from reactions involving *m*-chlorobenzoyloxy radical **10** (Figure 6A,B) and further corroborates our hypothesis that aroyloxy radicals derived from aromatic peracids cleave the C–H bonds of alkanes in the catalytic system.

5. The C–O Bond Formation Step. Having identified the free radical responsible for C–H bond cleavage, we investigated the step that forms the C–O bond. Three possible pathways can lead to the formation of a C–O bond from the carbon-centered radical generated by hydrogen-atom abstraction of the alkane by aroyloxy radical **10** (Scheme 2): (1) trapping by O_2 to generate an alkylperoxy radical, which subsequently decomposes to form alcohol and ketone products (eq 2–1); (2) trapping by a putative nickel(III) hydroxide species, which would be generated by the oxidation of the Ni(II) complex by *m*CPBA, to form the alcohol product and a Ni(II) species (eq 2–2); (3) trapping by *m*CPBA to afford the alcohol product and radical **10** (eq 2–3).

The decomposition of alkylperoxy radicals usually forms the corresponding alcohol and ketone products in an ~1:1 ratio,⁴⁵ whereas the Ni-catalyzed oxidation of **2** gave A/(K + E) ratios between 3.1 and 3.5 (Table 1A). Furthermore, the yield and selectivity of the catalytic oxidations of **2** and **3** under an atmosphere of N₂ were similar to those of the reactions under air. These straightforward observations suggest that the formation of the C–O bond does not involve O₂ and that the steps in eq 2–1 are unlikely to be the major ones forming the C–O bond in the Ni-catalyzed oxidations. Nonetheless, we decided

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Scheme 2. Three Possible Pathways for the Formation of C-O Bonds

$R' + O_2 \longrightarrow R-OO' \longrightarrow R-OH + R=O$	(2-1)
R [∙] + [Ni ^{III}]–OH → R–OH + [Ni ^{II}]	(2-2)
$R' + ArCO_3H \longrightarrow R-OH + ArCOO'$	(2-3)

to assess more precisely whether trapping of alkyl radicals by O_2 occurred and, if so, what percentage of the oxidized products were formed from O_2 .

To assess this pathway further, we determined the amount of alkylperoxy intermediates in the product mixture that would form by the trapping of the alkyl radical with O₂. Shul'pin et al. reported an experiment for this purpose (Figure 6).^{46,47} Alkylperoxy intermediates, such as cyclohexyl hydroperoxide (19), decompose by gas chromatography (GC) to generate the corresponding alcohol and ketone products 4a and 4b in a ~1:1 ratio. Treatment of a reaction mixture containing alcohol 4a, ketone 4b, and intermediate 19 with an excess of reductants, such as PPh₃, reduces 19 to 4a in quantitative yield without affecting the amount of alcohol or ketone formed before the addition of PPh₃. Thus, if intermediate 19 is present in a reaction mixture, the ratios of alcohol to ketone (A/K) derived from the GC trace of the mixture before and after the treatment with PPh₃ will be different. Moreover, the percentage of 19 in the total amount of oxidized products can be calculated from these ratios.

The A/K ratio derived from GC traces of the mixture from the Ni-catalyzed oxidation of 2 under an atmosphere of N₂ after 5 min before the addition of PPh₃ was identical to that after the addition of PPh₃ (Table 3, entries 1 and 2). This result indicates

Table 3. GC Results of the Ni-Catalyzed Oxidation^a of Cyclohexane under N₂ and Air

	<u> </u>	CPBA, 1a 5 min + 4a 4b)
entry	N_2/air	treatment with $\rm PPh_3$	A/K^{b}
1	N	yes	4.6 ± 0.1
2	IN ₂	no	4.5 ± 0.0
3	air	yes	6.1 ± 0.8
4	all	no	4.2 ± 0.7

^{*a*}Conditions: 0.125 mmol *m*CPBA, 7.5 equiv 2, 0.1 mol % 1a, DCM/ MeCN (3:1, 0.125 M), 50 °C, 5 min. ^{*b*}Arithmetic mean of three repeated experiments.

that intermediate **19** was not formed and that molecular O_2 was not generated in situ during the reaction under N_2 . The A/Kratio derived from GC traces of the reaction conducted under air before the addition of PPh₃ was 4.2 ± 0.7 , and the ratio after the addition of PPh₃ was 6.1 ± 0.8 (Table 3, entries 3 and 4). The small difference between these ratios suggests that some amount of intermediate **19** was formed under air by the pathway shown as eq 2–1 in Scheme 2. However, the percentage of **19** in the total amount of oxidized species (**4a** + **4b** + **19**) was estimated to be only 10% based on these two ratios (see the Supporting Information for details of the calculation). Thus, the trapping of alkyl radicals by O_2 , even under air, was not the major pathway for the formation of the C–O bond in the catalytic reactions.

The lack of effect of the ligands on the yield and selectivity of the Ni-catalyzed oxidation of alkanes does not support the potential formation of alcohol by reaction of the alkyl radical with a nickel hydroxide species (Scheme 2, eq 2-2). If the C–O bonds were formed by this species, then the *cis* fraction of the alcohols formed from the reactions of 1,2-dimethylcyclohexanes would be expected to depend on the electronic and steric properties of the nickel species, which in turn would depend on the identity of the ligand.

