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Why Are Organotin Hydride Reductions of Organic Halides So Frequently Retarded? Kinetic Studies, Analyses, and a Few Remedies

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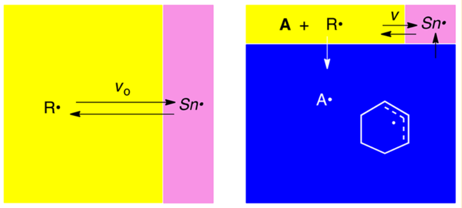
Ⓢ *Supporting Information*

ABSTRACT: Kinetic data for reduction of organic halides (RX) by tri-*n*-butylstannane (*Sn*H) reveal a serious flaw in the current view of the kinetic radical chain: the tacit but unproven assumption that the speed of reaction is determined by the slowest propagation step. Our results show this is rarely true for reductive chains and that the observed rate is in fact controlled by unseen side-reactions of propagating $R^\bullet$ and $Sn^\bullet$ radicals with the solvent (notably, benzene!) or solvent impurities (e.g., trace benzophenone dryness indicator in THF) or, crucially, with allylic-CH and conjugated unsaturated groups in substrates and products. Most $R^\bullet$ and/or $Sn^\bullet$ radicals are therefore converted into relatively inert delocalized species $\mathbf{A}^\bullet$ and/or $\mathbf{B}^\bullet$ that inhibit the chain. Retardation in the degraded chain is given by a simple sum of terms, each being the ratio of the chain-transfer rate divided by the rate of chain-return. The model kinetic equation is linear and easy to ratify, interpret, and apply: to calculate retarding rate constants, optimize reaction conditions, and identify additives or "remedies" that repair the chain and accelerate reaction. The present work is thus expected to have a helpful impact on the practice and design of *Sn*H radical chain based (and related) syntheses.



■ INTRODUCTION

Since its introduction in the 1960s, the "reduction of alkyl halides by organotin hydrides"[1] has been the most widely used free-radical method in organic synthesis research.[2] Reduction takes place by the two-step free-radical chain shown in Scheme 1.

Scheme 1. Organotin Hydride Free-Radical Chain

Initiation	*rate*	
*i*NN*i* → *i*• + *Sn*H → *Sn*•	R_i	(1)
Propagation		
Sn• + RX → *Sn*X + R•	$k_X[RX][Sn\bullet]$	(2)
R• + *Sn*H → RH + *Sn*•	$k_H[SnH][R\bullet]$	(3)
Termination		
2 x radical• → non-radicals	$2k_t[\bullet]^2$	(4)
Overall Reaction		
RX + *Sn*H → RH + *Sn*X	$v = -d[RX]/dt$	(5)

In Scheme 1, RX is most commonly an organic bromide or iodide and "*Sn*H" is usually $n\text{-Bu}_3\text{SnH}$[2a−g] or the less toxic $(Me_3Si)_3SiH$ (TMS_3SiH).[2h] The method offers a mild, versatile, and selective method for constructing organic molecules.[2]

The mechanism and kinetics shown in Scheme 1 have been extensively studied: As early as 1968 it was stated:[3] "The evaluation of the rate constants for both propagation reactions and for two out of the three possible termination reactions means that these processes are now among the best understood two-step chain reactions". Since that time, many more rate constants for the propagation reactions 2 and 3 have been measured using laser flash photolysis (LFP),[4] kinetic competition,[5] radical "clocks", and ESR methods.[6]

Kinetic analysis of Scheme 1 for an alkyl bromide or iodide (for which $k_X \gg k_H \approx 10^6\ M^{-1}\ s^{-1}$) yields the overall, *Sn*H-limited, maximum, or "ideal" rate:[7]

$$v_0 = d[RH]/dt = k_H[SnH](R_i/2k_t)^{1/2} \tag{6}$$

Reduction of an alkyl bromide under typical experimental conditions ($[SnH] = 0.085$ M, $R_i = 4 \times 10^{-8}$ M s^{-1}, $2k_t \approx 3 \times 10^9$ M^{-1} s^{-1}) would be expected to run to completion via a very long chain ($\delta_0 = v_0/R_i \approx 20000$) in just a few minutes. In practice, the reductions of most halides are much slower than the ideal rate of eq 6, often require large amounts of initiator, and have chain lengths much shorter than predicted. Moreover, it is reductions involving the most reactive $R^\bullet$, with the largest k_H values, that tend to have the slowest reaction rates.[8]

