Metal-Free, Selective Alkane Functionalizations

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Abstract: The present overview of alkane functionalization reactions presents comparisons between radical and metal-initiated (sometimes metal-catalyzed) methodologies. While metal-catalyzed processes are excellent approaches to this problem, metal-free alternatives are equally if not, at least from an environmental and cost perspective, more useful. This conclusion is supported by the fact that many so-called metal-catalyzed reactions also work without the metal present, and the large variety of metals showing the same product distributions emphasizes that the metal often just aids in the generation of the active species, i.e., the metal itself is *not* participating in the crucial C–H activation step. Highly selective alkane functionalization reactions such as those derived from nitroxyl and related radicals as well as through radical reactions conducted in phase-transfer catalyzed systems are available but generally underutilized. These systems, in contrast to typical metal-catalyzed approaches, are also applicable to highly strained alkanes and offer the highest 3°/2° C–H selectivities reported to date in a radical reaction. The article closes with representative experimental protocols for the PTC bromination of cubane as an example of the applicability of this method to strained hydrocarbons and the direct iodination of cyclohexane as well as adamantane as typical alkanes bearing secondary and tertiary C–H bonds.

Keywords: alkanes; C–H activation; halogenation; organocatalysis; oxidation; radical reactions; selectivity

1 Introduction

From a polarizing and provocative view one may say that, despite enormous efforts and significant progress in terms of mechanistic understanding, the preparatively useful liquid-phase functionalization of alkanes has not reached the stage of many other sophisticated transformations that are also applicable in industry on a large scale: they are either confined to simple chemistry of the last millennium or they are exclusively thermodynamically controlled.[1] There is certainly no doubt that the controlled substitution of an aliphatic C–H bond *is* a problem of global importance, a "holy grail" of chemistry as noted by Bard, Whitesides, Zare, and McLafferty in 1995.[2,3] Most research is aimed at the use of metals to tackle this problem, and this approach derives from several important considerations. First, metals can be varied in their reactivity by ligand design; chiral ligands may even lead to enantiomerically enriched products. Second, many metals *do* insert into unactivated C–H bonds,[3–9] and they often do it in a controlled and predictable fashion.[10] Third, Nature utilizes metals for hydrocarbon oxidation so there is good reason to mimic Nature's arsenal with chemical methods. As we will show in the present overview, many reactions claimed to be metal-catalyzed, produce similar results when either a different metal is used (non-specificity) or even in the absence of a metal! As we will argue, the metal often helps generate the reactive species, e.g., a hydroxyl radical in the presence of H_2O_2, and it is the follow-up chemistry of this intermediate that is being observed, independent of its method of generation. Many transition metal C–H activation reactions are oxygen- and water-sensitive

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The picture shows the two authors on a wooden platform amidst the Okefenokee Swamp in Southern Georgia, a wonderful refuge for wildlife and chemistry professors.

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and, above all, sometimes involve very expensive and poisonous metals. Some of these arguments also affect the industrial applicability: high-temperature radical or even surface-catalyzed reactions are easy to carry out on a large scale; transition metal complexes are much more difficult to handle, often require far more costly waste-water treatment, and do not scale up well in many cases.

On the other hand, Nature also accomplishes C–H oxygenations *without* metals in a highly selective fashion,[11] indicating that the role of the metal is by no means crucial (albeit useful). In short, the spectrum of possibilities for activating alkane C–H bonds is broad but has not been explored to the full, and this is particularly true for methods not relying on metal catalysis.

Superacid[12] and much of cationic zeolite chemistry (notable exceptions not involving cations are known)[13] for the functionalization of alkanes is hampered by the fact that carbonium or carbenium ions are involved.

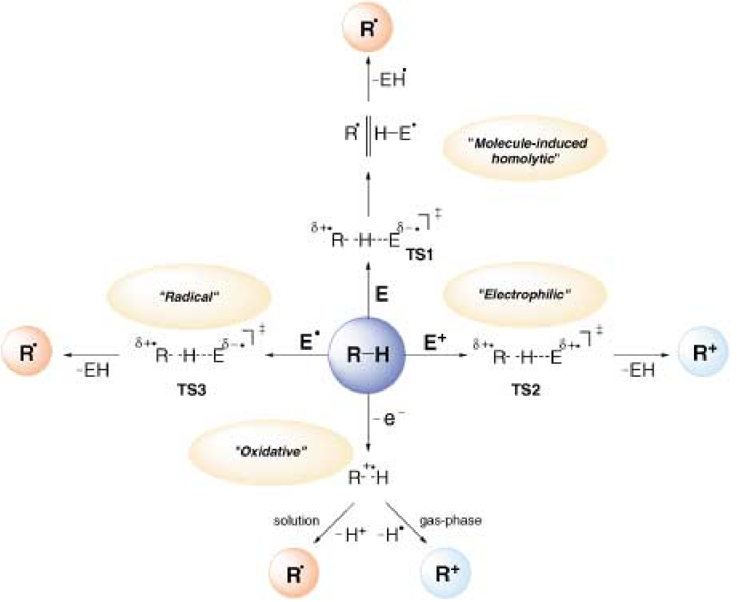
The present brief overview has the following structure. We begin by summarizing some common approaches for the alkane activation problem. These include radical transformations in the gas phase, followed by a larger chapter on radical oxygenations in the condensed state; comparisons between metallic and non-metallic approaches are made. We close with radical halogenations and emphasize our newly developed concept of combining radical chemistry initiated by single-electron transfer (SET) with phase-transfer catalysis. The latter approach is simple, scaleable, and broadly applicable. We close with representative examples and experimental procedures for these highly selective, preparatively useful alkane halogenations.

2 Background

Despite enormous efforts, alkane functionalizations with heavy metals like platinum[9,14] and mercury,[15] or through oxidative additions of bare metals[16] as well as transition metal complexes,[8] are still far from industrial utilization. As usual, Nature is much more advanced and a number of enzymes accomplish selective alkane oxygenations (e.g., with cytochrome P-450,[17] methane monooxygenase[18] and others[19]). The high-valent metal-oxo moieties are typically held responsible for the highly selective C–H activation step; however, enzymatic alkane chemistry still is not feasible preparatively partly because of our limited mechanistic understanding.[17,20] It is not entirely clear what kind of mechanism (radical, polar or concerted) is followed; the most recent two-state reactivity model[21] offers up-to-date explanations for a number of experimental observations. Nevertheless, tailoring enzymatic transformations with metal-based catalytic systems still is problematic.[22,23] Unsuccessful attempts to reproduce enzymatic processes by metal catalysis with oxygen or peroxides under GIF[24,25] or Fenton[26,27] conditions leave much to be discussed[28,29] in view of the fact that the C–H selectivities in these systems are similar to the conventional free-radical reactions of oxygen-centered radicals.[30,31] Radical reactions have a bad reputation for being not particularly selective although this picture has been changing dramatically over the last decade or so; stereoselective additions to double bonds and selective follow-up reactions are now commonplace.[32] C–H bond activations with radicals, however, have not witnessed the same pace of improvements.

Electrophilic alkane conversions may be good alternatives to radical chemistry, but they usually require environmentally unfriendly strong inorganic Brønsted or Lewis acids,[33] or even superacids.[12,34] As noted before, these approaches are thermodynamically predetermined; access to non-thermodynamically favorable (e.g., functionalization of highly strained hydrocarbons without rearrangements) paths is generally not possible. Thermodynamically driven products form from the most stable cationic intermediates. As we pointed out recently,[35] the overall *functionalizations* in such systems are selective (giving one predictable and well-defined product), while the *activations* are not (various starting materials give the same thermodynamic product through a series of rearrangements). Functionalizations in the presence of oxidizing electrophiles[12,34,36] are quite selective, but they are limited to a small number of reagents and are only applicable to the more reactive hydrocarbons. Selective single-electron transfer alkane oxidations are only possible with strong electron acceptors[37] and when structurally distinct alkane radical cations form.[35,38]

Mechanistic studies of alkanes reacting with electron-deficient species reveal common mechanistic features arising from the formation of radical-cationic transition states or intermediates.[35] The recently suggested[38,39] H-coupled electron transfer mechanistic model agrees well with the experimental features of alkane halogenations with electrophiles and may be extended to a wide range of alkane transformations: from uncharged metal-oxo species[40] and, possibly, dioxiranes[41,42] ("molecule induced homolytic" path, **TS1**, Scheme 1) to charged electrophiles like nitronium salts ("electrophilic" path



Scheme 1. Alkane C–H bond activation mechanisms with uncharged (**E**) and charged (**E**$^+$) electrophiles as well as with radicals (**E**$^\bullet$) and electron-acceptors (– **e**$^-$).

