

# Mechanism of Hydrocarbon Functionalization by an Iodate/Chloride System: The Role of Ester Protection

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**Supporting Information** 

**ABSTRACT:** Mixtures of chloride and iodate salts for light alkane oxidation achieve >20% yield of methyl trifluoroacetate (TFA) from methane with >85% selectivity. The mechanism of this C-H oxygenation has been probed by examining adamantane as a model substrate. These recent results lend support to the involvement of free radicals. Comparative studies between radical chlorination and iodate/chloride functionalization of adamantane afford statistically identical 3°:2° selectivities (~5.2:1) and kinetic isotope effects for C-H/C-D functionalization ( $k_{\rm H}/k_{\rm D} = 1.6(3)$ , 1.52(3)). Alkane functionalization by iodate/chloride in HTEA is proposed to accur through H atom abtraction by free radical species including Cl<sup>o</sup> to give



HTFA is proposed to occur through H-atom abstraction by free radical species including  $Cl^{\bullet}$  to give alkyl radicals. Iodine, which forms by in situ reduction of iodate, traps alkyl radicals as alkyl iodides that are subsequently converted to alkyl esters in HTFA solvent. Importantly, the alkyl ester products (RTFA) are quite stable to further oxidation under the oxidizing conditions due to the protecting nature of the ester moiety.

KEYWORDS: methane, ethane, chloride, partial oxidation, functionalization, radical, iodate

#### INTRODUCTION

The components of natural gas are increasing sources of energy and chemical feedstocks as a result of new technologies for economical shale gas extraction.<sup>1-4</sup> Current methods to convert light alkanes to more valuable compounds (e.g., methane to methanol, ethane to ethylene, and propane to propylene) require forcing conditions and are energy intense.<sup>5-9</sup> Accordingly, new processes, homogeneous or heterogeneous, for the direct conversion of light hydrocarbons into higher value functionalized compounds have been of interest.<sup>7,10</sup>

The mono-oxidation of a C–H bond of methane using 1/2O<sub>2</sub> to generate methanol is an exothermic reaction. However, the strong nonpolar bond between carbon and hydrogen presents challenges. For example, the weaker C-H bonds of methanol (96 kcal/mol versus 104 kcal/mol for methane) often lead to overoxidation.<sup>11–15</sup> To circumvent this problem, current methods for methanol production from methane generally rely on an indirect process. Methane is reformed with steam to yield a mixture of CO and  $H_2$  (known as synthesis gas or syngas), which can be transformed in a second step into methanol.<sup>7,16</sup> The generation of syngas requires high temperatures and pressures, which necessitates substantial capital investment as well as the benefit of "economy of scale". 7,14,17,18 Thus, nonsyngas processes that directly and selectively convert the C-H bonds of light alkanes to C-X (X = halide or heteroatom functionality) bonds have been of high interest.<sup>12,19–22</sup>

Free radical chain reactions such as chlorination and bromination offer a strategy to break the strong C–H bonds of alkanes.<sup>12</sup> For example, methane functionalization can be accomplished using catalytic oxychlorination, whereby alkanes are chlorinated using mixtures of HCl and O<sub>2</sub> at high temperature with a heterogeneous catalyst (eq 1).<sup>23–39</sup> However, overoxidation is a chronic issue for oxychlorination reactions because of the decreased C–H bond dissociation enthalpy (BDE) of CH<sub>3</sub>Cl (101 kcal/mol)<sup>40</sup> versus CH<sub>4</sub> (104 kcal/mol).<sup>41</sup> Thus, as the oxidized product is often more reactive than the parent hydrocarbon, the production of polyhalogenated species is a significant problem.<sup>42,43</sup> In order to achieve high selectivity, alkane conversion is generally limited to < 10%.<sup>44</sup> This issue is also problematic for ethane and propane.<sup>45</sup>

$$CH_4 + HX + 0.5O_2 \xrightarrow[heat]{catalyst} CH_3X + H_2O$$
 (1)

In another functionalization strategy, molecular metal complexes and elemental iodine have been used to initiate electrophilic functionalization of C–H bonds in oleum.<sup>46–53</sup> While promising, many of these transformations are limited by the need for superacidic reaction media, which renders product isolation difficult.<sup>54</sup> Recently, high-valent main-group com-

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pounds (e.g.,  $TI^{III}$  and  $Pb^{IV}$ ) have been shown to stoichiometrically functionalize the C–H bonds of alkanes in nonsuperacidic solvent by a proposed electrophilic process.<sup>55</sup> Additionally, a perfluoroaryl iodine(III) complex capable of activating and functionalizing the C–H bonds of methane and ethane selectively in HTFA (TFA = trifluoroacetate) has been reported.<sup>56</sup>

We recently reported the partial oxidation of light alkanes using combinations of iodate or periodate salts and chloride in HTFA to generate alkyl esters (RTFA), a process that we label hypervalent iodine/chloride alkane oxidation (HIAO).<sup>57,58</sup> Methane, ethane, and propane are functionalized to the corresponding ester with yields >20%, based on alkane, with >80% selectivity. The reactions occur in nonsuperacidic media and are tolerant of oxygen and water. Since oxygen, a radical trap,<sup>59</sup> does not inhibit alkane functionalization, it was initially proposed that a non-free-radical pathway is highly possible. The presence of chloride is essential, indicating that it may be necessary to generate the active species for C–H bond breaking. Similar activity was not obtained with I<sub>2</sub>, suggesting that HIAO is not merely due to the in situ generation of I<sub>2</sub>, which would then lead to a catalytically active species.<sup>57</sup>

We report herein an experimental mechanistic study of hydrocarbon oxidation by the chloride/iodate process (Scheme 1). The experimental results lead us to conclude that the HIAO

#### Scheme 1. Overview of the HIAO Process<sup>a</sup>

$$R-H \xrightarrow{NH_4|O_3} R-X$$

$$HX \qquad Up to 40%$$
180-200 °C yield

1401

<sup>*a*</sup>RH = methane, ethane, propane, adamantane, etc.; X = OAc, TFA.

occurs by a radical-based pathway with its unique selectivity resulting from the protecting effect of the ester moiety of the product. Importantly, under the HIAO reaction conditions, we conclude that the ester functionality protects the functionalized alkanes (e.g., MeTFA and EtTFA) against overoxidation. This is a surprising result, given the weaker C–H bonds of MeTFA and EtTFA (versus methane and ethane, respectively) and the evidence that the HIAO process involves free-radical-based homolytic C–H bond breaking.

