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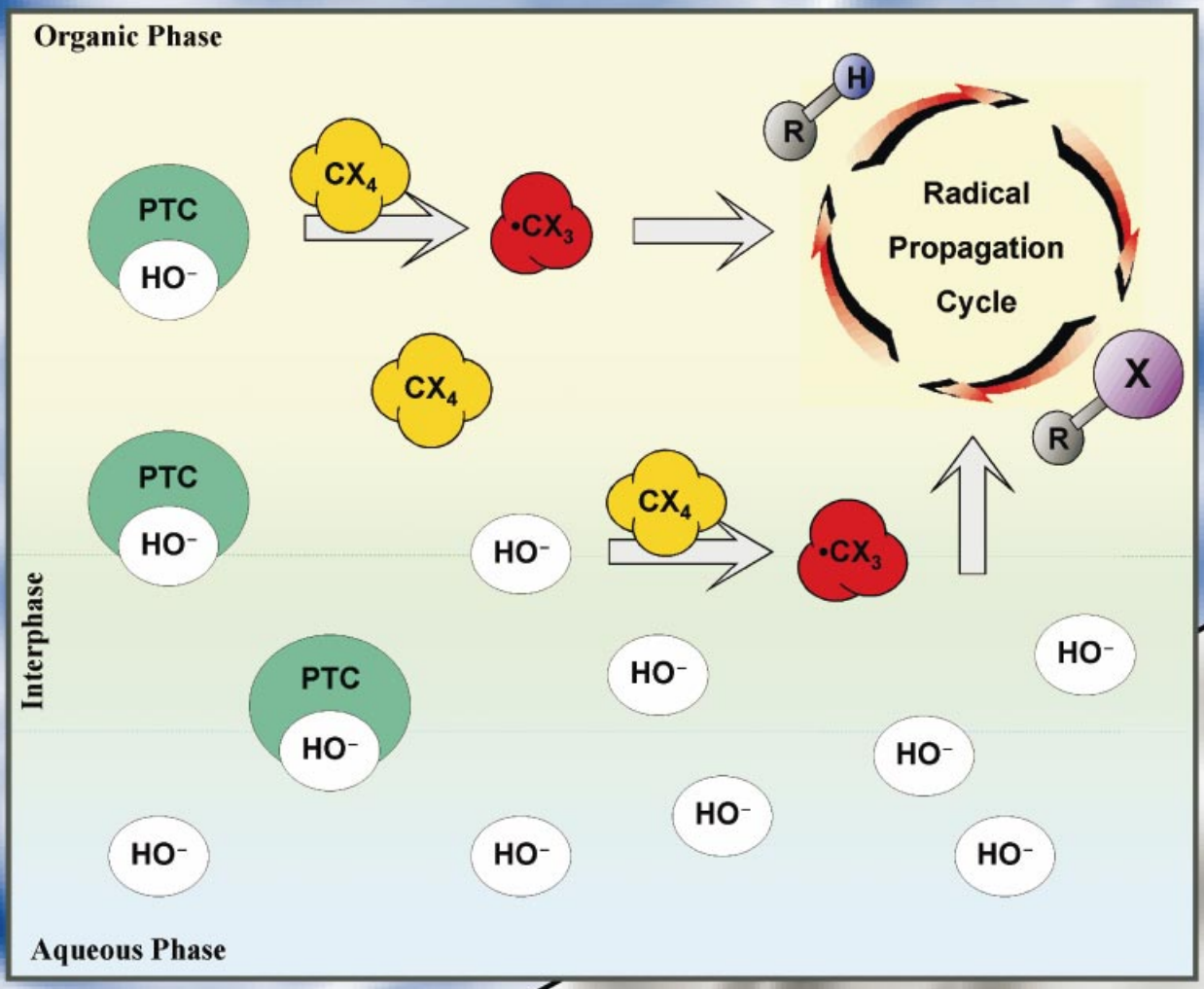

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Selective Radical Reactions in Multiphase Systems: Phase-Transfer Halogenations of Alkanes

Peter R. Schreiner,*[a] Oliver Lauenstein,[a] Ekaterina D. Butova,[b] Pavel A. Gunchenko,[b] Igor V. Kolomitsin,[b] Alexander Wittkopp,[a] Gerald Feder,[a] and Andrey A. Fokin*[b]