Having ruled out the two pathways described above, we considered that the trapping of carbon-centered radicals by *m*CPBA (Scheme 2, eq 2–3) would be the major pathway for the formation of the C–O bond. Indeed, the reaction of an alkyl radical with an aliphatic peracid by a free-radical chain process has been well-established by many examples of decarboxylative formation of alcohols from aliphatic peracids.⁴⁸

6. The Free-Radical Chain Mechanism. Having investigated both the C–H bond-cleaving and the C–O bond-forming steps, we propose a free-radical chain mechanism for the Ni-catalyzed oxidation of unactivated $C(sp^3)$ –H bonds by *m*CPBA (Scheme 3). Contrary to the hypotheses in the

Scheme 3. Free-Radical Chain Mechanism of Ni-Catalyzed Oxidation of Unactivated $C(sp^3)$ -H Bonds

$ArCO_3H \xrightarrow{(Ni)} ArCO_2 + other rac10$	dicals	(3-1)
$\begin{array}{rrrr} ArCO_2 \bullet & + & H-R & \longrightarrow & R \bullet & + & ArC\\ 10 & & & & \end{array}$	CO₂H	(3-2)
$ArCO_3H + R \cdot \longrightarrow R - OH + Ar$	CO ₂ • 10	(3-3)
Side reactions:		
$R \cdot + O_2 \longrightarrow ROO \cdot \longrightarrow R-OH +$	R=0	(3-4)
$\begin{array}{ccc} \text{ArCO}_2 \bullet & \xrightarrow{-\text{CO}_2} & \text{Ar} \bullet & \xrightarrow{\text{solvent}} & \text{Ar} \bullet \\ \textbf{10} & \textbf{12} \end{array}$	4r—Н 6	(3-5)
А	r = 3-chloro	ohenyl

literature 20,25,26 that Ni-oxygen intermediates cleave C–H bonds, our data suggest that the Ni complex catalyzes the reaction of mCPBA to generate the 3-chlorobenzoyloxy radical (10) among other products (eq 3-1). Equation 3-1 likely consists of several redox reactions, but our data do not allow conclusions about the mechanism of this step. Radical 10 abstracts a hydrogen atom from the alkane to form the mCBA byproduct and a carbon-centered radical (eq 3-2), which then reacts with *m*CPBA to afford the alcohol product and regenerate radical 10 (eq 3-3), thus propagating the radical chain. As discussed previously, the trapping of alkyl radicals by O₂ is a minor side reaction under air (eq 3-4). Decarboxylation of radical 10 to generate the 3-chlorophenyl radical 12, which captures a hydrogen atom from solvent molecules to form the chlorobenzene byproduct (eq 3-5), competes with the reaction of 10 with a C–H bond (eq 3-2).

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On the basis of this mechanism, the identity of the Ni complex influences the rate of decomposition of *m*CPBA and hence the rate of formation of radical **10**, but it does not change the selectivity for reaction at one C–H bond over another. This conclusion is consistent with our observation that reactions catalyzed by Ni complexes with more sterically hindered ligands are slower, but the selectivities of these reactions are similar to those catalyzed by complexes with less hindered ligands. This radical chain mechanism, in which the C–H bond is not cleaved by a nickel complex, reconciles the combination of low reactivity of Ni-oxygen species toward strong $C(sp^3)$ –H bonds and the well-documented formation of oxidation products in high yield from Ni-catalyzed oxidations occurring at strong aliphatic C–H bonds.

Alexanian and co-workers achieved tunable, selective chlorination of $C(sp^3)$ -H bonds via free-radical pathways by modifying the substituents on the *N*-chloroamide reagents.^{49,50} The free-radical mechanism we propose for the Ni-catalyzed oxidation of unactivated alkanes suggests that novel, substituted aromatic peracids, likewise, could modify the selectivity of the oxidation of $C(sp^3)$ -H bonds in complex molecules and polymers.

CONCLUSION

In conclusion, we report detailed mechanistic investigations of the oxidation of unactivated $C(sp^3)$ -H bonds by *m*CPBA catalyzed by Ni complexes coordinated by nitrogen-based ligands. We show the absence of an effect of the ligand on the yield and selectivity of this reaction, as well as a clear correlation between reaction rates and the steric hindrance of the ligands. Experiments with radical clocks indicate that this reaction generates a carbon-centered radical that is sufficiently long-lived to epimerize before the formation of the C–O bond.

On the basis of these results and the observation of Nicatalyzed decomposition of *m*CPBA, we propose an alternative pathway for oxidation that does not involve a nickel-oxo or -oxyl species. We conclude that the nickel facilitates the generation of the 3-chlorobenzoyloxy radical, which cleaves the C-H bonds in alkanes, as evidenced by a series of experiments on the selectivity for reactions of adamantane and 2,2,4,4-tetramethylpentane and on the oxidation of deuterium-labeled cyclohexane. We also conclude that trapping of alkyl radicals by *m*CPBA is the major pathway to form the C–O bond. Finally, we propose that the oxidation occurs by a free-radical chain mechanism. Our results and this proposed mechanism reconcile the lack of strong evidence for the reactivities of Ni-oxo or Ni-oxyl complexes toward strong $C(sp^3)$ -H bonds and the formation of oxidized products in good yield from Ni-catalyzed oxidations of unactivated alkanes with aromatic peracids. We envision that such mechanistic understanding can guide us to design more effective and selective organic oxidants, for example, substituted aromatic peracids, for the oxidation of unactivated $C(sp^3)-H$ bonds in complex molecules and polymers.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09157.

Experiment procedures, characterization of compounds (PDF)

X-ray crystallographic data for complex **1a** (CIF)

X-ray crystallographic data for complex 1f (CIF)

X-ray crystallographic data for complex 1g (CIF) X-ray crystallographic data for complex 1h (CIF)

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Notes

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