#### RESULTS AND DISCUSSION

Simple combinations of iodine oxides (in oxidation states III, V, and VII) with a catalytic amount of chloride in HTFA selectively oxidize light alkanes (methane, ethane, and propane) to alkyl esters (trifluoroacetate) and alkyl chlorides.<sup>57,58</sup> Our initial reports showed that this process is effective with a variety of hypervalent iodine oxides, including iodates, periodates,  $I(TFA)_{3}$ , and  $(IO)_{2}S_{2}O_{7}$ , but catalytic amounts of chloride are required for substantial yields of MeTFA. For example, with iodate in the absence of KCl <1% yield of MeTFA was observed, whereas with substoichiometric amounts (in comparison to iodate) of chloride, yields >20% based on methane were obtained.<sup>57</sup> Similarly, with  $I(TFA)_3$  the yields of MeTFA were 7% and 43%, with respect to I(TFA)<sub>3</sub>, in the absence and presence of chloride. Additionally, the ability of the reaction to tolerate nonsuperacidic solvent conditions, even water, indicated that the mechanism of the HIAO process likely differs from that of the iodine/oleum reaction for C-H functionalization.<sup>49</sup> Due to the ability of dioxygen to trap alkyl

radicals, the tolerance of the iodine oxide/chloride system to aerobic conditions initially led us to suspect that the reaction mechanism does not involve alkyl radicals as reaction intermediates.<sup>57,58,60</sup> Thus, on the basis of preliminary data, we speculated that there was a reaction pathway that did not involve free-radical-based C–H abstraction.

To aid in the mechanistic study of the HIAO process, adamantane was used. Adamantane contains a mixture of secondary and tertiary C-H bonds, which allows for the probing of functionalization selectivity. As shown in Scheme 2,

Scheme 2. Oxidation of Adamantane Using Potassium Chloride and Ammonium Iodate



adamantane is oxidized cleanly by iodate/chloride to the tertiary trifluoroacetate ester using neat trifluoroacetic acid as a solvent. Similar to observations with light alkanes, in the absence of KCl, only trace amounts of product are formed (<1%). During the reaction, molecular iodine is produced, indicating the reduction of the iodate anion under the reaction conditions (see Figure S1 in the Supporting Information). Quantification by UV–vis spectroscopy indicates that 0.152(8) mmol of I2 is produced after 1 h at 100 °C, 30% of the theoretical maximum (Scheme 2). The stoichiometry and high yield of 1-adamantyl trifluoroacetate suggest that the average oxidation state of iodine at the end of the reaction should be I(III); however, I(III) species such as iodites are known to disproportionate.<sup>61,62</sup> For this reaction, we have not attempted to achieve mass balance, but we assume that unaccounted-for iodine is likely unreacted iodate and perhaps some iodine(III) species.

We found that 2-adamantyl trifluoroacetate quickly rearranges in trifluoroacetic acid to the tertiary acetate compound, thus obscuring any mechanistic insight gained from the selectivity of the functionalization step. For example, heating 2-adamantyl trifluoroacetate in HTFA for 15 min resulted in quantitative conversion to 1-adamantyl trifluoroacetate (Scheme 3). The analogous rearrangement was not observed when acetic acid was used as a solvent, where both secondary and tertiary oxidation was observed (see below).

Scheme 3. Heating 2° Adamantyl Ester Derivatives in Acid, Generating the 3° Product for the Trifluoroacetate but Not for Acetate





Wavelength (nm)

**Figure 1.** UV–vis spectra resulting from the yellow mixture of potassium chloride and potassium iodate in HTFA (top, black), pure ICl (bottom, red), and pure  $ICl_3$  (middle, blue). Conditions for the black spectrum: 0.15 mmol of KCl, 1.0 mmol of KIO<sub>3</sub>, and trifluoroacetic acid at room temperature. The peak for  $Cl_2$  was determined experimentally by preparing an authentic standard in HTFA.

As chlorine formation is evident from the UV-vis spectrum of the iodate/chloride mixture in HTFA, the possibility of a chlorine-radical-based functionalization pathway was probed further. To examine whether chlorine radicals are possibly involved in the HIAO process for adamantane functionalization, the selectivity of the iodate/chloride reaction with adamantane was compared to the selectivity of a radical chlorination. In order to avoid the rearrangement observed in HTFA, we performed experiments in acetic acid (HOAc). As shown in Scheme 4, both the HIAO process and the functionalization promoted by N-chlorosuccinimide (NCS), which has been shown to yield chlorine radicals in the presence of a radical initiator such as benzoyl peroxide,<sup>63</sup> yield similar tertiary to secondary selectivity: ~5.2:1 on a per-hydrogen basis. Previous reports indicated that radical chlorination of adamantane in benzene using NCS or Cl<sub>2</sub> proceeded with tertiary to secondary selectivity similar to our results in HOAc on a per-hydrogen basis: 4.9:1 and 4.7:1, respectively.<sup>64,65</sup> In each case, only monofunctionalized products were observed. Additionally, as shown in Scheme 5, when a 1:1 mixture of perprotio- and perdeuteroadamantane are used, nearly identical kinetic isotope effects are observed for the HIAO process and radical chlorination using NCS and benzoyl peroxide. The reaction of adamantane and adamantane- $d_{16}$  with iodate/ chloride in acetic acid reveals a  $k_{\rm H}/k_{\rm D}$  value of 1.52(3), which is statistically identical with the  $k_{\rm H}/k_{\rm D}$  value, 1.6(3), for the reaction using NCS. These results are consistent with the HIAO process for adamantane oxidation likely involving

Scheme 4. Oxidation of Adamantane Using Potassium Chloride and Ammonium Iodate in Glacial Acetic Acid (Black) and Radical Chlorination of Adamantane Using N-Chlorosuccinimide (NCS) in Glacial Acetic Acid (Blue)<sup>a</sup>



"Data are from three separate experiments with  $3^{\circ}:2^{\circ}$  reported as an average with standard deviations shown for the ratios of  $3^{\circ}:2^{\circ}$  selectivity.