Herein we show that these "slow" reactions invariably involve the formation of relatively unreactive radicals by the transfer of some radical centers from the main chain (i.e., from $Sn^\bullet$ or $R^\bullet$) to create less reactive (often resonance-stabilized) radicals. These may be unable to abstract hydrogen from the *Sn*H (thus breaking the chain and stopping the reaction), may abstract hydrogen very slowly (thus retarding the reaction), or may

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undergo a reversal of transfer (which will also retard the reaction). Notably, chain-breaking radicals include cyclohexadienyls, and these may be formed by addition of the propagating $R^•$ radical to an arene, including benzene solvent! Such inhibition of the reaction is most dramatic with aryl and vinyl halides but can also occur with alkyl halides, *particularly at the very low SnH concentrations often employed in syntheses.* The overall rate is struck from a balance between the transfer of radical centers from the main chain (to form radicals of low reactivity) and the return of these low reactivity radical centers to the main chain. When return to the main chain can be hastened or catalyzed there is a consequent improvement in the reaction rate and product selectivity.

In the pioneering kinetic study,[3] Carlsson and Ingold used the rotating-sector method to obtain the propagation and termination rate constants for the *Sn*H reduction of alkyl halides under nitrogen in cyclohexane at 25 °C.[9] In this and related studies, it has been noted that *Sn*H reduction rates can vary erratically from adventitious factors such as traces of peroxides and olefins in organic halides and the presence of oxygen, O_2 (which can initiate, accelerate,[10] or retard a reaction depending on conditions[3]). Scatter was minimized in this early study by excluding oxygen and unwanted light and by using materials freshly purified by distillation and alumina filtration.[3]

■ RESULTS

1. Reduction of Organic Halides in Cyclohexane.

In the present work, reactions were thermally initiated using either di-*tert*-butyl hyponitrite (BONNOB: ***i*NN*i***, $\boldsymbol{i}^•$ = *t*-BuO$^•$) or azobismethylvaleronitrile (AMVN: $\boldsymbol{i}^•$ = ^{i}BuMe(CN)C$^•$), where the initiation rates are given by eqs 7 and 8:[11]

$$R_i = 10^{(14.9-28.1/2.3RT)}[\mathrm{BONNOB}]/\mathrm{s} \qquad (7)$$

$$R_i = 10^{(15.4-29.7/2.3RT)}[\mathrm{AMVN}]/\mathrm{s} \qquad (8)$$

In a typical experiment, a mixture of 1-bromoheptane (290 mM) and the azo-initiator (2.2 mM BONNOB) in cyclohexane was warmed (42 °C) in an argon-sparged ampule, and the reaction initiated by injection of neat deoxygenated *n*-Bu$_3$SnH (85 mM). Samples were removed at intervals and added to 10 volumes of CCl$_4$. The CCl$_4$ induces a fast, spontaneous reaction that consumes all of the remaining *Sn*H, converting it into Bu$_3$SnCl. This allows the reaction to be monitored using the tin halide product ratio: $\alpha = (Sn\mathrm{Br}/Sn\mathrm{Cl})_{\mathrm{gc}}$. This reduction was 42%, 73%, and 93% complete after 120, 240, and 480 s, corresponding to an average reaction rate constant, $k_{\mathrm{obs}} = 4.4 \pm 0.4 \times 10^{-3}\ \mathrm{s}^{-1}$, an initial reaction velocity, $v = 3.8 \times 10^{-4}$ M/s, and a kinetic chain length, $\delta = v/R_i = 3.8 \times 10^{-4}\ \mathrm{M/s}/4 \times 10^{-8}\ \mathrm{M/s} = 9500$. The propagation rate constant (k_H) can now be calculated from eq 6 using eq 7 for the initiation rate[11] and by assuming a diffusion-controlled termination rate constant, i.e.,