TS2, Scheme 1). The selectivities of these reactions are controlled by the charge transfer from the hydrocarbon to the electrophile through the C–H–E bonding arrangement in the transition structures. The selectivities often are similar[35,38] to those observed for alkane oxidations *via* SET ("oxidative" path, Scheme 1).[43]

It may be concluded that radical chemistry still is the preparatively most useful approach for alkane functiuonalizations. As the selectivities of radical reactions ("radical" path, **TS3**, Scheme 1) often are traced back to polar effects (especially with electrophilic radicals),[44] one may argue that the same is true for electrophilic alkane activations where the selectivities are also controlled by charge (electron) transfer. In other words, alkane activations with different electron-deficient reagents fit into the same mechanistic regime.[35] Exceptions *may* be C–H bond cleavages promoted by electron-deficient metal complexes where the occupied *d*-orbitals of the metal may be involved in agostic C–H bonding;[45] this usually inverts the 1° *vs.* 2° selectivities.[7] The activations of alkanes with transition metal complexes were the subject of a number of excellent recent reviews[6–8,17,46] and we will not cover these here.

3 Discussion

3.1 Radical Functionalizations of Alkanes in the Gas Phase

The chlorination of simple alkanes with elementary chlorine is one of the oldest organic reactions[47] and still is used industrially for methane.[5] This reaction is also important for atmospheric[48] and materials chemistry (growth of diamond films).[49] Owing to its simplicity it is also "attractive" for theoreticians:[50] The first true example of a vibrationally-controlled organic reaction was recently demonstrated with the reaction of $CH_4 + Cl^{\bullet}$.[51] Gas-phase oxygenations of methane mostly give CO_2 as well as CO, and only traces of the desired CH_3OH.[52] More reactive alkanes form a number of products as shown for 2,3-dimethylbutane even under mild conditions (Table 1, Entry 1). The selectivities of the oxygenations rise substantially in the presence of nitrogen oxides (Entry 2) but still are below 10%. The reaction of cyclohexane under similar conditions is unselective (Entry 3) because of fragmentations.

Direct imination of small alkanes in the gas phase was developed using alkane/NH_3 mixtures under irradiation in the presence of Hg vapor, that generates NH_2 radicals from Hg*/NH_3 exciplexes.[53] The reaction involves an $R{-}H + NH_2^{\bullet} \rightarrow R^{\bullet} + NH_3$ activation step; a mixture of products forms after recombination of the alkyl radicals that dynamically circulate through the photolytic chamber and the cold trap. Although this reaction might have practical applications, quite a number of C_1 to C_4 imines form in a static reactor (Entries 4 and 5). The aminations with methylamine generally are more selective giving only alkane dimerization by-products (Entry 6).

3.2 Radical Oxyfunctionalizations of Alkanes in the Condensed State

Traditional approaches for alkane oxyfunctionalizations are based on metal-catalyzed decompositions of hydrogen peroxide or oxygen in the presence of an alkane.[26,57] Such systems are still being thoroughly examined because they mimic the natural enzymatic processes with oxygenases.[27] The long-standing discussion about the radical *vs.* metal-oxo chemistry in Fenton- and GIF-like systems continues,[27,28,58] although most data provide evidence for the participation of oxygen-centered radicals in the C–H activation step.[26]

Functionalizations promoted by oxygen or H_2O_2 are usually unselective because of the formation of highly reactive OH-radicals. Table 2 presents some recent data showing that the original problem for such oxidizing systems still exists: The yields for the oxidations of small alkanes are low (Entries 1–3); the selective oxygenation of cyclohexane is still problematic with relatively new iron (Entry 4), tungsten (Entry 5), or copper (Entry 6) catalysts. The selectivity of the 3° *vs.* 2° C–H oxidation of adamantane is negligible (Entries 7 and 8); Keggin-type complexes are only slightly more selective

Table 1. Alkane functionalizations with radicals in the gas phase.

Entry	Hydrocarbon(s)	Reacting system	Product(s)	Reaction conditions	Ref.
1	2,3-Dimethylbutane	O_2	$(CH_3)_2CHC(OOH)(CH_3)_2$ (29%), acetone (47%), others (24%)	*hν*	[54]
2	Methane	O_2/NO_2	CH_2O (43%), CO (26%), CH_3OH (23%), CH_3NO_2 (5%), (conversion 7%)	400 °C	[55]
3	Cyclohexane	O_2/NO	$c\text{-}C_6H_{10}{=}O$ (0.32%), $c\text{-}C_6H_{11}ONO_2$ (0.16%)	25 °C	[56]
4	Methane	NH_3/Hg*	$CH_2{=}NH$ (32%), higher imines (28%)	*hν*	[53]
5	Ethane	NH_3/Hg*	$CH_2{=}NH$ (39%), higher imines (60%)	*hν*	[53]
6	Cyclohexane	CH_3NH_2/Hg*	$c\text{-}C_6H_{11}NHCH_3$ (40%), $c\text{-}C_6H_{11}{-}c\text{-}C_6H_{11}$ (50%)	*hν*	[53]

Table 2. Selected examples of oxygenations of alkanes with H_2O_2 and/or O_2.

Entry	Hydrocarbon(s)	Reacting system	Product(s) [Yield(s)]	Reaction conditions	Ref.
1	Methane	$H_2O_2/[Fe_2(HPTB)(OH)(NO_3)_2]^{2+}$; HPTB = *N,N,N',N'*-tetrakis(2-benzimidazolylmethyl)-2-hydroxo-1,3-diaminopropane	CH_3OOH, $CH_2{=}O$, total yield: 0.3%	25 °C, 6 h, CH_3CN	[59]
2	Methane	$H_2O_2/SiW_{10}[Fe(OH)_2]_2O_{38}^{6-}$	CH_3OH (0.3%), CH_3COOH (10.2%), CO_2 (16.6%)	80 °C	[60]
3	Ethane	$H_2O_2/[Fe_2(HPTB)(OH)(NO_3)_2]^{2+}$; HPTB = *N,N,N',N'*-tetrakis(2-benzimidazolylmethyl)-2-hydroxo-1,3-diaminopropane	C_2H_5OOH, $CH_3CH{=}O$, total yield: 1.4%	25 °C, 6 h, CH_3CN	[59]
4	Cyclohexane	$H_2O_2/[Fe_2(HPTB)(OH)(NO_3)_2]^{2+}$; HPTB = *N,N,N',N'*-tetrakis-(2-benzimidazolylmethyl)-2-hydroxo-1,3-diaminopropane	*c*-$C_6H_{11}OOH$ (12%)	25 °C, 6 h, CH_3CN	[59]
5	Cyclohexane	$O_2/SiW_{10}[Fe(OH)_2]_2O_{38}^{6-}$	*c*-$C_6H_{11}OH$ (53%), *c*-$C_6H_{10}{=}O$ (47%), conversion: 1.1%	70 °C, 96 h, $Cl(CH_2)_2Cl$	[61]
6	Cyclohexane	$H_2O_2/[Cu(i\text{-}PrSPy_2)]^-$	*c*-$C_nH_{2n-1}OH$ (44%), *c*-$C_nH_{2n-2}{=}O$ (19%), (relative to the complex used)	25 °C, 30 min, CH_3CN	[62]
7	Adamantane	$H_2O_2/O_2/[n\text{-}Bu_4N]^+\ [VO_3]^-$/PCA; PCA = pyrazine-2-carboxylic acid	1-AdOH, 2-Ad=O; 3°:2° = 1.3	50 °C, CH_3CN	[63]
8	Adamantane	H_2O_2/O_2	1-AdOH, 2-Ad=O; 3°:2° = 1.4	*hν*, 25 °C, CH_3CN	[63]
9	Adamantane	$Na_4W_{10}O_{32}/O_2$	1-AdOOH, 2-Ad=O; 3°:2° = 5 : 1	CH_3CN, *hν*	[64]
10	Isobutane	O_2/Zeolite BaY	*t*-BuOOH (98%) (conversion: 50%)	*hν*	[65]
11	Cyclohexane	O_2/Zeolite NaY	*c*-$C_6H_{11}OOH$, *c*-$C_6H_{10}{=}O$ (conversion: 40%)	*hν*	[66]
12	Cyclohexane	$H_2O_2/H_2O/CF_3COOH$	*c*-$C_6H_{11}OC(O)CF_3$ (73%)	25 °C	[67]
13	Cyclohexane	H_2O_2/urea/CF_3COOH	*c*-$C_6H_{11}OC(O)CF_3$ (80%)	25 °C	[68]
14	Adamantane	*m*-ClC_6H_4COOOH	1-AdOH (30%), 2-AdOH (0.9%), 1-AdOC(O)C_6H_4Cl-*m* (4.6%); 3°:2° = 115	65 °C, 24 h, $Cl(CH_2)_2Cl$	[69]
15	Adamantane	PhCOOOH	1-AdOH (88%), 2-AdOH (12%); 3°:2° = 22	100 °C	[70]
16	Cyclohexane	$CH_3COOOH/CF_3COOH/RuCl_3$	*c*-$C_6H_{11}OC(O)CF_3$ (76%), *c*-$C_6H_{10}{=}O$ (13.5%)	20 °C, 4 h, CH_2Cl_2	[71]
17	Adamantane	*m*-$ClC_6H_4COOOH/[RuCl_2(TPA)]^+$	1-AdOH (10%), 2-AdOH (0.4%), 2-Ad=O (0.9%); 3°:2° = 23	25 °C, 24 h, CH_3CN	[72]

(Entry 9). The situation improves somewhat with using zeolites for the partial oxidation of alkanes with O_2 that minimizes overoxidations at relatively high alkane conversions (Table 2, Entries 10 and 11).[13] Consequently, the *selective* oxidation of cyclohexane is achieved with 40% conversion (Entry 11) which is more than four times higher than for the industrial liquid-phase metal catalyzed oxidation to *c*-$C_6H_{11}OH$ and *c*-$C_6H_{10}{=}O$.