Scheme 5. (A) Intermolecular Deuterium KIE for the Chloride/Iodate Catalytic Oxidation of Adamantane in Acetic Acid and (B) Intermolecular Deuterium KIE for Radical Chlorination of Methane of Adamantane<sup>a</sup>



chlorine radicals. We note that the use of *N*-chlorosuccinimide as an unambiguous source of chlorine atoms has been contested.<sup>66</sup> While the role of the succinimidyl versus chlorine radical has not been resolutely elucidated, *N*-chlorosuccinimide was utilized in this selectivity study to provide a reference for radical-based functionalization that results in chlorination.

*N*-Hydroxyphthalimide (NHPI), a well-studied reagent for hydrogen atom abstraction,<sup>67</sup> was tested as a substitute for chloride in order to determine if the chloride in the HIAO process ultimately acts as a hydrogen atom abstraction agent. In acetic acid at 180 °C, adamantane was converted to the functionalized product in 86% yield with NHPI and NH<sub>4</sub>IO<sub>3</sub> (Scheme 6). Thus, chloride is potentially acting as a precursor for a hydrogen atom abstraction reagent. The NHPI-mediated functionalization of adamantane is likely more selective than that with iodate/chloride due to the lower reactivity of the phthalimide *N*-oxyl (PINO) radical in comparison to chlorine radical,<sup>68–70</sup> as the BDE of the O–H bond of NHPI is 14 kcal/ mol weaker than that of the H–Cl bond.<sup>45</sup>

The previously observed tolerance of the HIAO system to dioxygen could indicate a nonradical reaction pathway, as the Scheme 6. Functionalization of Adamantane Using a Mixture of *N*-Hydroxyphthalimide (NHPI) and Ammonium Iodate in Acetic Acid



trapping of methyl radicals by dioxygen occurs at nearly diffusion-controlled rates.<sup>60</sup> Thus, if alkyl free-radical intermediates were formed, it was anticipated that alkyl radicals would be rapidly trapped by dioxygen and prevent the formation of alkyl esters.<sup>60</sup> However, the rate of reaction between alkyl radicals and molecular iodine, which is produced under reaction conditions for the iodate/chloride functionalization process, is approximately half as rapid as trapping by dioxygen ( $2.5 \times 10^9$  L mol<sup>-1</sup> s<sup>-1</sup> for I<sub>2</sub> versus  $4.9 \times 10^9$  L mol<sup>-1</sup> s<sup>-1</sup> for O<sub>2</sub>).<sup>60,71,72</sup> This indicates that, if iodine is present in significant concentration, it could intercept a putative alkyl radical prior to a reaction with dioxygen. Because MeI reacts rapidly with NH<sub>4</sub>IO<sub>3</sub> in HTFA to form MeTFA in nearly quantitative yield,<sup>57</sup> the formation of MeI as an intermediate is unlikely to be detected. Under oxidizing conditions, alkyl iodides have been reported to convert to alcohols and acetates.<sup>73-77</sup>

As a test for possible formation of alkyl iodide intermediates, we probed two aspects: (1) if ethyl iodide converts to ethyl acetate in acetic acid quickly under reactions conditions and (2) if ethyl radical can be trapped by iodine under reaction conditions. As shown in Scheme 7 and Figure 2, when *tert*-butyl

## Scheme 7. Heating *tert*-Butyl Propaneperoxoate in the Presence of Iodine Yields Ethyl Iodide<sup>a</sup>



tert-butyl propaneperoxoate

"Ethyl iodide yield is reported as the average and standard deviation of four trials.



**Figure 2.** <sup>1</sup>H NMR spectrum resulting from heating *tert*-butyl propaneperoxoate in the presence of iodine. Conditions: 0.1 mmol of *tert*-butyl propaneperoxoate, 0.05 mmol of iodine, 1 mL of acetic acid- $d_4$  at 180 °C for 1 h. Cyclopentane (0.05 mmol) was added as an internal standard.

propaneperoxoate, an ethyl radical precursor,<sup>78</sup> is heated in acetic acid in the presence of stoichiometric iodine, ethyl iodide is produced as the main product. With these results in hand, we probed for the formation of ethyl iodide in the iodate/chloride functionalization of ethane in acetic acid. In fact, heating (180  $^{\circ}$ C) a mixture of ethane, iodate, and chloride in acetic acid and analyzing the reaction mixture by <sup>1</sup>H NMR spectroscopy reveals the formation of ethyl iodide (Scheme 8). This result is

Scheme 8. Functionalization of Ethane in Acetic Acid Using Iodate/Chloride Yielding a Mixture of Ethyl Iodide, Ethyl Chloride, Ethyl Acetate, and Methyl Acetate<sup>*a*</sup>

	KCI (0.67 mmol) NH <sub>4</sub> IO <sub>3</sub> (7.7 mmol)		EtOAc	+	EtCl
CH <sub>3</sub> CH <sub>3</sub> (300 psi) (~30 mmol)		0.3	81(3) mmc	ol	0.27(1) mmol
	HOAc/Ac <sub>2</sub> O (19:1 v:v) 180 °C, 1 h	+ 0.0	Etl 96(1) mmc	+	MeOAc 0.46(9) mmol

<sup>a</sup>See text and Scheme 14 regarding MeOAc production.

consistent with the formation of an ethyl radical, which is trapped by molecular iodine formed in situ. Thus, the formation of methyl iodide from methyl radicals during methane functionalization in HTFA is also viable, but rapid conversion of MeI to MeTFA would prevent detection.