$$2k_t \approx 2.6 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}\ (T/298\ \mathrm{K})/(\eta/\mathrm{cP}) \qquad (9)$$

or $4 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for cyclohexane at 315 K.[12] The foregoing data for the hept-1-yl radical indicate

$$k_H = (2k_t/R_i)^{1/2} k_{\mathrm{obs}} = 1.5 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1} \qquad (10)$$

This value for k_H is approximately half the LFP value for a primary alkyl radical ($3 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 315 K)[4a] but it is close to the range found in the original rotating sector study[3] for hex-1-yl$^•$ ($0.7-1.4 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 298 K). Reductions of cyclohexyl and *tert*-butyl bromides under matched conditions indicated, as expected,[3] similar propagation rate constants ($k_H \approx 1-2 \times 10^6\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$); see Table 1.

Table 1. Reduction Rates and Calculated Propagation Rate Constants in Cyclohexane (315 K)*[a,b]*

halide, R–X	k_{obs} (10^{-4} s^{-1})	k_H (10^5 M^{-1} s^{-1})
CH_3–I	90	40 (110)[c]
$CH_3(CH_2)_5CH_2$–Br	40 (±4)	14 (30)[c]
c-C_6H_{11}–Br	38 (±4)	13 (22)[c]
t-Bu–Br	32 (±3)	10 (25)[c]
Br–CH_2CO_2Et	55	18
Br–$CH(CH_3)CO_2Et$	50	16 (44)[d]
Br–$C(CH_3)_2CO_2Et$	8 (±1)	3 (2)[d]
Br–$CH(CO_2Et)_2$	65	18

[a] *Sn*H/RX/BONNOB = 80:300:2.2 mM; stannane decay rate, $k_{\mathrm{obs}} = [[\ln(1+\alpha)]/t]_{\mathrm{av}}$ (±SD), $\alpha = (Sn\mathrm{Br}/Sn\mathrm{Cl})_{\mathrm{gc}}$. [b] $k_H = k_{\mathrm{obs}}/(R_i/2k_t)^{1/2}$ (eqs 7, 9, and 10 with $R_i = 4 \times 10^{-8}$ M/s and $2k_t = 4 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). [c] Reference 4a. [d] Reference 13.

Reduction of methyl iodide was 80% complete by the first sampling and was thus roughly 4-fold faster than that for the alkyl bromides. Replacement of the Bu$_3$SnH with TMS$_3$SiH[2h] afforded 5-fold slower reduction, indicating $k_{\mathrm{heptyl}^•/\mathrm{TMS3SiH}} = 3 \times 10^5\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 315 K (cf.[2h] $4 \times 10^5\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at 298 K). All these results are in fair agreement with literature values[3,4] (given in parentheses in Table 1) and indicate that reasonable absolute values for k_H can be calculated from observed reaction rates in cyclohexane solvent.

Likewise, reductions of α-ester-substituted bromides BrCH$_2$CO$_2$Et, BrCMeHCO$_2$Et, and BrCH(CO$_2$Et)$_2$ were all faster than the alkyl bromides, indicating that the α-ester group increases these radicals' reactivity toward the *Sn*H. These results are consistent with those reported by Newcomb et al. using the LFP-calibrated "clock" PTOC ester method.[13] The faster reactions of electron-deficient $R^•$ radicals with *Sn*H are usually attributed to favorable polar effects in the transition state, $Sn^{\delta+}...H^•...R^{\delta-}$. The slower reduction rate for tertiary species Br–CMe$_2$CO$_2$Et (Table 1) may result from the diminished polar effect and greater radical stabilization in $^•$CMe$_2$CO$_2$Et.