One may conclude that the hydrogen peroxide oxidations (both metal-free and metal-catalyzed) are ineffective because OH radicals are involved in the C–H activation step. However, if H_2O_2 reacts in the presence of strong acids, the transformations are far more selective, because peracids or protonated hydrogen peroxide are involved instead.[73] As a result, cyclohexyl trifluoroacetate is the only product in the oxidation of cyclohexane with H_2O_2 in trifluoroacetic acid (Table 2, Entry 12) or in the presence of urea (Entry 13). Adamantane oxidations with peracids show 3°:2° selectivities up to 115 (Entries 14 and 15). In the presence of metal catalyst these reactions are generally *less* selective (Entries 16 and 17). The mechanistic interpretations and the origins of the selectivities are not clear yet,[74] however, the concerted mechanism of the C–H insertion of the peracid through a highly polarized transition structures is likely.[74] The mechanistic dichotomy in the reactions of alkanes with peracids, i.e., concerted

$$L_mM^{n+} + t\text{-BuOOH} \longrightarrow L_mM^{(n+1)+} + t\text{-BuO}^{\bullet} + OH^{-} \quad (1)$$

$$t\text{-BuO}^{\bullet} + R\text{–}H \longrightarrow t\text{-BuOH} + R^{\bullet} \quad (2)$$

$$R^{\bullet} + O_2 \longrightarrow ROO^{\bullet} \quad (3)$$

$$ROO^{\bullet} \longrightarrow \text{products} \quad (4)$$

$$\text{NHPI} + NO_2 \longrightarrow \text{PINO}^{\bullet} + HNO_2 \quad (5)$$

$$\text{PINO}^{\bullet} + R\text{–}H \longrightarrow \text{NHPI} + R^{\bullet} \quad (6)$$

$$R^{\bullet} + NO_2 \longrightarrow R\text{–}NO_2 \quad (7)$$

$$3\,HNO_2 \longrightarrow HNO_3 + H_2O + 2\,NO \quad (8)$$

$$2\,NO + O_2 \longrightarrow 2\,NO_2 \quad (9)$$

insertion *vs.* molecule induced homolysis[75] is somewhat reminiscent of dioxirane chemistry, where clear evidence for concerted[76] paths was identified recently.[42]

The selectivities for radical oxyfunctionalizations may also be substantially increased with the less reactive and bulky *t*-BuO radical. When generated from *t*-butyl chlorite (*t*-BuOCl) the participation of Cl radicals lowers the selectivities and even CH_3 groups are attacked (Table 3, Entry 1). More practical is the generation of the *t*-BuO radicals by photolysis of *t*-BuO–N=N–OBu-*t*[77] or from *t*-BuOOH in the presence of metal-containing catalysts (Eq. 1). Under these conditions the methyl groups remain untouched (Table 3, Entry 2).

Cyclohexane, which is a useful model hydrocarbon for testing the efficiency of oxidative systems, shows *very* similar results with *t*-BuOOH in the presence of different heavy metal-containing catalysts. The analogous oxidation products cyclohexanone (c-C_6H_{10}=O), cyclohexanol (c-$C_6H_{11}OH$) and, sometimes, cyclohexyl hydroperoxide, were obtained with Fe- (Entries 3–6), Cu- (Entries 7 and 8), Mn- (Entry 9), and Ru- (Entry 10) containing catalysts. These are only a limited number of representative examples – the literature data on such systems are massive.

However, it is agreed now that the metal does not participate in the C–H activation step (despite a number previous claims)[25,78] and that the chemistry of the *t*-BuO radical is observed (Eq. 2). For instance, the oxidation of a number of cycloalkanes with *t*-BuOOH in the presence of a metal catalyst and with *t*-BuONNOBu-*t* as the radical starter gives similar results (Entry 11). Simple biphasic Fe_2O_3 (Entry 12) or $RuCl_3$ (Entry 13) colloids behave very similarly in the oxidations of cycloalkanes with *t*-BuOOH. The ratio of the products varies slightly because of the metal-dependent decomposition (Eq. 4) of the peroxides that are transiently formed in the reaction with oxygen (Eq. 3). The c-$C_6H_{11}OH$/c-C_6H_{10}=O ratio also depends on the amount of *t*-BuOOH used (Entry 4 *vs.* 5). Surface effects are also important in cyclohexane oxidations; while the oxidation on mica gives low yields (Entry 14), the oxidation with modified zeolites (Entry 15) shows high conversions to cyclohexanone without formation of side products.

Adamantane oxidation with *t*-BuOOH gives a mixture of tertiary (1-AdOH), and secondary (2-AdOH and 2-Ad=O) products. Remarkably, the 3°:2° ratio ($\approx$9) remains almost constant with rather different catalysts (Entries 16–20). Hence, the *t*-BuO radical must be responsible for all hydrogen abstractions in these reactions. The slightly varying alcohol to ketone ratios may be explained by the different reactivities of the metal complex salts toward 1- and 2-adamantyl radicals. The 3°:2° ratio is still comparable for the oxidations on surfaces (Entry 21), but is distinctly different for *t*-BuOCl as the reagent because Cl radicals compete for the C–H bond in the abstraction step (Entry 22).

For adamantane the selectivities are virtually identical under metal-free (Entry 23) or metal-catalyzed (Entry 24) conditions in presence of aldehydes. The fact that the R–C$^{\bullet}$=O radicals generated from an aldehyde, rather than the M=O species, are responsible for the C–H activation is based on the observation that the reaction is similarly selective without the metal (Entry 25).

Recently developed catalytic radical approaches involve highly electrophilic R_2N–$O^{\bullet}$ radicals. The *N*-hydroxyphthalimide (NHPI) catalyzed alkane nitration with NO_2 under oxygen atmosphere involves the phthalimide *N*-oxyl (PINO) radical generated *via* hydrogen abstraction from NHPI (Eq. 5).[98] The H-abstraction from the hydrocarbon regenerates NHPI (Eq. 6) and the recombination of $R^{\bullet}$, thus formed with NO_2 (Eq. 7) completes the cycle. HNO_2 produced at the first step regenerates NO_2 in the presence of oxygen (Eqs. 8 and 9).

Functionalizations with the NHPI/NO_2/O_2 system are the first examples of *catalytic* selective nitrations of alkanes under mild conditions and they may be applied to linear (Table 4, Entry 1), cyclic (Entries 2 and 3), as well as polycyclic (Entry 4) hydrocarbons. The selectivity for the adamantane nitration is exceptionally high as only 1-nitroadamantane forms (Entry 4). These selective oxidations are possible in the NHPI/O_2 system due to the involvement of the electrophilic PINO radical in the activation step that gives 1-AdOH as the sole product (Table 4, Entries 5 and 6), albeit only in low to moderate yields. This is in marked contrast to the metal-catalyzed aerobic oxidations of adamantane where both 3° and 2° positions are attacked (Table 2). Attempts to increase the reaction rates by running the NHPI/O_2 oxidations in the presence of metals *lower* the selectivities. For instance, the NHPI/O_2/Co(acac)$_2$ oxidation of adamantane at different temperatures gives 8–9% of adamantan-2-one (Table 4, Entries 7 and 8). For other

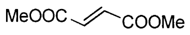
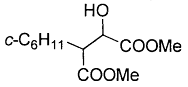
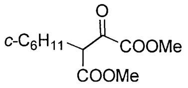
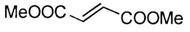
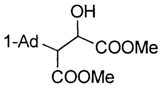
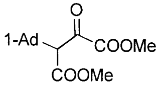
Table 3. Oxygenations of alkanes involving the *t*-BuO radical.