To determine the relative stabilities of RI and RTFA (R = Me, Et) under the HIAO conditions, each was tested under a standard set of conditions (Schemes 9 and 10). Both alkyl

### Scheme 9. MeI Conversion to MeTFA and MeCl under Functionalization Conditions

	KCI (0.67 mmol) NH <sub>4</sub> IO <sub>3</sub> (7.7 mmol) Ar (100 psi)			
Mel	HTFA	MeTFA	+	MeCl
(1 mmol)	180 °C, 20 min	0.62(3) mmol		0.11(1) mmol

Scheme 10. EtI Conversion to EtTFA, EtCl, and Difunctionalized Ester Product under Functionalization Conditions

	KCI (0.67 mmol)	EtTFA +	EtCl
	NH <sub>4</sub> IO <sub>3</sub> (7.7 mmol) Ar (100 psi)	0.66(3) mmol	0.17(4) mmol
Etl (1 mmol)	HTFA 180 °C, 20 min	+ TFA 0.008(4	TFA •) mmol

iodides, MeI and EtI, are completely consumed under these conditions after 20 min. MeI is converted to MeTFA and MeCl (Scheme 9). While EtI is observed in HOAc (see Scheme 8), EtI is consumed quickly to form EtTFA, EtCl, and 1,2-bis(trifluoroacetyl)ethane in the stronger acid, HTFA. Mean-while, the ester-protected species, MeTFA and EtTFA, are moderately stable under these HIAO reaction conditions with 90% and 55%, respectively, remaining after heating at 180 °C for 20 min. The trifluoroacetate moiety prevents overoxidation (Figures 3 and 4), to a higher degree for MeTFA than for EtTFA.

In order to compare the rate of functionalization of the light alkanes to form the RTFA products to the rate of RTFA consumption, the conversion of methane and ethane to MeTFA and EtTFA and the consumption of MeTFA and EtTFA were studied at 140 °C (Figures 3 and 4). The products of MeTFA and EtTFA conversion were not characterized.



Figure 3. Methane functionalization and MeTFA decay in the presence of KCl, NH<sub>4</sub>IO<sub>3</sub>, and HTFA at 140 °C as a function of time.



Figure 4. Ethane functionalization (left) and EtTFA decay (right) in the presence of KCl, NH<sub>4</sub>IO<sub>3</sub>, and HTFA at 140 °C as a function of time.

Because the methane functionalization reaction to yield MeTFA is complete within 1 h at 180 °C, the lower temperature (140 °C) was used such that methane functionalization could be examined over a longer period of time to provide a better comparison to the rate of MeTFA decay. MeTFA is very stable under the reaction conditions, with 85% remaining after 16 h at 140 °C. However, this places an upper limit on loss of MeTFA due to chemical oxidation, as some MeTFA is lost due to its high volatility. Under the HIAO reaction conditions, EtTFA is less stable than MeTFA, with 41% of the added EtTFA remaining after 8 h at 140 °C. Although the rates of decay and functionalization cannot be rigorously compared directly due to the unknown concentration of alkane in solution during the reaction, the relative rates of decay and functionalization under the reaction conditions used can be determined from the slopes of plots of MeTFA decay and production over time. While the plot of MeX (X = Cl, TFA) production versus time is linear for the reaction with methane ( $R^2 = 0.96$ , Figure 3 and Figure S14), the plot of EtX production versus time is not. To compare the rates of functionalization and decay, the rate of RX production was determined using the first data point, and linear fits of the RTFA decay data were used (Figure S15). Accordingly, the ratios of RX production versus decay are 11 and 9 for  $R = Me_{e}$ Et, respectively.

Free-radical-based functionalization of methane generally operates with poor selectivity, as the products contain weaker bonds in comparison to those in methane, which leads to undesired overoxidation. While the HIAO process exhibits high selectivity, it may occur by a radical pathway as a result of the protecting effect of the TFA ester moiety. Under typical radical chlorination conditions using *N*-chlorosuccinimide and benzoyl peroxide (Scheme 11, without added iodine), MeTFA is not produced. However, upon addition of small amounts of  $I_2$ 

Scheme 11. Radical Chlorination of Methane in the Presence of Added Iodine (See Figure 5) Producing MeTFA and  $MeCl^a$ 

<sup>*a*</sup>Note that MeCl formation was not quantified due to partial overlap with the <sup>1</sup>H NMR resonance from succinimide, which is generated from *N*-chlorosuccinimide (NCS).

(Scheme 11 and Figure 5), MeTFA is generated. A decrease in MeTFA yield is observed with  $\geq 0.34$  mmol of iodine.



**Figure 5.** MeTFA production as a function of added iodine to radical chlorination functionalization of methane in HTFA.

Although we are unsure of the cause of this decrease in MeTFA yield, it is possible that  $I_2$  traps radical intermediates that are important for the methane functionalization chemistry. Because MeCl does not rapidly convert to MeTFA under the reaction conditions, this demonstrates that iodine is an efficient radical trap that produces MeI, which is quickly converted to MeTFA. The effect of adding  $I_2$  to the HIAO methane functionalization reaction was also investigated for comparison. As shown in Figure 6, the addition of  $\geq 0.3$  mmol of iodine similarly inhibits



**Figure 6.** Functionalization of methane with KCl (0.67 mmol) and NH<sub>4</sub>IO<sub>3</sub> (7.7 mmol) in HTFA at 180 °C for 1 h with added I<sub>2</sub>. The plot shows the yield of MeX after 1 h of reaction as a function of added I<sub>2</sub>.

methane functionalization. To determine the stability of MeTFA under radical chlorination conditions, MeTFA was heated at 180  $^{\circ}$ C in the presence of *N*-chlorosuccinimide and benzoyl peroxide (Scheme 12). In agreement with the study of MeTFA stability under HIAO conditions, MeTFA is relatively stable under chlorination conditions, with about 83% remaining after 1 h at 180  $^{\circ}$ C.