Abstract: The present paper shows that selective radical reactions can be initiated and carried out in multiphase systems. This concept is applied to the selective functionalization of unactivated aliphatic hydrocarbons, which may be linear, branched, and (poly)cyclic, strained as well as unstrained. The phase-transfer system avoids overfunctionalization of the products and simplifies the workup; the selectivities are excellent and the yields are good. This is the only method for direct preparative iodination of alkanes applicable to large scale as well. We demonstrate that the reaction systems are indeed phase-transfer catalyzed through a systematic study of variations of the reactants, solvents, catalysts, and by measuring as well as computing the H/D kinetic isotope effects for the rate-limiting C–H abstraction step by $^{\bullet}CHal_3$ radicals which are held responsible for the observed radical reactions. In the case of $^{\bullet}CBr_3$, this key intermediate could also be trapped under otherwise very similar reaction conditions. To stimulate further work, the tolerance of some functional groups was tested as well.

Keywords: alkanes · electron transfer · halogenation · phase-transfer catalysis · radicals

[a] Prof. Dr. P. R. Schreiner, Dr. O. Lauenstein, Dr. A. Wittkopp, Dr. G. Feder
Institut für Organische Chemie
Georg-August-Universität Göttingen
Tammannstr. 2, 37077 Göttingen (Germany)
current address:
Department of Chemistry, University of Georgia
1001 Cedar St., Athens, GA 30602-2556 (USA)
Fax: (+1) 706-542-9454
E-mail: prs@chem.uga.edu

[b] Prof. Dr. A. A. Fokin, Dr. E. D. Butova, Dr. P. A. Gunchenko, Dr. I. V. Kolomitsin
Department of Organic Chemistry
Kiev Polytechnic Institute
pr. Pobedy, 37, 252056 Kiev (Ukraine)
E-mail: aaf@xtf.ntu-kpi.kiev.ua

Introduction

Having been neglected for all too long, radical reactions have shown to be far more useful than their "reputation" would imply. Many mild methods for the generation of free radicals in solution are now available making their reactions amenable to very sensitive substrates. Stereoselective radical reactions[1, 2] are now possible and commonplace for the construction of complex molecular scaffolds.[3–5] Many radical reactions can also be carried out in the environmentally benign solvent water because the O–H bonds of water are exceptionally strong and are unlikely to be cleaved by the typical radicals used in organic transformations.[6] Despite these tremendous developments, some of the most important radical reactions, namely in the selective functionalization of alkanes have virtually been left out. The present paper introduces a new concept combining radical chemistry initiated by single-electron transfer (SET) with phase-transfer catalysis.

Alkanes and their halogenation reactions with elementary free radicals are usually introduced very early in organic chemistry courses and textbooks so that it is often overlooked that these transformations are neither particularly selective nor broadly applicable. Fluorinations occur explosively and are very hard to control; chlorinations and brominations are more moderately exothermic but also lead to product mixtures. As these halogenation reactions often are thermodynamically driven, sensitive hydrocarbons undergo cracking, isomerization, or oligomerization making this procedure very often entirely useless for strained alkanes.[7] Iodinations of unstrained aliphatic hydrocarbons with I_2 are not possible using this route due to their overall endergonicity (see below). Hence, despite the fact that haloalkanes are some of the most important industrial chemicals, the ways of making them from alkanes are archaic, in part by choice (the chemicals for the above reactions are cheap) but also because there were no good alternatives.

Selective alkane functionalization[8–14] is generally difficult because the products are almost inevitably more reactive than the starting materials; the regioselectivities usually are rather low as well with little discrimination of primary, secondary,

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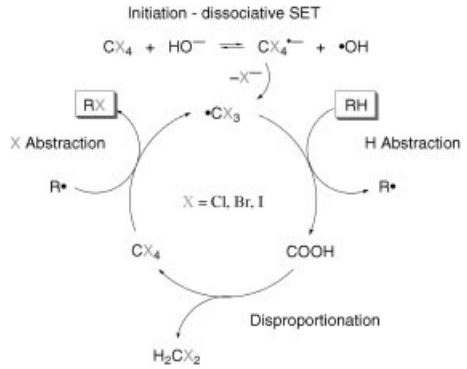
and tertiary C–H bonds. The present article describes a nontraditional approach to this problem, namely the use of phase-transfer catalysis.[15–20] The key idea is that the reactive species are confined to a small interphase zone or are transported with a phase-transfer catalyst.[21] Since the products are of much lower concentration in the reactive region, unselective over-functionalization is much less likely.[22–24]