Entry	Hydrocarbon(s)	Reacting system	Product(s) [Yield(s)]	Reaction conditions	Ref.
1	*n*-Hexane	*t*-BuOCl/Cl_2/Alk_3B	$C_6H_{13}Cl$; 2°:1° = 12–13	20 °C	[79]
2	*n*-Hexane	*t*-BuOOH/[Ti(*i*-PrO)$_4$]	*sec*-$C_6H_{13}OH$; mixture 1:1 (8%)	20 °C, 1 h, MeCN	[80]
3	Cyclohexane	*t*-BuOOH/[Fe(PMA)]$^{2+}$; PMA = (2-pyridylmethyl)amine	*c*-$C_6H_{11}OH$ (10%), *c*-C_6H_{10}=O (9%), *c*-C_nH_{2n-1}OO*t*-Bu (3%) (based on *t*-BuOOH)	25 °C, CH_3CN	[23]
4	Cyclohexane	*t*-BuOOH (150 equiv. excess)/[$Fe_2O(TPA)_2(H_2O)_2$]$^{4+}$; TPA = *tris*(2-pyridylmethyl)amine	*c*-$C_6H_{11}OH$ (18%), *c*-C_6H_{10}=O (9%), *c*-C_6H_{11}OO*t*-Bu (21%); conversion: 18% (based on *t*-BuOOH)	25 °C, CH_3CN	[81]
5	Cyclohexane	*t*-BuOOH ($<$ 20 equiv. excess)/[$Fe_2O(TPA)_2(H_2O)_2$]$^{4+}$; TPA = *tris*(2-pyridylmethyl)amine	*c*-$C_6H_{11}OH$ (4%); conversion: 40% (based on *t*-BuOOH)	25 °C, CH_3CN	[81–83]
6	Cyclohexane	*t*-BuOOH/[Fe_2LOH]$^{3+}$; L = 1,4,10,13-tetrakis(2-pyridyl)methyl-1,4,10,13-tetraaza-7,16-dioxacyclooctadecane	*c*-$C_6H_{11}OH$ (25%), *c*-C_6H_{10}=O (29%), *c*-C_6H_{11}OOBu-*t* (11%)	25 °C, CH_3CN	[84]
7	Cyclohexane	*t*-BuOOH/[Cu(*i*-PrSPy$_2$)]$^-$	*c*-$C_6H_{11}OH$ (34%), *c*-C_6H_{10}=O (24%)	25 °C, 30 min, CH_3CN	[62]
8	Cyclohexane	*t*-BuOOH/[CuPyL]$^+$; L = tris(1-pyrazolyl)borate	*c*-$C_6H_{11}OH$ (1.3%), *c*-C_6H_{10}=O (8.5%)	25 °C, 24 h	[85]
9	Cyclohexane	*t*-BuOOH/[MnL$_2$]; L = *N,N'*-ethylenebis(salicylideneamine)	*c*-$C_6H_{11}OH$ (4%), *c*-C_6H_{10}=O (11%)	25 °C	[86]
10	Cyclohexane	*t*-BuOOH/[RuLbipy]; H_2L = *N*-(hydroxyphenyl)salicylimine	*c*-$C_6H_{11}OH$ (16%), *c*-C_6H_{10}=O (4%)	4 h, CH_2Cl_2, PT catalyst	[87]
11	Cycloalkanes (*c*-C_nH_{2n}); n = 6–8	*t*-BuOOH/[$FeCl_2TPA$]$^+$ or [$Fe_2OAcO(TPA)_2$]$^{3+}$; TPA = *tris*(2-pyridylmethyl)amine or *t*-BuOOH/*t*-BuON$_2$OBu-*t*	*c*-$C_nH_{2n-1}OH$ (0.2–8%), *c*-C_nH_{2n-2}=O (0.6–5%), *c*-C_nH_{2n-1}OO*t*-Bu (1–11%)	25 °C, CH_3CN	[88]
12	Cycloalkanes (*c*-C_nH_{2n}) n = 6–8	*t*-BuOOH/Fe_2O_3/H_2O	*c*-$C_nH_{2n-1}OH$, *c*-C_nH_{2n-2}=O, *c*-C_nH_{2n-1}OO*t*-Bu (50–70%)	50 °C, 48 h, H_2O	[89]
13	Cycloalkanes (*c*-C_nH_{2n}); n = 5–8	*t*-BuOOH/$RuCl_3$/H_2O	*c*-$C_nH_{2n-1}OH$, *c*-C_nH_{2n-2}=O, *c*-C_nH_{2n-1}OO*t*-Bu (total: 13–54%)	25–50 °C	[90]
14	Cyclohexane	*t*-BuOOH/M-exchanged fluorotetrasilicic mica M = Mn, Cr, Na, Cu, Co	*c*-$C_6H_{11}OH$ (11.2%), *c*-C_6H_{10}=O (2.2%); M = Mn^{2+}	60 °C, 48 h, benzene	[91]
15	Cyclohexane	*t*-BuOOH/Zeolite NaX/RuF$_{16}$Pc; Pc = phthalocyanine	*c*-$C_6H_{11}OH$ (1.6%), *c*-C_6H_{10}=O (98.4%) (total: 70%)	25 °C, acetone	[92]
16	Adamantane	*t*-BuOOH/$W_{11}M(L)O_{39}^{n-}$; M = Co, Fe, Cr; L = H_2O, OH^-	1-AdOH, 2-Ad=O, 2-AdOH; 3°/2° = 9.6	20 °C, 8 h, CH_2Cl_2	[93]
17	Adamantane	*t*-BuOOH/ML; M = Fe, Mn; L = tetra(2,6-dichlorophenyl)porphyrin	1-AdOH (71–72%), 2-Ad=O (8–10%), 2-AdOH (12–13%) (conversion: 8–9%) 3°:2° = 9.2–10	25 °C, 30 min, CH_2Cl_2	[94]
18	Adamantane	*t*-BuOOH/$Fe_2OL_4Y_n^{m+}$; L = 2,2′-bipyridine; 4,4′-dimethyl-2,2′-bipyridine	1-AdOH (22–24%), 2-Ad=O (3%), 2-AdOH (3–4%); 3°:2° = 9.5	30 min, CH_3CN/benzene	[95]
19	Adamantane	*t*-BuOOH/[CuPyL]$^+$; L = tris(1-pyrazolyl) borate	1-AdOH (18.1%), 2-Ad=O (6.5%), 2-AdOH (0.3%); 3°:2° = 8	25 °C, 24 h	[85]
20	Adamantane	*t*-BuOOH/[Ti(*i*-PrO)$_4$]	1-AdOH (44%), 2-Ad=O (7%), 2-AdOH (7%); 3°:2° = 9.4	20 °C, 1 h, MeCN	[80]

Table 3 (cont.)

Entry	Hydrocarbon(s)	Reacting system	Product(s) [Yield(s)]	Reaction conditions	Ref.
21	Adamantane	t-BuOOH/M-exchanged fluorotetrasilicic mica M = Mn, Cr, Na, Cu, Co	1-AdOH (26.1%), 2-Ad=O (12.7%), 2-AdOH (0.7%); M = Mn^{2+}; 3°/2° = 6	60 °C, 48 h, benzene	[91]
22	Adamantane	t-BuOCl	1-AdCl (48%), 2-AdCl (52%); 3°:2° = 2.7	hν, CH_2Cl_2	[96]
23	Adamantane	t-BuOOH/3-methylbutanal/O_2	1-AdOH (78%),1,3-Ad(OH)$_2$ (10%), others (12.2%)	25 °C, 70 h	[97]
24	Adamantane	t-BuOOH/3-methylbutanal/O_2/M(acac)$_2$; M = Pd, Co, Fe, Ni, Mn, Cu	1-AdOH (66–77%), 1,3-Ad(OH)$_2$ (12–18%), others (0–13%)	25 °C, 70 h	[97]
25	Adamantane	C_6H_5CHO/O_2	1-AdOH (84%), 2-AdOH (1.4%), others (12%)	70 °C, 24 h	[69]

Table 4. Oxygenations of alkanes involving PINO radicals generated from *N*-hydroxyphthalimide (NHPI).

Entry	Hydrocarbon	Reacting system	Product(s) [Yield(s)]	Reaction conditions	Ref.
1	*n*-Hexane	NHPI/NO_2/O_2	1-$C_6H_{13}NO_2$, 2-$C_6H_{13}NO_2$, 3-$C_6H_{13}NO_2$ (54% in total); 2°:1° = 24	70 °C, 14 h	[98]
2	Cyclohexane	NHPI/NO_2/O_2	*c*-$C_6H_{11}NO_2$ (53%)	70 °C, 14 h	[98]
3	Cyclohexane	NHPI/NO_2/argon	*c*-$C_6H_{11}NO_2$ (43%)	70 °C, 14 h	[98]
4	Adamantane	NHPI/NO_2/O_2	1-AdNO_2 (66%)	70 °C, 14 h, $PhCF_3$	[98]
5	Adamantane	NHPI/O_2	1-AdOH (12%)	100 °C, 6 h, PhCN	[101]
6	Adamantane	NHPI/O_2	1-AdOH (52%)	75 °C, 6 h, AcOH	[102]
7	Adamantane	NHPI/O_2/Co(acac)$_2$	1-AdOH (71%), 2-Ad=O (9%), 1,3-Ad(OH)$_2$ (17%)	100 °C, 6 h, AcOH	[99]
8	Adamantane	NHPI/O_2/Co(acac)$_2$	1-AdOH (43%), 2-Ad=O (8%), 1,3-Ad(OH)$_2$ (40%)	75 °C, 6 h, AcOH	[102]
9	Isobutane	NHPI/O_2/Co(acac)$_2$	*i*-BuOH (84%), acetone (13%)	100 °C, 8 h, PhCN	[100]
10	Cyclohexane	NHPI/O_2/Fe(acac)$_2$	*c*-C_6H_{10}=O (90%) (conversion: 5%)	100 °C, HOAc	[99]
11	Cyclohexane	NHPI/O_2/Co(acac)$_2$	*c*-C_6H_{10}=O (31%), adipic acid (44%)	100 °C, 6 h, HOAc	[99]
12	Adamantane	NHPI/O_2/CO	1-AdCOOH (54%), 2-Ad=O (5%), 1-AdOAc (2%); 3°:2° = 33	95 °C, 4 h, AcOH/Cl(CH_2)$_2$Cl	[103]
13	Cyclohexane	NHPI/O_2/Co(acac)$_3$/Co(acac)$_2$/ 	 (37%),  (16%)	70 °C, 14 h, PhCN	[104]
14	Adamantane	NHPI/O_2/Co(acac)$_3$/Co(acac)$_2$/ 	 (49%),  (22%)	70 °C, 14 h, PhCN/PhCl	[104]

alkanes the NHPI/O_2/M(acac)$_2$ catalytic system (Entries 9–11) does not offer significant advantages over aerobic oxidations involving the *t*-BuO radical. The role of the metal co-catalyst in the generation of the active species from NHPI is not yet clear; the involvement of the metal-oxygen complex in the generation of the PINO-radical from NHPI was recently suggested.[99,100]