### Scheme 12. Stability of MeTFA under Radical Chlorination Conditions in HTFA<sup>*a*</sup>

MeTFA - (0.35 mmol)	Ar (500 psi) NCS (3.5 mmol) benzoyl peroxide (0.035 mmol)	_	
	HTFA 180 °C, 1 h	-	0.29(2) mmol MeTFA remaining
aNCS = N-ch	lorosuccinimide.		

To further compare the HIAO process for light alkane functionalization to free-radical-based chlorination, propane was used to probe the selectivity for 2° versus 1° functionalized products. Propane oxidation was performed with either KCl/ NH<sub>4</sub>IO<sub>3</sub> or NCS/benzoyl peroxide in HTFA at 120 °C for 30 min (Scheme 13). Low temperature, short reaction time, and subsequently, low conversions were used in order to minimize the generation of difunctionalized products so that the selectivity of the monofunctionalization process could be probed. The selectivity for internal versus terminal functionalization of propane differs between the two processes, with a 2°:1° ratio of 17.0(8):1 for KCl/NH<sub>4</sub>IO<sub>3</sub> and 5.6(6):1 for NCS/benzoyl peroxide on a per-hydrogen basis (Scheme 13). Difunctionalized products were produced in minor amounts under these conditions and are not used in the calculation of the 2°:1° selectivity.

While previous findings indicated that the reaction of iodate/ chloride with methane in acetic acid produces MeOAc,<sup>57</sup> recent results show that the MeOAc formed under these conditions is the result of reaction with acetic acid and not methane functionalization. Pressurizing a mixture of KCl and NH<sub>4</sub>IO<sub>3</sub> in HOAc with argon, rather than methane, gave MeOAc yields statistically identical with those for reactions with methane (Scheme 14). Furthermore, GC-MS analysis of a reaction with perprotiomethane in acetic acid- $d_4$  indicated that the fully deuterated product  $CD_3CO_2CD_3$  accounts for > 90% of MeOAc production, while the product that would arise from methane functionalization,  $CD_3CO_2CH_3$ , accounts for < 2%. Consistent with these observations, UV-vis analysis indicates that Cl<sub>2</sub> and ICl/ICl<sub>3</sub>, which have been proposed as the reactive intermediate species, are not produced in HOAc (Figure 7, overlaid with data in HTFA for comparison).

The experimental results reported herein are consistent with recent computational efforts that indicate that the HIAO system might proceed through a pathway that involves free radical intermediates.<sup>79</sup> The computational modeling predicts that transient intermediates  $IO_2Cl_2^-$  and  $IOCl_4^-$  are formed, which can lead to the formation of  $IO_2^{\bullet}$  and  $Cl^{\bullet}$  radicals (Scheme 15). Both  $IO_2^{\bullet}$  or  $Cl^{\bullet}$  are capable of abstracting a hydrogen atom from methane, and the methyl radicals are predicted to react with iodine to give MeI, which is converted to MeTFA and protected from overoxidation.

The reduction of iodate should produce water during the hydrocarbon functionalization process. In order to probe for the production of water experimentally, the change in the chemical shift of the HTFA <sup>I</sup>H NMR resonance was analyzed for a series of DTFA/H<sub>2</sub>O mixtures using methylene chloride as the internal standard. As the water concentration increases, the resonance due to HTFA shifts upfield (Figure S20). The methane functionalization reaction was then performed in DTFA. Following the functionalization reaction, methylene chloride was added as an internal standard, and the reactions were analyzed by <sup>1</sup>H NMR spectroscopy. In each of the three trials, the resonance was observed from  $\delta$  10.32 to 10.33 ppm, corresponding to a solution with approximately 1.6 mmol of  $H_2O$ . This corresponds to an ~28% yield of  $H_2O$  based on the starting amount of iodate (note that 100% yield of H<sub>2</sub>O is achieved through formation of 3 equiv of H<sub>2</sub>O per equivalent of iodate).

These data indicate that HIAO likely occurs by a pathway that involves free radicals. Scheme 16 shows a simplified reaction scheme based on our combined computational and experimental studies. While this does not include all intermediates or reactions predicted to be present or occurring in situ, it is useful as an overall representation of the proposed key intermediates and transformations for HIAO. We propose that chloride is oxidized to chlorine, which is homolytically cleaved to give chlorine radicals that can abstract a hydrogen atom from an alkane to give alkyl radical and HCl. In addition, C–H bond breaking by  $IO_2^{\bullet}$  is possible. The alkyl radical reacts with iodine, formed in situ, to give alkyl iodide, which converts to protected alkyl esters in HTFA. The HIAO process differs from traditional chlorination processes in that the chloride is catalytic for the HIAO process rather than stoichiometric.

Unlike traditional radical-based alkane functionalization, HIAO exhibits good selectivity at reasonable conversions for the monofunctionalized product. This is demonstrated by the stability of RTFA (R = Me, Et) under the reaction conditions (Figures 3 and 4). Despite the C–H bond energy of MeTFA

Scheme 13. Product Yields with Respect to Propane for the Reaction of  $KCl/NH_4IO_3$  or N-Chlorosuccinimide (NCS) and Benzoyl Peroxide in HTFA at 120 °C<sup>a</sup>



<sup>a</sup>Approximate yields are shown with respect to propane (~9 mmol). Difunctionalized products were not used in the calculation of 2°:1° selectivity.





Figure 7. UV–vis spectra of mixtures of KCl (0.10 mmol) and  $NH_4IO_3$  (1 mmol) in 3 mL of HTFA or HOAc.