A typical PTC halogenation protocol involves a solution of the desired alkane in an inert organic solvent (liquid alkanes may also be used in excess without additional solvent) over a highly concentrated basic solution (for instance, 50 % NaOH) or solid base. A quaternary ammonium salt serves as the phase-transfer catalyst to transport the reagents among the phases. An arguably reasonable mechanistic proposal for our reactions involves the hydroxide ion as the initiator species, which *may* be extracted[16, 19, 20, 25–27] into the organic phase where it is highly activated due to partial loss of its solvating water molecules. As the first solvation shell of the hydroxide ion requires about four to five water molecules,[28] even a 50 % NaOH solution (stoichiometrically with about two water molecules per one hydroxide ion) contains highly activated OH^- because of desolvation:[29, 30] in such solutions even allyl benzene with a pK_a of 34 can be deprotonated![31, 32]

A more extreme situation arises when the hydroxide is bound to the catalyst at the interphase region or is even transferred into the organic phase[18] where it apparently no longer behaves as a typical base. Instead, it acts as a reducing agent and transfers an electron to a strong electron acceptor such as a tetrahalomethane which we presently employ in some of our reactions (Scheme 1).



Scheme 1. Radical propagation cycle for the single-electron transfer initiated production of CX_3 radicals from CX_4 and functionalization of an alkane (RH).

Hence, the hydroxide ion reduces the tetrahalomethane in a single-electron transfer step to the corresponding radical anion (this reaction with CBr_4 is 9.1 kcal mol^{-1} exothermic based on the heats of formation of all involved species[33]); such electron transfer steps were proposed by Sawyer and Roberts for reactions involving CCl_4.[34] The tetrahalomethane radical anion dissociates in an equilibrium reaction into halide and the trihalomethyl radical which abstracts hydrogens from alkanes to produce alkyl radicals; these react with unused tetrahalomethane to produce the respective alkyl halide and a new chain-carrying CX_3 radical. The haloform produced from the abstraction step also re-enters the cycle by base-initiated disproportionation[35–37] into tetrahalo- and dihalomethane. Hence, the overall reaction products are the halogenated alkane and dihalomethane. The latter could be identified in the NMR spectra in the organic phase of quenched reaction mixtures, but is, however, typically not isolated in our experiments and usually reacts further to unidentified higher molecular weight compounds. The work-up procedure is usually very easy: the layers are separated, the

Abstract in German: *Wir zeigen hier, daß selektive Radikalreaktionen in Mehrphasensystemen initiiert und durchgeführt werden können. Dieses neue Konzept eignet sich zur Anwendung auf die selektive Funktionalisierung nichtaktivierter linearer, (poly)cyclischer, ungespannter sowie gespannter, aliphatischer Kohlenwasserstoffe. Im Mehrphasensystem wird die Überfunktionalisierung vermieden und die Aufarbeitung vereinfacht; die Selektivitäten sind ausgezeichnet, die Ausbeuten gut bis sehr gut. Der vorliegende Ansatz ist die einzige Methode zur präparativen direkten Iodierung von Alkanen. Durch systematische Variation der Reaktanden, Katalysatoren, Lösungsmittel, sowie durch die experimentelle und rechnerische Bestimmung der H/D kinetischen Isotopeneffekte zeigen wir ferner, daß die vorliegenden Reaktionssysteme in der Tat phasentransferkatalytisch und $^{\bullet}CHal_3$ Radikale die H-abstrahierende Spezies im geschwindigkeitsbestimmenden Schritt sind. Für die Bromierung konnte das $^{\bullet}CBr_3$ Schlüsselintermediat unter ansonsten identischen Bedingungen abgefangen werden. Im Hinblick auf ein breiteres Anwendungsspektrum wurde auch die Toleranz einiger funktioneller Gruppen untersucht.*