The direct radical carbonylation of alkanes usually requires drastic reaction conditions (several thousands atmospheres of pressure) or the use of peroxides.[105] The NHPI-catalyzed alkane carboxylation with CO under oxygen occurs at much lower pressures (15 atm)[103] and involves selective H-abstraction with the PINO radical (Eq. 10), carbonylation of the alkyl radical (Eq. 11), and its further oxidation to a carboxylic acid (Eqs. 12 and 13). 1-Adamantanecarboxylic acid was obtained from adamantane in 54% yield with high selectivity 3°:2° = 33 (Entry 12). The fact that the 1-acyladamantyl radical rather than the cation is involved in the reaction, was supported by experiments with ^{18}O-labeled water: most of the oxygen atoms in the carboxylic acid are incorporated from the air (Eq. 12).

The alkyl radicals ($R^\bullet$) produced in the presence of unsaturated compounds may be trapped through the formation of a new C–C bond. Oxidations of hydrocarbons in the presence of methyl acrylate or methyl fumarate (Entries 13 and 14) under oxygen atmosphere give ketones or alcohols in different ratios. The proposed scheme involves hydrogen abstraction with the PINO radical (Eq. 14) and addition of the hydrocarbon radical to the C=C bond of methyl fumarate (Eq. 15). The addition product is trapped by oxygen to give the respective peroxy radical, which then forms ketones or alcohols similarly to conventional aerobic oxidations (Eq. 16).

Oxidation of aryl azides in the presence of oxygen gives nitrenes, which, after trapping, produce nitroso oxides ArNOO$^\bullet$, that are able to abstract hydrogen atoms effectively. However, the selectivities and the yields of alkane functionalized products are low (Table 5, Entries 1 and 2). Another electrophilic radical (PyCl$_2$NO$^\bullet$) reacts with adamantane selectively, although the presence of the Ru catalyst makes mechanistic interpretations difficult: the participation of Ru=O species formed in the Ru^{III}/Ru^{V} cycle cannot be excluded (Entry 3). However, this reaction may not involve radicals.[106]

The highly electrophilic nitroxyl radical (NO$_3^\bullet$), generated under metal-free conditions, demonstrates remarkable selectivities and excellent yields of functionalized alkanes at low temperatures. The oxidation of adamantane with NO$_3^\bullet$ generated (Eq. 17) in the NO$_2$/O$_3$ system (Kyodai nitration) yields 1-adamantyl derivatives with 3°:2° = 92 (Table 5, Entry 4). The adamantyl radical formed after the C–H abstraction step (Eq. 18) in the *non-chain* radical process gives nitro and nitroxyl derivatives (Eq. 19) due to the ambient nature of NO$_2$. The NO$_3$ radical generated at higher temperatures from the photolysis of cerium ammonium nitrate is only slightly less selective (3°:2° = 62, Table 5, Entry 5).

The high selectivity in the substitution with the NO$_3$ radical is due to its electrophilic nature that enhances the polar contributions in the transition structure **TS3** for hydrogen abstraction (Eq. 18 and Scheme 1). As only a single structure of the adamantane radical cation

$$\text{PINO}^\bullet + \text{R–H} \longrightarrow \text{NHPI} + \text{R}^\bullet \qquad (10)$$

$$\text{R}^\bullet + \text{CO} \longrightarrow \text{R–C}^\bullet\text{=O} \qquad (11)$$

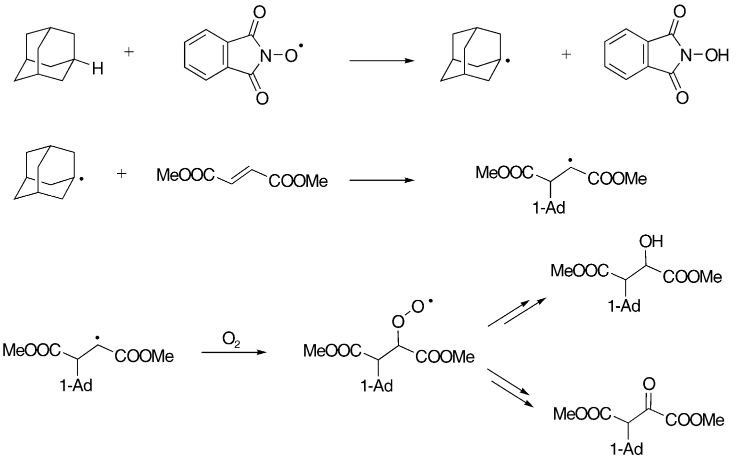
$$\text{R–C}^\bullet\text{=O} + \text{O}_2 \longrightarrow \text{R–COOO}^\bullet \qquad (12)$$

$$\text{R–COOO}^\bullet \longrightarrow \text{R–COOOH} \qquad (13)$$

$$\text{NO}_2 + \text{O}_3 \longrightarrow \text{NO}_3^\bullet + \text{O}_2 \qquad (17)$$

$$\text{Ad–H} + \text{NO}_3^\bullet \longrightarrow [^{\delta+\bullet}\text{Ad---H---ONO}_2^{\delta-\bullet}] \longrightarrow \text{Ad}^\bullet + \text{HONO}_2 \qquad (18)$$

$$2\,\text{Ad}^\bullet + 2\,\text{NO}_2 \longrightarrow \text{Ad–NO}_2 + \text{AdONO} \qquad (19)$$



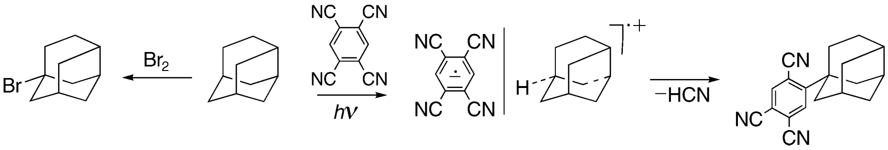
(14)

(15)

(16)

Table 5. Functionalizations of alkanes with $R_2N{-}OO^{\bullet}$ and $O_2N{-}O^{\bullet}$.

Entry	Hydrocarbon(s)	Reacting system, (active reagent)	Product(s) [Yield(s)]	Reaction conditions	Ref.
1	Isopentane	O_2/*p*-$O_2NC_6H_4N_3$/ CH_3CN/*hν* (*p*-$O_2NC_6H_4N{-}OO^{\bullet}$)	Pentanols (3.3%); 3°:2°:1° = 5.8:1.5:1	25 °C, 8 h	[107]
2	Cyclohexane	O_2/*p*-$O_2NC_6H_4N_3$/CH_3CN/C_6H_6/*hν* (*p*-$O_2NC_6H_4N{-}OO^{\bullet}$)	*c*-$C_6H_{11}OH$ (30%), PhOH (1.4%)	25 °C, 8 h	[107]
3	Adamantane	[Ru(TPFPP)(CO)]/pyCl$_2$NO] (pyCl$_2$NO$^{\bullet}$); TPFPP = 5,10,15,20-tetrapentafluorophenylporphyrinato	1-AdOH (59%), 1,3-Ad(OH)$_2$ (6%)	65 °C, 2 h, CH_2Cl_2	[108]
4	Adamantane	NO_2/O_3 ($NO_3^{\bullet}$)	1-AdNO$_2$ (82%), 1-AdONO$_2$ (10%), 1-AdOH (1%), 2-AdONO$_2$ (1%), 2-Ad=O (1%); 3°:2° = 92	− 78 °C, 30 min, CH_2Cl_2	[109]
5	Adamantane	CAN ($NO_3^{\bullet}$); CAN = cerium ammonium nitrate	1-AdNHCOCH$_3$ (53%), 1-AdOH (30%), 2-AdNHCOCH$_3$ (4%); 3°:2° = 62	*hν*, 2 h, CH_3CN	[37]



Scheme 2. Selective bromination and SET oxidation of protoadamantane.

with elongated 3° C–H bond exists[39,110] polarization through the 3° position of the adamantane cage favors the hydrogen abstraction with $NO_3^{\bullet}$. In the reaction with charged electrophiles this effect is maximized and the selectivities usually are even higher. The similarities between the transition structures for the C–H activation with radicals and electrophiles were shown only recently:[38] both reactions proceed through linear transition structures where the electron is transferred from the hydrocarbon to the electrophile (**TS2**, Scheme 1). This H-coupled electron transfer mechanism explains a number of experimental findings in polar hydrocarbon halogenations, e.g., the regiospecific 3° bromination of adamantane with neat bromine (Table 6, Entry 1) and the chlorination with I^+Cl^- (Entry 2). Positively charged halogen species may be generated under acidic conditions and even methane can be functionalized in the $H_2SO_4/SO_3/I_2$ system (Entry 3). Interestingly, the reaction between methane and Cl_3^+ gives two products (Entry 4), where $[H_3C{-}Cl{-}Cl]^+$ can form only *via* a abstraction/recombination process, rather than through insertion of an electrophile into the C–H bond.