Scheme 15. Likely Intermediates Determined from Computational Modeling (in Blue) Reacting with Iodine Radical To Give Cl<sup>-</sup> and Two Species That Are Predicted to Activate Methane C-H Bonds under the HIAO Reaction Conditions (in Red)



Scheme 16. General Overview Depicting the Catalytic Nature of Chloride in the HIAO Process<sup>*a*</sup>



<sup>*a*</sup>Possible hydrogen atom abstraction from RH by IO<sub>2</sub> radical has been omitted for clarity, but according to computational modeling the IO<sub>2</sub> radical is a possible intermediate.

being 2.3 kcal/mol lower than that of methane,<sup>79</sup> MeTFA consumption is relatively slow. *The most fundamental advance*-

ment of the study is that this free-radical-based C–H bond functionalization method protects the mono-oxidized product from overoxidation.

Such a protecting effect might find application in other strategies for hydrocarbon oxidation. Importantly, the reactivity is not merely a facet of the C-H bond energy. The reaction rate varies inversely with C-H bond energy, as the weaker internal C-H bond of propane appears to react more rapidly than the stronger terminal C-H bond.<sup>57</sup> Rather, the influence of the ester functionality appears to be more nuanced than just reducing the C-H bond energy. We interpret the effect of TFA as a protecting group to overoxidation to possibly be a manifestation of the polar effect, as discussed originally by Walling et al.<sup>80</sup> Thus, while for the HIAO process the explanation of this effect is not yet entirely clear, the TFA group could serve to reduce the polarity of the transition state (compare the expected polarity of TFA-C(H)<sub>2</sub>...H...Cl vs that of H<sub>3</sub>C···H···Cl), which can result in an increase in the activation barrier relative to the more polar transition state for H atom abstraction from the alkane.<sup>81</sup> Recent treatments using DFT have shown dramatic effects (~10 kcal/mol) of strongly electron withdrawing substituents on energy barriers for C-H hydrogen abstraction by chlorine atoms.<sup>82</sup> Thus, the protecting effect that we have observed might be extended to other conditions, suggesting the potential for broad impact for radical-based alkane functionalization processes.

#### SUMMARY AND CONCLUSIONS

Our new experimental results are consistent with the oxidation of hydrocarbons using mixtures of chloride and iodate proceeding through a pathway that involves the generation of free radicals, chlorine, and  $IO_2^{\bullet}$ , which are likely responsible for homolytic C-H bond cleavage. The oxidation of adamantane by KCl/NH<sub>4</sub>IO<sub>3</sub> in acetic acid shows both product selectivity and C-H/C-D deuterium KIEs similar to those of radical chlorination under similar reaction conditions. Additionally, the reaction of alkyl radicals with molecular iodine, generated in situ under the HIAO reaction conditions, is likely facile even under aerobic conditions, suggesting that the presence of oxygen does not influence the reaction. The high selectivity of the HIAO process for the mono-oxidized product is particularly notable, given its likely operation through a free-radical-based pathway. The protection of the mono-oxidized alkyl ester from further oxidation is crucial in order to obtain both high selectivity and high yields on the basis of the starting light alkane.

#### EXPERIMENTAL SECTION

*Caution*! Many of the reagents and conditions described herein are potentially hazardous.<sup>83</sup> Appropriate safety procedures should be consulted prior to handling concentrated acids, strong oxidants, and mixtures of hydrocarbon substrates and oxygen.

Materials. Unless indicated otherwise, all reactions were carried out under ambient atmosphere. Adamantane, potassium chloride, ammonium iodate, tert-butyl hydroperoxide, iodine, trifluoroacetic acid, glacial acetic acid, propionic acid, trifluoroacetic anhydride, methyl trifluoroacetate, ethyl trifluoroacetate, ethyl iodide, methyl iodide, cyclopentane, chloroform, dichloromethane, dodecane, trifluoroacetic acid-d, acetic acid- $d_4$ , benzene- $d_6$  and benzoyl peroxide were purchased from commercial sources and used without further purification. N-Chlorosuccinimide was purchased commercially and recrystallized from glacial acetic acid prior to use. Methane, ethane, propane, and argon were purchased from GTS-Welco and used as received. Authentic standards of adamantyl ester products were prepared by published literature methods from the commercially available alcohols.<sup>84</sup> GC-MS analysis was performed using an Agilent Technologies 7890A gas chromatograph equipped with a fused silica column and electron impact mass analyzer or using a Shimadzu GCMS-QP2010 Plus system with a 30 m  $\times$  0.25 mm SHRXI-5MS column with 0.25  $\mu$ m thickness using electron impact ionization. NMR analysis was performed using a Bruker 300 Avance, Avance III 800, Avance III 600, or Avance DRX-600 or a Varian Inova 500 spectrometer. NMR data of reaction mixtures from methane and ethane functionalization reactions were obtained using neat HTFA or HOAc with a capillary of C<sub>6</sub>D<sub>6</sub> as an internal lock reference. Chemical shifts for <sup>1</sup>H NMR are reported relative to the internal standards of HOAc ( $\delta$  2.04), nitromethane ( $\delta$  4.18) or dichloromethane ( $\delta$  5.03). UV–vis spectra were collected on a Carey Varian Bio 300 UV-vis spectrophotometer.

Oxidation of Adamantane Using Ammonium lodate and Potassium Chloride in Acid. In a typical reaction, an 8 mL microwave vial equipped with a stir bar was charged with ammonium iodate (1 mmol), adamantane (1 mmol), and potassium chloride (0.15 mmol). Neat acid (4 mL) was then added to the solution and the vial sealed with a crimp cap. The vials were then heated in an oil bath at 180 °C for 1 h with vigorous stirring (1150 rpm). After 1 h, the reaction mixture was cooled to room temperature and was subsequently added to a solution of dodecane (1 mmol) in chloroform (5 mL). This mixture was then extracted twice with 10 mL of water, and the organic washings were dried over MgSO<sub>4</sub>. The mixture was then analyzed via GC-MS, and the yields of adamantyls were determined relative to dodecane, the added internal standard. Each reaction condition was repeated a minimum of three times with the average of all reactions reported.