Abstract in Ukrainian: В даній статті показано, що селективні радикальні реакції можуть бути ініційовані та проведені в багатофазних системах. Ця концепція застосована до селективної функціоналізації неактивованих аліфатичних вуглеводнів, які можуть бути лінійними, розгалуженими, (полі)циклічними, а також як напруженими, так і ненапруженими. Система межфазового переносу дозволяє уникнути поліфункціоналізації продуктів та спрощує обробку; селективності перетворень відмінні, а виходи є добрими. Зазначений метод є єдиним для прямого препаративного йодування алканів, та може бути застосований у масштабних синтезах. Ми показали, що вищезгадані реакційні системи є дійсно межфазними шляхом систематичного дослідження різних реагентів, розчинників, каталізаторів, а також як експериментальними вимірюваннями, так і обчисленням H/D кінетичних ізотопних ефектів для лімітуючої стадії C–H абстракції радикалами $^{\bullet}CHal_3$, яка є відповідальною за радикальні реакції, що спостерігаються. У випадку $^{\bullet}CBr_3$ цей ключовий інтермедіат може також бути зафіксований в інших подібних умовах реакції. Для подальшої роботи була також визначена стійкість деяких функціональних груп в умовах реакційного середовища.

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aqueous layer is extracted with organic solvent and distillation or column chromatography gives the product in high yield (up to 92%).

Discussion

Our PTC protocol allows the preparatively useful bromination and iodination of a wide variety of alkanes (Figure 1): straight-chain (**1**), monocyclic (**2**), and polycyclic (e.g., **3** and **4**) aliphatic hydrocarbons give the respective bromo- and iodoalkanes with yields of up to 92% (**2**, $n=1$, Hal = I, cyclopentyl iodide). Hence, apart from being a convenient method for bromination, this is the only *truly preparatively* useful iodination of alkanes.[38–41] An interesting finding is that many base- and hydrolysis-sensitive substrates are stable under these conditions. For instance, the elimination of HI or hydrolysis of iodocyclohexane is very slow; tertiary substrates eliminate more readily. This also supports our working hypothesis that the hydroxide ion does not show its typical base or nucleophile behavior when extracted into the organic phase or at the phase boundary.

Chlorinations with CCl_4 are also possible under similar conditions but were thus far only realized for some special alkanes such as adamantanes and cubanes.[42] These transformations are much slower than the brominations or iodinations due to the increased stability of CCl_4.

The reactivity order is typical for reactions involving alkyl radicals: tertiary C–H bonds are broken most readily, followed by functionalization of methylene groups; longer ($n=4$) straight-chain alkanes give mixtures of secondary haloalkanes. As trihalomethyl radicals are relatively bulky, the site of abstraction also depends highly on steric demand and not necessarily on the stability of the radical formed. For instance, the 2-adamantyl radical has about the same thermodynamical stability as the bridgehead radical,[43] but the latter is sterically much less hindered. Hence, bulkier radicals should only abstract from the tertiary position, and the ratio of 1- to 2-haloadamantane products can directly be related to the steric demand of the abstracting radical. The behavior of $^{\bullet}CBr_3$ and the sterically even more demanding $^{\bullet}CI_3$ is contrasted to that of bromo-, trichloromethyl-, and CH_2Br radicals in Table 1.

Table 1. Regioselectivities for the halogenations of adamantane using bromo-, bromomethylene, tribromomethyl, and triiodomethyl radicals.

Radical source /radical	Initiation	Reactivity ratio of 1-/2-adamantane C–H bonds[b]
$Br_2/Br^{\bullet}$	$h\bar{\nu}$	5.58[53]
NBS/$Br^{\bullet}$	$h\bar{\nu}$	5.82[54]
$CH_2Br_2/^{\bullet}CH_2Br$	DBPO[a]	9.00[53]
$CCl_4/^{\bullet}CCl_3$	AIBN	17.2
$CCl_4/^{\bullet}CCl_3$	DBPO	22.3[53]
$CCl_4/^{\bullet}CCl_3$	PTC	28.5
$CBr_4/^{\bullet}CBr_3$	PTC	30.1
$CI_4/^{\bullet}CI_3$	PTC	132.0

[a] DBPO = dibenzoyl peroxide; [b] statistically corrected for number of C–H bonds.