Strong oxidizers like the sulfate radical anion $S_2O_8^{\bullet -}$, generated from $K_2S_2O_8$ in H_2SO_4 act similarly and convert methane (Entries 5 and 6) as well as ethane (Entry 7) to their sulfur derivatives. Oxidations with $K_2S_2O_8/H_2SO_4$ in the presence of CO give carboxylic acids (Entries 8 and 9, respectively). It is important to note that this metal-free approach is apparently as effective as functionalizations with Co(III) salts (Entry 10) under acidic conditions. The reactions with acidic zeolites, unfortunately, are much less successful even for hydrocarbons that are more reactive than methane (Entries 11 and 12).

Thus, the selectivities in alkane transformations with charged electrophiles as well as with electrophilic radicals are determined by the structure of the hydrocarbon radical cation.[35,122] When the intermediate hydrocarbon radical cation possesses a distinct structure (as in the case of adamantane), 100% selectivity is observed for the substitution under electrophilic conditions. The outer-sphere electron transfer oxidation of adamantane regiospecifically gives only tertiary products both with photoexcited 1,2,4,5-tetracyanobenzene (TCB) (Table 6, Entry 13) and under anodic oxidation (Entry 14). This SET oxidation is used successfully for selective functionalizations of a number of hydrocarbons (Entries 15–17). Protoadamantane, which can theoretically form four different radical cations with elongated 3° C–H bonds, exists as a single structure with an electron-depleted C^6–H bond. As a result the photooxidation with TCB gives a single C_6-substituted product;[123] the polar halogenations of protoadamantane[124] show similar selectivities (Scheme 2).

In contrast to TCB, photoexcited chloranil is a weak SET oxidant and acts as a hydrogen radical abstractor giving a mixture of products with low selectivities (Table 6, Entry 18). *Charged* hydrogen abstractors like

Table 6. Selective alkane functionalizations with electrophiles and SET oxidizers.

Entry	Hydrocarbon	Reacting system, (active reagent)	Product(s) [Yield(s)]	Reaction conditions	Ref.
1	Adamantane	Br_2, “Br_n^+”	1-AdBr (100%)	80 °C, 24 h	[111]
2	Adamantane	ICl, “ICl_n^+”	1-AdCl (100%)	25 °C, 10 h, CCl_4	[112]
3	Methane	$H_2SO_4/SO_3/I_2$ ($I_2^{\bullet+}$)	CH_3OSO_3H (45%)	195 °C, 60 min	[113]
4	Methane	Cl_3^+	$[ClH_2C{-}Cl{-}H]^+$, $[H_3C{-}Cl{-}Cl]^+$	gas phase	[114]
5	Methane	$H_2SO_4/K_2S_2O_8$ ($SO_4^{\bullet-}$)	CH_3OSO_3H (39%)	180 °C, 24 h	[115]
6	Methane	$H_2SO_4/SO_3/K_2S_2O_8$ ($SO_4^{\bullet-}$)	CH_3SO_3H (8%)	90 °C, 2 h	[116]
7	Ethane	$H_2SO_4/K_2S_2O_8$ ($SO_{4\bullet}^{-}$)	$HOSO_3(CH_2)_2SO_3H$	180 °C, 24 h	[115]
8	Methane	$H_2O/CO/K_2S_2O_8$ ($SO_4^{\bullet-}$)	CH_3COOH (48.6% relative to $K_2S_2O_8$)	105–115 °C, 10–16 h	[117]
9	Ethane	$H_2O/CO/K_2S_2O_8$ ($SO_4^{\bullet-}$)	CH_3COOH (2.5%), CH_3CH_2COOH(40.8%) (relative to $K_2S_2O_8$)	105–115 °C, 10–16 h	[117]
10	Methane	$CF_3COOH/Co(OCOCF_3)_3/O_2$	$H_3COCOCF_3$ (90%) [based on Co(III)]	180 °C, 3 h	[118]
11	Propane	Zeolite H-ZSM-5/CO/H_2O	CH_4, C_2H_6, *i*-PrCOOH, (combined yield: 1–2%)	200 °C	[119]
12	Isobutane	Zeolite H-ZSM-5/CO/H_2O	H_2, *t*-BuCOOH (combined yield 2%)	200 °C	[119]
13	Adamantane	[a]ArCN	1-AdAr (80%), 1,3-$AdAr_2$ (12%)	*hν*, CH_3CN	[37,43]
14	Adamantane	anode	1-$AdNHCOCH_3$ (70%)	25 °C, CH_3CN	[120]
15	*n*-Hexane	ArCN[a]	2-hexyl-Ar (42%), 3-hexyl-Ar (32%)	*hν*, CH_3CN	[43]
16	Cyclohexane	ArCN[a]	*c*-C_6H_{11}Ar (80%)	*hν*, CH_3CN	[43]
17	Norbornane	ArCN[a]	2-norbornyl-Ar (70%)	*hν*, CH_3CN	[43]
18	Adamantane	Chloranil ($O{=}C_6Cl_4{=}O^*$)	1-$AdNHCOCH_3$ (43%), others (31%); 3°:2° = 7	*hν*, 2 h, CH_3CN	[121]
19	Adamantane	H_2SO_4/*i*-$Pr_2NCl/FeSO_4$ (*i*-$Pr_2N^{\bullet+}$)	1-AdCl (91.3%), 2-AdCl(8.6%); 3°:2° = 30	30 °C, CCl_4	[96]

[a] Ar = 2,4,5-tricyanobenzyl.

amine radical cations $R_2N^{\bullet+}$[96] are far more selective due to polar contributions to the transition structures for H-abstractions: the selectivity for adamantane chlorination with *i*-$Pr_2N^{\bullet+}$ rises significantly (3°:2° = 30, Entry 19).

3.3 Metal-Free Alkane Halogenations

Free-radical chlorinations are almost useless for higher alkanes as the discrimination between the primary (1°), secondary (2°), and tertiary (3°) C–H bonds is too low.[125] In the condensed state the functionalizations are slightly more selective, depending on the solvent used. For instance, the 2°:1° ratio for the chlorinations of *n*-alkanes in EtBr increases, relative to CCl_4, from 2 to 9.[126] The radical bromination of cyclohexane is effective even in water.[127] Direct fluorinations of alkanes are difficult to control because of high exothermicities and low barriers.[128] In contrast, the activation step for alkane brominations $R{-}H + Br^\bullet = R^\bullet + H{-}Br$ is endothermic and is characterized by substantial barriers[129] resulting in appreciable selectivities. As a consequence, the correlation between the stabilities of the resulting alkyl radicals for radical brominations is more pronounced than for radical chlorinations. The brominations (Table 7, Entries 1–3) and chlorinations (Entry 4) of adamantane show only 3°:2° = 2.5–5.7 due to the similar stabilities of the 1-adamantyl ($\Delta_f H^\circ = 15$ kcal/mol) and 2-adamantyl ($\Delta_f H^\circ = 12$ kcal/mol) radicals.[130] The C–H brominations of strained hydrocarbons are usually even more problematic than the chlorinations because the bromine radical typically attacks carbon atoms and breaks the C–C bonds (cage-opened, less strained products result). This was shown for a number of strained hydrocarbons: cyclopropane,[131] cubane[132] and some others.[133] The direct iodinations of unactivated C–H bonds of alkanes with $I^\bullet$ are not possible, and all approaches are based on indirect methods (*vide infra*).

Substantial improvements of the selectivities of radical alkane halogenations may be achieved if halogen radicals are *not* involved in the C–H activation step. Carbon-centered radicals are usually far more selective due to polar and steric effects.[134] Even for the methyl radical the observed 3°:2°:1° selectivities are 61 : 5 : 1 for small alkanes.[135] The involvement of the $BrCH_2$ radical increases the selectivities further with or without metal catalyst (Table 7, Entries 5 and 6). Simple trihalomethyl radicals are generated through photolytic,[136] ther-

Table 7. Regioselectivities for the functionalizations of adamantane using halogen and carbon-centered radicals as the abstracting species.