Chlorination of Adamantane with *N*-Chlorosuccinimide. Chlorination of adamantane was carried out according to a literature procedure.<sup>85</sup> An 8 mL microwave vial equipped with a stir bar was charged with adamantane (1 mmol), *N*chlorosuccinimide (1 mmol), and benzoyl peroxide (0.01 mmol, to act as a radical initiator) and sealed with a crimp cap equipped with a Teflon septum. The vial was then flushed with argon for 20 min. Glacial acetic acid (4 mL), which had been degassed by refluxing under Ar(g) for 1 h, was then added via syringe. The sealed vial was then heated to 180 °C for 1 h in an oil bath with vigorous stirring (1150 rpm). After 1 h, the reaction mixture was cooled to room temperature and was subsequently added to a solution of dodecane (1 mmol) in chloroform (5 mL). This mixture was then extracted twice with 10 mL of water, and the organic washings were dried over MgSO<sub>4</sub>. The mixture was then analyzed via GC-MS, and the yields of adamantyls were determined relative to dodecane, the added internal standard. Each reaction condition was repeated a minimum of three times with the average of all reactions reported.

Synthesis of tert-Butyl Peroxypropionate. The title compound was synthesized by adapting the method described by Yur'ev and co-workers.<sup>86</sup> A 100 mL round-bottom flask equipped with a stir bar was charged with CDCl<sub>3</sub> (5 mL) and propionic acid (5 mmol). The mixture was cooled to 0 °C, and pyridine (5 mmol) was added dropwise to the vigorously stirred solution. The solution was then stirred at 0 °C for 15 min. Then, tert-butyl hydroperoxide (3 mmol) and pyridine (5 mmol) were added dropwise to the stirred solution in sequence. The solution was stirred for 45 min and then slowly warmed to room temperature. The solution was then washed with saturated aqueous sodium bicarbonate  $(3 \times 5 \text{ mL})$  and 1 M HCl  $(2 \times 5 \text{ mL})$ , and the organic washings were dried over MgSO<sub>4</sub>. The solution was then concentrated in vacuo (behind a blast shield) to yield the title compound. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz,  $\delta$ ): 2.27 (q, CH<sub>3</sub>CH<sub>2</sub>CO<sub>3</sub>C(CH<sub>3</sub>)<sub>3</sub>, <sup>3</sup>J<sub>HH</sub> = 8 Hz, 2H), 1.25 (s,  $CH_3CH_2CO_3C(CH_3)_3$ , 9H), 1.13 (t,  $CH_3CH_2CO_3C(CH_3)_3$ ,  $^3J_{HH} = 8$  Hz, 3H).  $^{13}C$  NMR (CDCl<sub>3</sub>, 125 MHz,  $\delta$ ): 172.1 (CH<sub>3</sub>CH<sub>2</sub>CO<sub>3</sub>C(CH<sub>3</sub>))<sub>3</sub>, 83.6  $(CH_3CH_2CO_3C(CH_3))_{3_2}$  26.4  $(CH_3CH_2CO_3C(CH_3))_{3_2}$  25.0  $(CH_3CH_2CO_3C(CH_3))_{3}$ , 9.5  $(CH_3CH_2CO_3C(CH_3))_{3}$ .

**Pyrolysis of** *tert***-Butyl Peroxypropionate in the Presence of lodine.** A J. Young NMR tube was charged with *tert*-butyl peroxypropionate (0.1 mmol), iodine (0.05 mmol), cyclopentane (0.05 mmol as internal standard), and acetic acid- $d_4$  (1 mL). The NMR tube was sealed and heated in an oil bath at 180 °C for 1 h. The mixture was cooled to room temperature and analyzed by <sup>1</sup>H NMR spectroscopy. Ethyl iodide production was quantified relative to the integration of the cyclopentane internal standard, and the presence of ethyl iodide was confirmed by spiking the reaction with an authentic standard of ethyl iodide. This reaction was repeated four times, and the yield was reported as an average of the four trials.

Intermolecular KIE Determination for the Functionalization of Adamantane by N-Chlorosuccinimide/Benzoyl Peroxide and KCl/NH<sub>4</sub>IO<sub>3</sub>. Intermolecular KIEs for functionalized adamantyl products were determined by performing the reactions in the presence of a 1:1 stoichiometric ratio of perprotioadamantane (0.5 mmol) and perdeuterioadamantane (0.5 mmol). Only 20 mol % of oxidant relative to the total molar amount of substrate was added to make sure that conversion was kept below 20%. The intermolecular deuterium KIE was then obtained by determining the ratio of protio product to deuterio product using GC-MS. The reported KIE ratio is the average of at least three individual experiments.

Oxidation of Ethane with the lodate/Chloride System in Acetic Acid. In air, a custom-built stainless steel pressure reactor with a Teflon liner<sup>57,58</sup> was charged with  $NH_4IO_3$  (7.7 mmol), KCl (0.67 mmol), HOAc/Ac<sub>2</sub>O (8.0 mL, 19:1 v/v), and a stir bar. The reactor was sealed, purged with Ar, and subsequently pressurized to 300 psi with ethane. After the mixture was stirred (800 rpm) at 180 °C for 1 h, the reactor was cooled to room temperature. The reactor was carefully vented, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. Using a standard of methylene chloride, 0.31(3) mmol of EtOAc, 0.27(1) mmol EtCl, 0.06(1) mmol EtI and 0.46(9) mmol MeOAc were detected. This procedure was performed in triplicate.

Consumption of Functionalized Products (RI and RTFA) under HIAO Conditions. A custom-built stainless steel pressure reactor with a Teflon liner<sup>57,58</sup> was charged with RI or RTFA (1 mmol, R = Me, Et), NH<sub>4</sub>IO<sub>3</sub> (7.7 mmol), KCl (0.67 mmol), HTFA (8.0 mL), and a stir bar. The reactor was sealed and pressurized with 100 psi of Ar. After the mixture was stirred (800 rpm) at 180 °C for 20 min, the reactor was cooled to room temperature. The reactor was carefully vented, and nitromethane was added as an internal standard. The reaction mixture was stirred, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. This procedure was performed in triplicate.