Non-activated methyl groups are never attacked in these reactions; toluene can be functionalized but isolation of the resulting benzyl halides from these PTC mixtures is difficult. Most remarkable is that strained hydrocarbons such as 2,4-didehydroadamantane (product **5**) or cubane (products **6** and **8**) can also be halogenated with conservation of the cage (Figure 1),[42] in marked contrast to the halogenation reactions

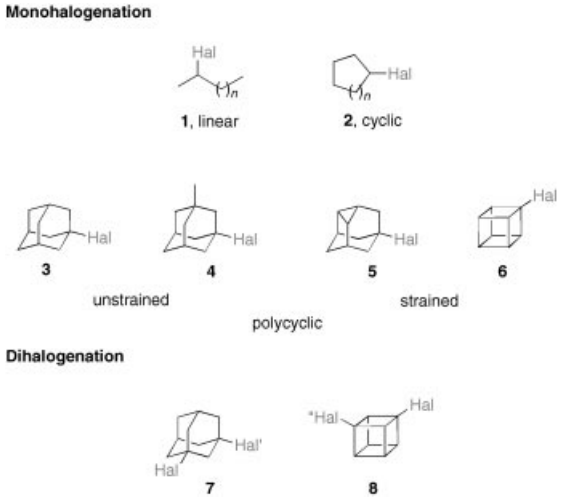
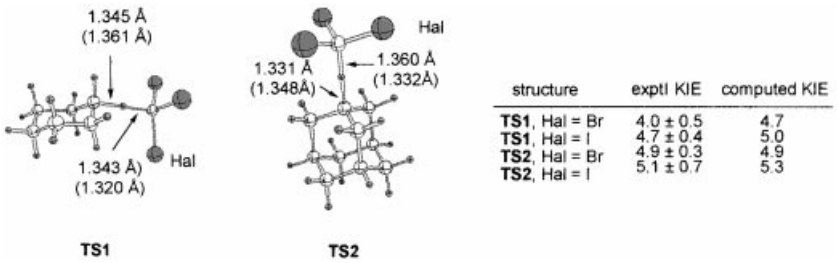


Figure 1. Range of halogenation reactions under phase-transfer catalysis. The yields for these compounds are in the range of 11–92%; Hal = Br, I; Hal′ = F, Cl, Br, I; Hal″ = Cl, Br, I.

of these substrates with halogen radicals.[44, 45] This is due to fact that the hydrogen-abstracting species, $^{\bullet}CX_3$, is a carbon-centered radical which typically does not cleave C–C bonds (see below). Dihalogenations with either the same or a different halogen (**7** and **8**) are also possible showing that exchange (as often found for halogen radicals)[37] does not occur. This again contrasts typical halogen-radical transformations where selectivities are much lower and over-functionalization sometimes leading to inseparable product mixtures may become a problem.

Our mechanistic hypothesis is supported by several key findings. First of all, we were able to show that the rate-determining step indeed involves the abstraction of a hydrogen atom by trihalomethyl radicals by comparison of experimentally determined and computed kinetic isotope effects (KIEs).[24] These KIEs for cyclohexane and adamantane are around 5 (in contrast to, for instance, radical bromination of cyclohexane with $Br^{\bullet}$ which gives a KIE value of about 2.4[46] or 4[47]) and show that the transferred hydrogen atom lies about half-way between the carbon centers in the transition structures (**TS1** and **TS2**, Figure 2).[24] This is also in line with our findings that cubane and other highly strained hydrocarbons could be functionalized without cage opening or rearrangement due to the stabilized nature and steric demand of trihalomethyl radicals.[42]

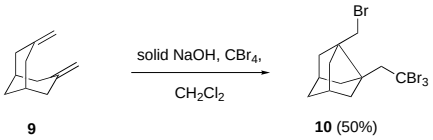
The CBr_3 radical could be captured by bismethylene compound **9**[48] which serves as an "internal" trap[49] for the incipient radical upon addition of the trihalomethyl radical to the terminal end of one of the methylene groups (Scheme 2).[24] We note that **9** is easy to prepare and a



structure	exptl KIE	computed KIE
TS1, Hal = Br	4.0 ± 0.5	4.7
TS1, Hal = I	4.7 ± 0.4	5.0
TS2, Hal = Br	4.9 ± 0.3	4.9
TS2, Hal = I	5.1 ± 0.7	5.3

Figure 2. Structural presentations for the abstraction of a hydrogen atom from an equatorial position of cyclohexane (**TS 1**) and a tertiary position of adamantane (**TS 2**) with CBr_3 (first entry) and CI_3 (in parentheses) radicals, along with the experimental and computed (B3LYP/6-31G** (3-21G* on iodine)) kinetic isotope effects at 296 K.

particularly useful radical trap which can potentially also be used to estimate approximate lifetimes by measuring the distribution between noradamantane and adamantane products; the latter appear as a very minor quantity in the experiment depicted in Scheme 2.



Scheme 2. Trapping of the CBr_3 radical under PT conditions.