Entry	Radical source/abstracting radical	Solvent, temperature	Initiation	Relative reactivity of 3°:2° C–H bonds
1	NBS/Br$^{\bullet}$	PhCl, 95 °C	$(PhCO)_2O_2$	2.5[140]
2	NBS + Br_2/Br$^{\bullet}$	CH_2Cl_2, 25 °C	*hν*	5.8 [96]
3	Br_2/Br$^{\bullet}$	$H_2O/Cl(CH_2)_2Cl$, 100 °C	thermal	2.9 [96]
4	NCS/Cl$^{\bullet}$	C_6H_6, 80 °C	AIBN	2.5–3.7[141]
5	$CH_2Br_2/BrH_2C^{\bullet}$	CH_2Br_2, 95 °C	$(PhCO)_2O_2$	9.0[140]
6	$CH_2Br_2/BrH_2C^{\bullet}$ $[FeCl_2TPA]^{2+}$; TPA = tris(2-pyridylmethyl)amine	CH_3CN, 25 °C	*t*-BuOOH	9.5[142]
7	Cl_2/Cl$^{\bullet}$	CCl_4, 25 °C	*hν*	4.8[143]
8	Br_2/Br$^{\bullet}$	CCl_4, 25 °C	*hν*	5.6[141]
9	CCl_4 /$Cl_3C^{\bullet}$	CCl_4, 95 °C	$(PhCO)_2O_2$	24.3[140]
10	CCl_4 /$Cl_3C^{\bullet}$	CCl_4	*t*-BuOOBu-*t*	21.5[141]
11	$BrCCl_3/Cl_3C^{\bullet}$	$BrCCl_3$, 95 °C	*t*-BuOOBu-*t*	27[140]
12	GIF + $BrCCl_3/Cl_3C^{\bullet}$	$BrCCl_3$/Py/AcOH, 60 °C	*t*-BuOOH	8.2[31]
13	$BrCCl_3/Cl_3C^{\bullet}$, $H_3C^{\bullet}$	acetone	DMD[a]	18[75]
14	*n*-C_4F_9I/*n*-$C_4F_9^{\bullet}$	AcOH, 120 °C	*t*-BuOOH	16.6[144]
15	CCl_4 /$Cl_3C^{\bullet}$	CCl_4, 78 °C	PTC	28.5[145]
16	CBr_4 /$Br_3C^{\bullet}$	CH_2Cl_2, 25 °C	PTC	30.1[145]
17	$CI_4/I_3C^{\bullet}$	CH_2Cl_2, 25 °C	PTC	132.0[145]

[a] DMD = dimethyldioxirane.

$$CHal_4 \longrightarrow CHal_3^{\bullet} + Hal^{\bullet} \qquad (20)$$

$$CHal_3^{\bullet} + R\text{–}H \longrightarrow HCHal_3 + R^{\bullet} \qquad (21)$$

$$Hal^{\bullet} + R\text{–}H \longrightarrow HHal + R^{\bullet} \qquad (22)$$

$$R^{\bullet} + CHal_4 \longrightarrow RHal + CHal_3^{\bullet} \qquad (23)$$

mal[137] or heterogeneously-catalyzed[138] decompositions of tetrahalomethanes (Eq. 20). Although the alkane activation step with $CHal_3^{\bullet}$ (Eq. 21) is more selective, the selectivities of functionalizations are typically lowered due to the participation of Hal-radicals in the C–H abstraction (Eq. 22) especially for Hal = Cl. Alkane radicals thus formed propagate the chain process (Eq. 23).[139]

For the electrophilic and more bulky radicals like $C_nHal_{2n+1}^{\bullet}$ the selectivities increase dramatically. The selectivities of the radical chlorination (Entry 7) and bromination (Entry 8) of adamantane with Hal_2 in CCl_4 are about 5. For the chlorinations with CCl_4 (Entries 9 and 10) and brominations with $BrCCl_3$ (Entry 11) the selectivities of the halogenations of adamantane increase to 21.5–27. The halogenations under metal-catalyzed GIF conditions (Entry 12) or in the presence of dioxirane (Entry 13) show lower selectivities due to the participation of oxygen-centered (GIF) or methyl (DMD) radicals.

Thermolysis of trifluoroacetic acid at 70 °C in the presence of H_2O_2 serves as a source for the trifluoromethyl radical $CF_3^{\bullet}$ that readily abstracts hydrogens

$$CF_3^{\bullet} + C_6H_{12} \longrightarrow HCF_3^{\bullet} + C_6H_{11}^{\bullet} \qquad (24)$$

$$C_6H_{11}^{\bullet} + CF_3CO_2OH \longrightarrow C_6H_{11}OH + CF_3CO_2^{\bullet} \qquad (25)$$

$$CF_3CO_2^{\bullet} \longrightarrow CF_3^{\bullet} + CO_2 \qquad (26)$$

$$C_nF_{2n+1}I \longrightarrow C_nF_{2n+1}^{\bullet} + I^{\bullet} \qquad (27)$$

$$C_nF_{2n+1}^{\bullet} + R\text{–}H \longrightarrow C_nF_{2n+1}H + R^{\bullet} \qquad (28)$$

$$R^{\bullet} + C_nF_{2n+1}I \longrightarrow C_nF_{2n+1}^{\bullet} + R\text{–}I \qquad (29)$$

from cyclohexane (Eqs. 24–26).[146] The evidence for a radical chain process involving the CF_3 radical comes from the evolution of CO_2 and formation of CDF_3 with cyclohexane-d_{12}.

A new method for homolytic iodination of alkanes involves the homolysis of perfluoroalkyl iodides (namely *n*-C_4F_9I in the presence of catalytic amounts of *t*-BuOOH) forming perfluoroalkyl radicals (Eq. 27) that are responsible for the C–H activation (Eq. 28). The alkyl radicals abstract iodine atoms from perfluoroalkyl iodide in the propagation step (Eq. 29).[44,144] Polar effects, i.e., the polarization in the transition structures for the hydrogen abstractions of type **TS3** (Scheme 1) are largely responsible for the observed selectivities.[147] The 3°:2° selectivity of the iodination of adamantane with *n*-C_4F_9I/*t*-BuOOH is 17:1,[144] which is, however, slightly lower than for the $BrCCl_3$/*t*-BuOO*t*-Bu bromination (27:1)[140] where $Cl_3C^{\bullet}$ is the abstracting radical.

Other perfluoroalkyl radicals, generated from perfluoroalkyl iodides under mild conditions in the presence of radical starters (di-*tert*-butyl hyponitrite),[148] also give iodoalkanes. The branched radical *i*-$C_3F_7^\bullet$ is substantially more reactive than linear *n*-$C_4F_9^\bullet$, also indicating the importance of polar effects in the transition structures for hydrogen abstractions: the 2°:1° selectivities for *n*-heptane are higher than for the relatively selective *t*-$BuO^\bullet$ radical (*vide supra*).[148]

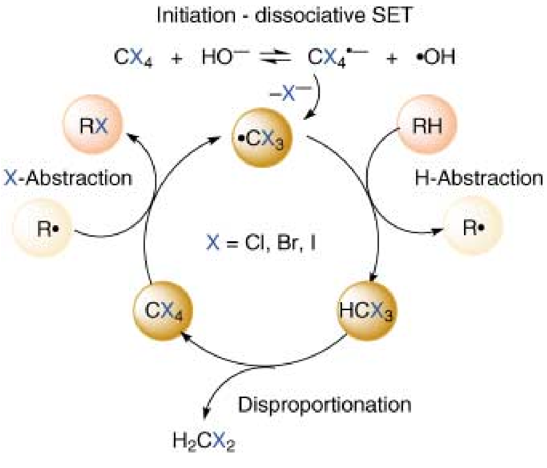
3.4 Phase-Transfer Catalyzed Alkane Halogenations

Our recently developed[145] phase-transfer catalytic (PTC) alkane halogenation protocol is useful for chlorinations,[149] brominations,[150] and iodinations[151] of unactivated, aliphatic hydrocarbons, which may be linear, branched, and (poly)cyclic, strained as well as unstrained. Under the PTC conditions the reactive species are confined to a small interphase zone or are transported with a phase-transfer catalyst. Since the products are of much lower concentration in the reactive region, unselective over-functionalization is much less likely. A typical halogenation procedure involves stirring a solution of the desired alkane in an inert organic solvent (or the alkane itself) with concentrated aqueous or solid base (for instance, NaOH) in the presence of the halogenating reagent (CX_4 or CHX_3, X = halogen) and PT catalyst (typically a quaternary ammonium salt).[152] The initiation step involves the SET oxidation of poorly solvated OH^- with CX_4,[153] resulting in a radical anion that dissociates into a halide anion and a CX_3 radical (Scheme 3); the latter is responsible for the C–H activation.[154] The haloform HCX_3, produced after the C–H abstraction from the alkane, re-enters the cycle through base-catalyzed disproportionation into tetrahalo- and dihalomethane. The overall reaction produces a haloalkane and dihalomethane.