**Oxidation of Propane with KCI/NH<sub>4</sub>IO<sub>3</sub>.** In air, a custombuilt stainless steel pressure reactor with a Teflon liner<sup>57,58</sup> was charged with NH<sub>4</sub>IO<sub>3</sub> (7.7 mmol), KCl (0.67 mmol), HTFA (8.0 mL), and a stir bar. The reactor was sealed and pressurized with 100 psi of propane. After the mixture was stirred (800 rpm) at 120 °C for 30 min, the reactor was cooled to room temperature. The reactor was carefully vented, and acetic acid was added as an internal standard. The reaction mixture was stirred, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. This procedure was performed in triplicate.

Oxidation of Propane with N-Chlorosuccinimide and Benzoyl Peroxide. A custom-built stainless steel pressure reactor with a Teflon liner<sup>57,58</sup> was charged with Nchlorosuccinimide (7 mmol), benzoyl peroxide (0.07 mmol), HTFA (8.0 mL), and a stir bar in the glovebox. HTFA was heated to reflux for 1 h under N<sub>2</sub> prior to being added to the reactor. The reactor was sealed and pressurized with 100 psi of propane. After the mixture was stirred (800 rpm) at 120 °C for 30 min, the reactor was cooled to room temperature. The reactor was carefully vented, and acetic acid was added as an internal standard. The reaction mixture was stirred, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. This procedure was performed in triplicate.

Calibration Curve for Quantification of Water Production. A series of DTFA (99.5% D)/H<sub>2</sub>O mixtures were made by serially diluting a 50 mol% H<sub>2</sub>O and DTFA solution (Figure S20). Each was placed in an NMR tube with a  $C_6D_6$  capillary, and dry dichloromethane was added as an internal standard, referenced to  $\delta$  5.03 ppm. These were analyzed by <sup>1</sup>H NMR spectroscopy using the  $C_6D_6$  capillaries as internal lock references. The shifts of the TFA resonances varied as a function of the water concentration. A control with neat DTFA was also analyzed and referenced to dichloromethane. This calibration curve was used to determine the amount of water that was produced from methane functionalization by HIAO in DTFA.

**Methane Functionalization Reaction in DTFA.** A scaleddown methane functionalization reaction (100 psi of  $CH_4$ , 0.17 mmol of KCl, 1.9 mmol of  $NH_4IO_3$ , 2 mL of DTFA) was run in triplicate using DTFA from the same ampule. The reactors were heated at 180 °C for 1 h and the mixtures stirred at 800 rpm. Dichloromethane was added as an internal standard after the reaction. The reaction mixtures were analyzed as in previously mentioned light alkane functionalization reactions, using a  $C_6D_6$  capillary as an internal lock reference. The volumes of the reaction mixtures following the reaction were also measured. The calibration curve discussed above was used to determine the mole percent of added water on the basis of the chemical shift of the TFA resonance. To determine the amount of water that was produced, the total volume of the mixture following the reaction was measured and used to calculate an amount using the mole percent obtained from the calibration curve.

Oxidation of Methane with *N*-Chlorosuccinimide and Benzoyl Peroxide with or without Added Iodine. A custom-built stainless steel pressure reactor<sup>57,58</sup> was charged with *N*-chlorosuccinimide (3.5 mmol), benzoyl peroxide (0.035 mmol), HTFA (8.0 mL), iodine (0.0335, 0.067, 0.335, or 0.67 mmol, if added), and a stir bar in the glovebox. HTFA was heated to reflux for 1 h under N<sub>2</sub> prior to being added to the reactor. The reactor was sealed and pressurized with 500 psi of argon. After the mixture was stirred (800 rpm) at 180 °C for 1 h, the reactor was cooled to room temperature. The reactor was carefully vented, and acetic acid was added as an internal standard. The reaction mixture was stirred, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. This procedure was performed in triplicate.

**Consumption of MeTFA under Radical Chlorination Conditions.** A custom-built stainless steel pressure reactor<sup>57,58</sup> was charged with *N*-chlorosuccinimide (3.5 mmol), benzoyl peroxide (0.035 mmol), HTFA (8.0 mL), and a stir bar in the glovebox. HTFA was heated to reflux for 1 h under N<sub>2</sub> prior to being placed in the reactor. The reactor was sealed and pressurized with 500 psi of argon. After the mixture was stirred (800 rpm) at 180 °C for 1 h, the reactor was cooled to room temperature. The reactor was carefully vented, and acetic acid was added as an internal standard. The reaction mixture was stirred, and an aliquot was removed and centrifuged for <sup>1</sup>H NMR analysis. This procedure was performed in triplicate.

**Conversion of Adamantyl Esters in Acid.** A custom-built stainless steel pressure reactor<sup>57,58</sup> was charged with the secondary adamantyl ester (trifluoroacetate or acetate) and 4 mL of the corresponding acid (HTFA or glacial HOAc). The reactor was sealed and pressurized with 100 psi of argon. After the mixture was stirred (800 rpm) at 180 °C for 15 min, the reactor was cooled to room temperature. The reactor was carefully vented, and nitromethane was added as an internal standard. The reaction mixture was stirred, and 5 mL of DCM was added. The reaction mixture was then washed with water (2 × 10 mL), and the organic washings were dried over MgSO<sub>4</sub>. The mixture was then analyzed via GC-MS. Each reaction condition was performed three times.

#### ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b04397.

UV/vis spectra, representative GC traces and <sup>1</sup>H NMR spectra, standard curves for the determination of water and iodine concentrations, and GC-MS fragmentation data (PDF)

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#### Notes

The authors declare no competing financial interest.

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