The PTC halogenations are strongly solvent dependent (Figure 3), and seem to be favored in more polar media (compare the reactions in benzene and 1,1,1-trifluoromethyl benzene, TFT), probably due to the increased solubility of polar components (catalyst, water) in the organic layer.[50] The reactions can also be carried out in chlorobenzene, 1,3-ditrifluoromethyl benzene, and methyl *tert*-butyl ether. Methylene chloride seems to play a special role as the reactions with phase-transfer catalyst are only marginally faster than those without, and because this solvent actively participates in the mechanism as evident from a small amount of chloro products formed ($\leqslant$3 % at low CBr_4 concentrations). The effect of the catalyst is far more pronounced in all other solvents tested. For further mechanistic studies we therefore utilized fluorobenzene as our solvent of choice because the reactions are reasonably fast, catalyst-dependent, and cleaner than with methylene chloride. For high-yield reactions we recommend, however, higher-boiling solvents such as TFT or chlorobenzene.

The conversion rate of adamantane in the course of the PTC bromination in fluorobenzene clearly depends on the NaOH concentration (Figure 4). These reactions can, of course, also be initiated by other bases (Li, K, Cs, Ba hydroxides), with a continuous increase in reactivity for the alkali hydroxides with increasing solubility in water, that is, growing cation radius.[51] The reactions can also be initiated with aqueous NaOAc but are considerably slower due to the much smaller amount of hydroxide ions present. Remarkably, $NaClO_3$ also triggers the bromination of adamantane under otherwise identical conditions (assuming a similar mechanism); of course, the chlorate radical also is an oxidizer but this reaction seems to play a minor role because the reaction time and product purity in the case of adamantane is quite comparable to that of the reactions with NaOH.

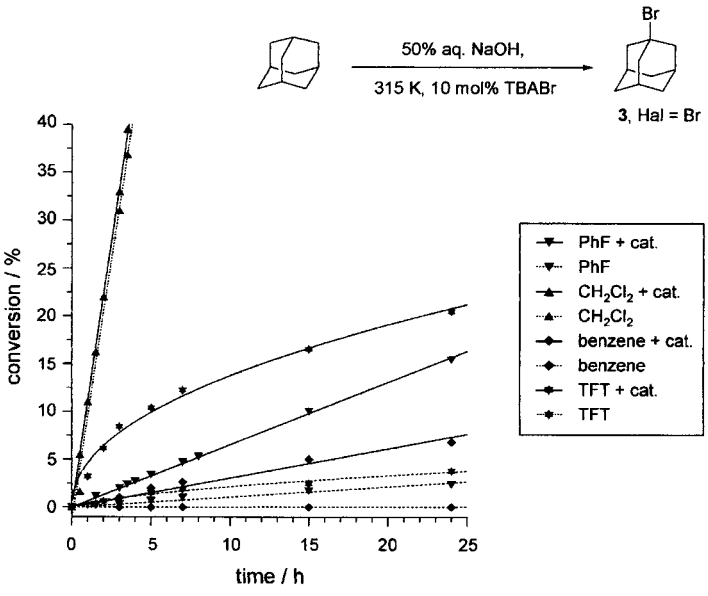


Figure 3. Solvent dependence of the bromination of adamantane under phase-transfer conditions; TBABr = tetra *n*-butyl ammonium bromide, TFT = 1,1,1-trifluoromethyl benzene, PhF = fluorobenzene, cat. = phase-transfer catalyst.