The PTC halogenations are strongly catalyst dependent in non-interacting solvents (e.g., fluorobenzene): Figure 1 exemplifies the catalyst's influence on the bromination of adamantane showing the true PTC nature of this approach.

The PTC-functionalizations differ considerably from traditional free-radical alkane halogenations since they do *not* involve highly reactive and therefore unselective halogen radicals. The C–H activation[154] selectivities for halogenations of adamantane are higher under PT conditions due to the exclusive participation of $CHal_3$ radicals (Table 7, Entries 15–17); the selectivities are the highest for any alkane radical halogenation reaction reported to date. There are a number of important preparative advantages[155] of our PT catalytic approach over other halogenation methods.

- A relatively inexpensive iodination reagent (HCI_3) could be used as shown for the iodination of cyclohexane (Eq. 30, Scheme 4, and Experimental Section) and adamantane (Table 7, Entry 17, and Experimental Section).[151]
- The brominations with CBr_4 occur with high yields and a number of functional groups are tolerated (Eq. 31 shows the selective 3° bromination of 1-phenyladamantane).[150]
- Unactivated hydrocarbons could be halogenated (even iodinated) easily (Eqs. 32 and 33 exemplify the direct bromination of *n*-butane and the iodination of *n*-hexane).[150]
- The C–H bonds of highly strained hydrocarbons are halogenated *without* concomitant fragmentations or rearrangements of the cages [Eqs. 34 and 35 show the brominations of cubane (see also Experimental Section) and 2,4-dehydroadamantane].[149]



Scheme 3. Radical propagation cycle for the single-electron transfer initiated production of CX_3 radicals from CX_4 (X = Hal) and functionalization of an alkane (RH).

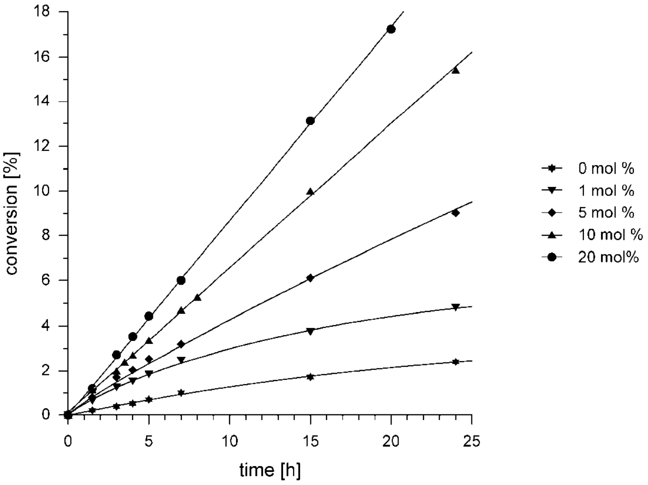
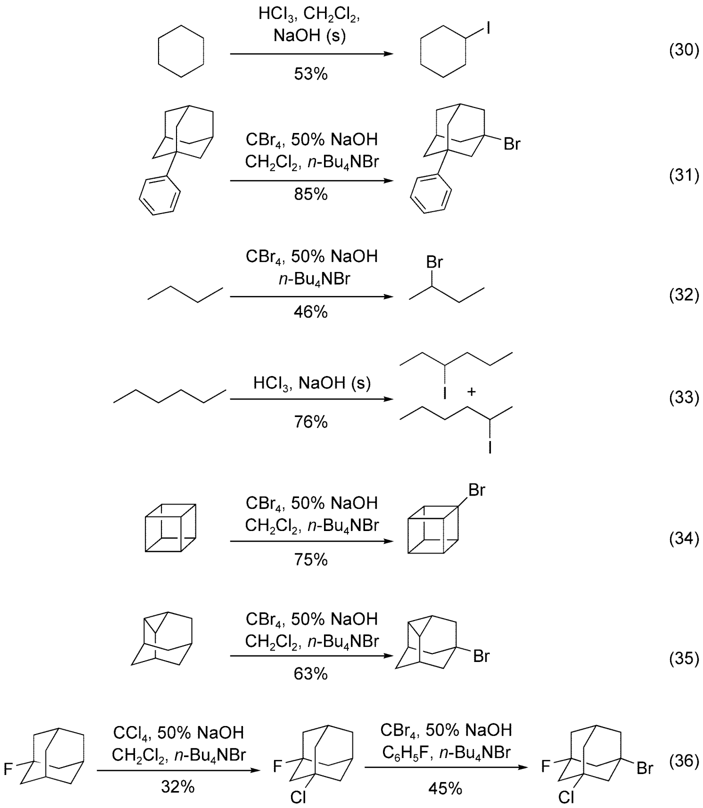


Figure 1. Catalyst (mol % of tertabutylammonium bromide) concentration dependence of the bromination of adamantane in fluorobenzene under phase-transfer conditions.



Scheme 4. Range of halogenation reactions under phase-transfer catalytic conditions.

- Polyhalogenations, as well as mixed halogenations without halogen exchange could be achieved (Eq. 36 describes the multistep preparation[155] of 1-bromo-3-chloro-5-fluoroadamantane *via* subsequent introduction of different halogen atoms into 1-fluoroadamantane).[149]

The relatively long reaction times of our original procedure for the iodination of alkanes under PTC can be significantly shortened by ultrasonication.[156]

4 Conclusions

The selective activation *and* functionalization of alkanes remains challenging and leaves much to be discovered. Although metal-catalyzed processes are a good approach for tailoring metal reactivities toward C–H bond activation, this is by no means the only one. Our comprehensive comparisons show that many so-called metal-catalyzed reactions also work *without* the metal present. The fact that a large variety of metals shows the same product distributions emphasizes that the metal often just aids in the generation of the active species, i.e., the metal itself is *not* participating in the crucial C–H activation step. Particular examples are Fenton and GIF-type chemistries that in virtually all cases can be traced back to the generation of oxygen-centered radicals (mostly HO$^\bullet$). At the same time, there are highly selective, metal-free alkane functionalization reactions such as those derived from nitroxyl and related radicals as well as through radical reactions conducted in phase-transfer catalyzed systems. The latter are, in contrast to all metal and most free-radical approaches, also applicable to highly strained systems and offer the highest 3°/2° selectivities for radical reactions reported to date. Furthermore, these reactions are easy to carry out and, owing to their organic solvent/water or solvent/solid base two-phase nature, equally easy to work-up. As these reactions clearly are PT-catalyst dependent, endeavors toward stereoselective alkane functionalizations seem well justified.

5 Experimental Section

The representative procedures given here are applicable to a wide range of alkanes. The bromination of cubane should emphasize the fact that highly strained systems can be halogenated without rearrangement of the strained hydrocarbon moiety.

5.1 Bromination of Cubane[149]

A mixture of 208 mg (2 mmol) of cubane, 1.28 g (4 mmol) of CBr_4, 5 mL of CH_2Cl_2, 3 mL of 50% aqueous NaOH, and 25 mg of tetrabutylammonium bromide was stirred at room temperature for 24 h, then diluted with 10 mL of water, and extracted with CH_2Cl_2 (3 × 5 mL). The extracts were washed with water, dried over Na_2SO_4, and excess CH_2Cl_2 was removed at atmospheric pressure. Column chromatography (silica/pentane) gave cubane (20 mg) and bromocubane identical to the material described earlier by NMR[157] and MS[158] data; yield: 274 mg (75%).

5.2 Iodination of Cyclohexane

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 150 mL of cyclohexane, 65 g (0.62 mol) of NaOH, 9.0 g (0.023 mol) of iodoform and closed with a polished cap. The mixture was stirred vigorously for 48 h at 25 °C. Then the mixture was filtered and the precipitate washed with pentane. The filtrate was evaporated under reduced pressure (300 torr) and 2.8 g of the crude product were obtained. Vacuum distillation (75–77 °C/17–19 torr, Lit. 68–70 °C/10 torr) gave iodocyclohexane; yield: 2.5 g (0.012 mol, 53% relative to iodoform).

5.3 Iodination of Adamantane

In a 25-mL screw-capped vial 1.36 g (0.01 mol) adamantane, 0.16 g tetrabutylammonium bromide (0.001 mol) and 3.94 g iodoform were dissolved in 15 mL of CH_2Cl_2. Then 5 mL of sodium hydroxide solution (50% aqueous) were added and the vial was equipped with a magnetic stirring bar. The mixture was heated with an oil bath at 40 °C under vigorous stirring for 72 hours. The organic layer was separated and the aqueous part extracted with 5 × 25 mL of pentane. Removal of the solvents under reduced pressure and column chromatography of the residue (pentane, silica gel) gave of 1-iodoadamantane (yield: 1.36 g, 0.0052 mol, 52%, TLC: $R_f = 0.47$) and 1,3-diiodoadamantane (yield: 0.78 g, 0.0020 mol, 20%, TLC: $R_f = 0.25$).

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