Benzyl bromide ($R^• = \mathrm{PhCH_2}^•$) was reduced ~20-fold more slowly than 1-bromoheptane: $k_{\mathrm{obs}} = 1.8 \times 10^{-4}\ \mathrm{s}^{-1}$, corresponding to $k_H^{\mathrm{PhCH2}^•} = 5 \pm 1 \times 10^4\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$. This value is in good agreement with Franz et al.'s[14] $k_H^{\mathrm{PhCH2}^•} = 10^{(8.65-5.58/2.3RT)} = 6.3 \times 10^4\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ (315 K). The reduction rates (v_{RX}) of other benzylic and allylic halides (RX) were then measured *relative* to that of benzyl bromide under matched conditions using the formula

$$k_H = (v/v_{\mathrm{PhCH2Br}}) \times 6.3 \times 10^4\ \mathrm{M}^{-1}\ \mathrm{s}^{-1} \qquad (11)$$

The reduction rates for allyl and crotyl bromides (Table 2) were ~8-fold slower than for benzyl bromide, indicating that these allylic radicals were 8-fold less reactive than the 1°- and 2°-benzylic radicals ($k_H^{\mathrm{allylic}^•} \approx 4-8 \times 10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$).

The reactions of 2-cyclohexenyl bromide, 2-cyclopentenyl bromide, and BrCHPh$_2$ were very slow, each taking 4 h to produce a 2% conversion, which is ca. 100-fold slower than benzyl bromide ($k_H^{2°\text{-allylic}^•} \approx k_H^{\mathrm{Ph2CH}^•} \approx 5 \pm 2 \times 10^2\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). This is close to the lower limit of reactivity suitable for the present overall rate method, with the chain lengths being only

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Table 2. Reduction of Benzylic and Allylic Halides in Cyclohexane Solvent (315 K)[a]

halide, R−X	$100v_{RX}/v_{PhCH2Br}$	k_H (10^3 M^{-1} s^{-1})
$PhCH_2$−Br[b]	100	63[c]
Ph(Me)CH−Br	40 ± 3[d]	25
Ph_2CH−Br	1.1	0.7
CH_2=$CHCH_2$−Br	14 ± 2	8
CH_3CH=$CHCH_2$−Br	11 ± 1	7
2-cyclohexenyl−Br	0.9	0.5
2-cyclopentenyl−Br	1.1	0.6

[a] Relative rates in matched ampules. [b] $v_{PhCH2Cl} \approx v_{PhCH2Br}$. [c] The benchmark value. [d] ± 1SD.

~3−5. An even slower R• + *Sn*H reaction has been calibrated by a different method:[16] $k_H = 10^{(7.65-7.8/2.3RT)}$ or 180 M^{-1} s^{-1} at 315 K for *Sn*H = Et_3SnH and the "clock" radical R• = *c*-$C_3H_5Ph_2C$•.

The remarkably good linear correlation between $\log(k_{R^\bullet/SnH})$ and the R−H bond dissociation enthalpy *D*(R−H) for nonpolar radicals[17] will be examined later.[15] Suffice it to note here that for the reduction to be a chain process, the H atom transfer to R• from *Sn*H must be faster than radical/radical termination, i.e., $k_H[SnH] > 15$ s^{-1} (vide infra). This may not be the case for nonpolar R• radicals for which *D*(R−H) ≤ 82 kcal/mol. (For *D*(R−H) = 82 kcal/mol, $k_H \sim 500$ M^{-1} s^{-1}). Thus, 2°- and 3°-allylic radicals do not carry the chain in the dilute *Sn*H solutions often used for radical synthesis,[18] while bis-allylic radicals would be chain-terminating at any [*Sn*H] (see below, arene addition).

2. Reduction Rates in Common Solvents. The azo-initiated *Sn*H reduction of 1-bromoheptane was not retarded in the solvents cyclohexane, *n*-hexane, ethyl acetate, *tert*-butyl acetate, *tert*-butyl alcohol, or THF[19] (see Table 3). The rate was somewhat slower in acetone probably because of a reaction of the *Sn*• radical with this solvent, since the rate of reduction of the much more reactive 1-iodoheptane was the same in acetone as in the other nonaromatic solvents (see footnote *b* in Table 3).