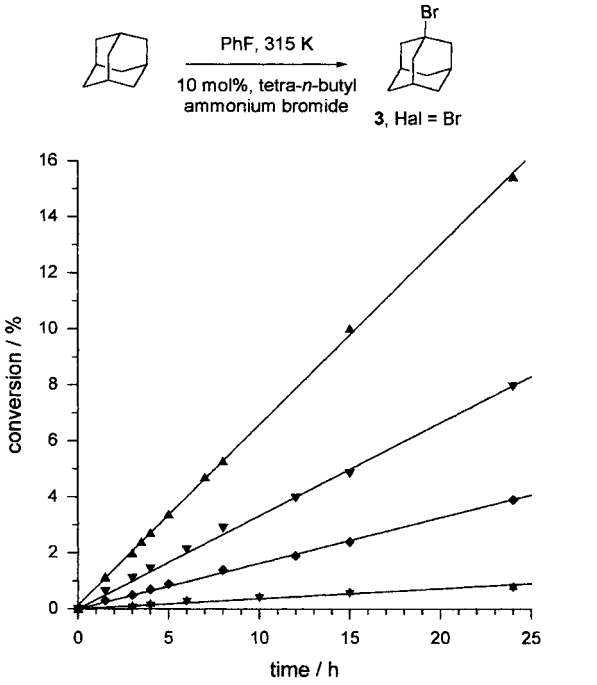


Figure 4. Base concentration dependence of the bromination of adamantane under PT conditions. ✱, 0% aq. NaOH; ◆, 10% aq. NaOH; ▼, 25% aq. NaOH; ▲, 50% aq. NaOH.

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The catalyst plays a decisive role for the title reactions in fluorobenzene (Figure 5). As the initial rate of conversion is faster with increased alkyl chain lengths for the three tetraalkyl ammonium salts examined (ethyl, *n*-butyl, and *n*-octyl ammonium bromide), transfer of the key reactants across the phase boundary must play an important role and hints to an extraction mechanism.[18] Although tetra-*n*-octyl ammonium bromide (TOctABr) displays the highest initial rate, the catalyst activity is reduced in the course of the reaction probably due to functionalization or Hofmann degradation of the catalyst under the strongly basic conditions; this is enhanced for longer alkyl chain lengths in the ammonium salts due to increased solubility in the organic phase. Hence, we found that tetra-*n*-butyl ammonium bromide (TBABr) is most suitable in these transformations, and we used this catalyst for all other mechanistic studies. The TBABr concentration dependence for the bromination of adamantane (Figure 6) further emphasizes that these reactions *are* indeed phase-transfer catalyzed.

Although we initially focused on alkanes only, we have begun studying functional group tolerance in the functionalization of unactivated compounds utilizing our new PTC method. As adamantane derivatives were studied most extensively (but not exclusively) and are ideal model substrates for these types of studies, we examined the reactions of ethers, non-enolizable keto-derivatives, phenyl- and phenoxy-adamantane (**11**–**18**) under conditions very similar to the ones described above (Figure 7). Several important functional groups are tolerated; the halogenation of ketals (**13**) is particularly encouraging because ketones can thus be protected and functionalized in positions more remote than C_α. Halogens can also be introduced in phenyl group containing alkanes without attack of the aromatic ring (**17** and **18**) which nicely complements electrophilic aromatic substitution chemistry.

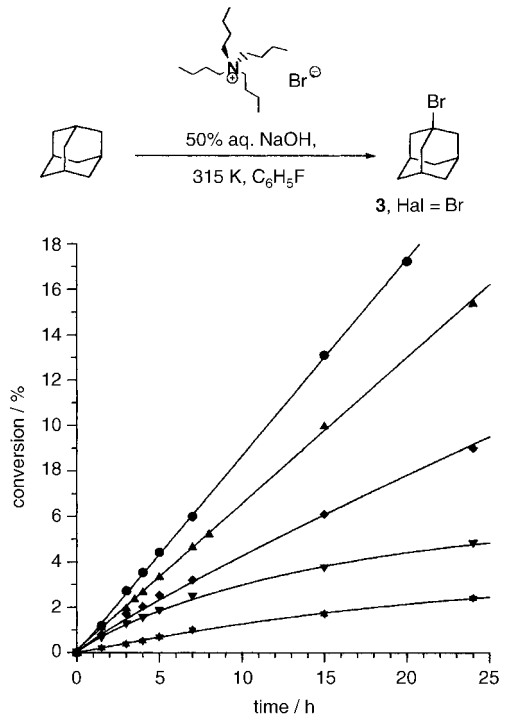

Figure 6. Catalyst concentration dependence of the bromination of adamantane in fluorobenzene under phase-transfer conditions. ✱, 0 mol %; ▼, 1 mol %; ◆, 5 mol %; ▲, 10 mol %; ●, 20 mol %.

Concluding Remarks and Future Directions

Radical reactions can efficiently be carried out under phase-transfer conditions in a controlled and selective fashion. Here we have shown a first example of this concept applied to the functionalization of alkanes. Thus, haloalkanes can be synthesized conveniently from unactivated saturated hydrocarbons with good to excellent preparative yields utilizing selective radical reactions likely to be initiated by dissociative single-electron transfer under phase-transfer conditions. Linear, branched, and (poly)cyclic, strained as well as unstrained aliphatics can be halogenated with high selectivities without rearrangement or fragmentation. The multiphase system avoids overfunctionalization of the products and simplifies the workup; the synthetic protocol is simple yet efficient and safe enough to be carried out in undergraduate labs where it is currently already in use for instructional purposes at several universities.