Table 3. Reduction Rates of 1-Bromoheptane in Common Solvents and Derived k_H (315 K)[a]

solvent	k_{obs} (10^4 s^{-1})	k_H (10^5 M^{-1} s^{-1})
cyclohexane	40 (±4)	14
n-hexane	26 (±2)	13
ethyl acetate	28	15
tert-butyl acetate	34 (±2)	15
tert-BuOH	80	16
THF	24 (±4)	11
Me_2C=O	9/36[b]	3/15[b]
benzene	8 (±1)	3

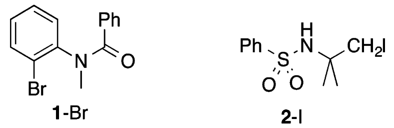
[a] Per Table 1 (η^{315K} from *CRC Handbook of Chemistry & Physics*; CRC Press: Boca Raton, FL, 2005. [b] Value for RX = 1-iodoheptane.

The k_H values calculated using eqs 9 and 10, i.e., adjusted for the effect of solvent viscosity on radical/radical termination rate constants, show even smaller kinetic solvent effects than those seen in the raw reaction rate data (see Table 3), which assume a constant[20] R_i. The k_H value for the hept-1-yl radical is therefore rather insensitive to solvent polarity and to chain-transfer to these solvents.

By comparison, reductions in the aromatic solvents: PhH, PhCl, $PhCF_3$ $PhCH_3$, and $PhCMe_3$ (i.e., in the "traditional" solvents used for free-radical syntheses) were up to 50-fold slower, depending on the *Sn*H and initiator concentrations. This large "solvent effect" is due to side reactions of propagating radicals with the solvent and/or substrate (in the case, e.g., of ArBr or ArI) and is examined below following a brief account of the relevant chain-transfer kinetic equations.

3. Chain-Breaking Chain Transfer. The origins of the present investigations were some unexpectedly slow *Sn*H reductions during synthetic studies in the Beckwith group.[21] Aryl bromide, **1**−Br, and the alkyl iodide, **2**−I (and related species), proved extraordinarily difficult to reduce and required large amounts of initiator and long heating times (Scheme 2).

Scheme 2



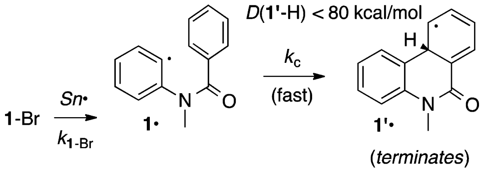
Rates of halogen abstraction from these compounds by the *Sn*• radical were measured by competition kinetics (Experimental Section) and, despite the very long reaction times, were "normal":

$$k_{Sn^\bullet/\mathbf{1}-\mathrm{Br}} \approx 1.7k_{Sn^\bullet/\mathrm{PhCH2Cl}} = 2 \times 10^6\ \mathrm{M^{-1}\ s^{-1}} \quad (12)$$

$$k_{Sn^\bullet/\mathbf{2}-\mathrm{I}} \approx 1.3k_{Sn^\bullet/\mathrm{PhCH2Br}} = 2 \times 10^9\ \mathrm{M^{-1}\ s^{-1}} \quad (13)$$

It soon became clear that after **1**• underwent intramolecular arene addition, it produced a resonance-stabilized radical that was incapable of propagating the chain. Treatment of **1**−Br under standard conditions produced only ~1% reduction after 2 h, indicating a chain length *δ* = 1−2 (i.e., no "chain") (Scheme 3).

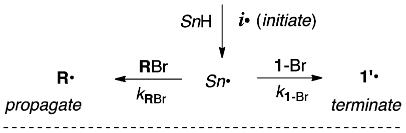
Scheme 3



This phenomenon was investigated further. The addition of **1**−Br to an ongoing reduction of 1-bromoheptane greatly retarded the reaction and the rate became approximately first order in R_i and in [bromoheptane] but was zero order in [*Sn*H]!