We are presently examining the possibilities for *enantiose-*

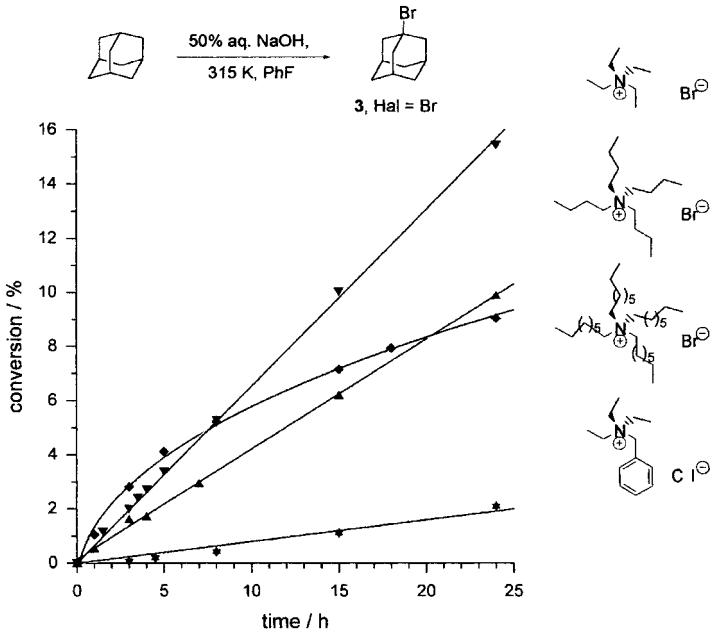

Figure 5. Bromination of adamantane with CBr_4 under PT conditions with different catalysts; ✱, TEtABr = tetraethyl ammonium bromide, ▼, TBABr = tetra-*n*-butyl ammonium bromide, ◆, TOctABr = tetra-*n*-octyl ammonium bromide, and ▲, TEBACl = triethylbenzyl ammonium chloride.

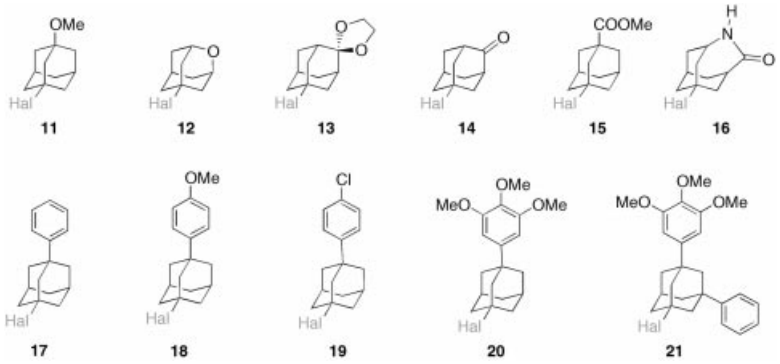

Figure 7. First assessment of functional group tolerance of PTC halogenations; halogenated products from the respective starting materials. The reaction conditions are similar to the ones presented above for alkanes; absolute yields (not run to full conversion to avoid polyhalogenation, unreacted starting materials were recovered almost quantitatively): **11** = 35 % (I), **12** = 61 %, **13** = 31 % (Br), 39 % (I), **14** = 31 % (Br), **15** = 25 % (Br), **16** = 18 % (Br), **17** = 56 % (Cl), 61 % (Br), 64 % (I), **18** = 56 % (Br), 59 % (I), **19** = 63 % (Br), 66 % (I), **20** = 59 % (Br), 62 % (I), and **21** = 52 % (Br), 53 % (I).

lective alkane C–H bond functionalization by using chiral bases (e.g., alkoxides), chiral halogen-transfer reagents, or, and this is the most promising avenue, chiral PTC catalysts.[52] With the design of new sterically well-defined PTC catalysts we also hope to achieve regioselectivities for activating thermodynamically less favored C–H bonds which could otherwise not be functionalized. Our studies on functional group tolerance also are on-going and promise access to new or otherwise far less easily accessible starting materials of high synthetic value.

Acknowledgements

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