The kinetics of this situation are modeled in Scheme 4. It is proposed **1**−Br acts as a chain-breaking trap for *Sn*• (not R•). Each time a propagating *Sn*• radical reacts with **1**−Br, a radical chain is terminated. For long ($v \gg R_i$) but strongly retarded ($v_0 \gg v$) chains, the chain length (*δ*) can be approximated by eq 14, which is derived from a simple kinetic competition between propagation and termination. The rate constant ratio $k_{1\text{-Br}}/k_{RBr}$ calculated from the chain length, viz., $k_{1\text{-Br}}/k_{\text{heptyl-Br}} = \delta_{obs}^{-1}$ [RBr]/[**1**−Br] ≈ 0.08, is in good agreement with the ratio derived from the known absolute rate constants[4] ($1.8 \times 10^6/3 \times 10^7 = 0.06$). This supports the premise that abstraction of Br

Scheme 4. Chain Length Kinetic Model: $Sn^\bullet$ Type



chain length = propagation rate / termination rate

$$\delta = \frac{k_{\mathrm{RBr}}[\mathrm{RBr}][Sn\bullet]}{k_{1\mathrm{Br}}[\mathbf{1}\text{-}\mathrm{Br}][Sn\bullet]} = \frac{k_{\mathrm{RBr}}[\mathrm{RBr}]}{k_{1\text{-}\mathrm{Br}}[\mathbf{1}\text{-}\mathrm{Br}]} \quad (14)$$

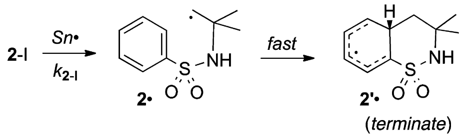
reduction rate = initiation rate x chain length

$$v = d[\mathrm{RH}]/dt = R_{\mathrm{i}}\delta = R_{\mathrm{i}}\left(\frac{k_{\mathrm{RBr}}}{k_{1\text{-}\mathrm{Br}}}\right)\frac{[\mathrm{RBr}]}{[\mathbf{1}\text{-}\mathrm{Br}]} \quad (15)$$

from **1**−Br invariably leads to the termination of one bromoheptane reduction chain.

Iodide, **2**−I, behaved similarly but was vastly more active as a chain terminator than **1**−Br because alkyl iodides are more reactive toward $Sn^\bullet$ than aryl bromides ($k_{2-\mathrm{I}} \sim 10^3 \times k_{1-\mathrm{Br}} \sim 2 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) (Scheme 5).

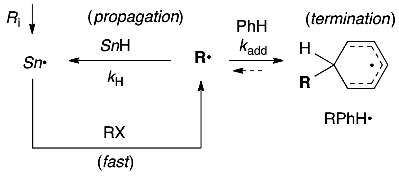
Scheme 5



Indeed, **2**−I acted as a true inhibitor[22] of alkyl bromide reductions. The addition of just 50 μM **2**−I to 7 M 1-bromoheptane containing *Sn*H and initiator produced an inhibition period that lasted until the **2**−I had been consumed (~30 min by GC); thereafter, the reaction resumed its pre-**2**−I reduction rate.

It had by now become clear that the slow reactions seen in aromatic solvents resulted from chain-breaking chain transfer via intermolecular $R^\bullet$ radical addition to the solvent. While the chain-transfer from $R^\bullet$ to benzene yields only a trace of addition products (~0.1%), its effect on the chain redefines the reduction kinetics as per Scheme 6 (see the Supporting Information for reversible addition).

Scheme 6. Chain Length Kinetic Model: $R^\bullet$ Type



chain length

$$\delta = \frac{\textit{propagation rate}}{\textit{termination rate}} \sim \left(\frac{k_{\mathrm{H}}}{k_{\mathrm{add}}}\right)\frac{[Sn\mathrm{H}]}{[\mathrm{PhH}]} \quad (16)$$

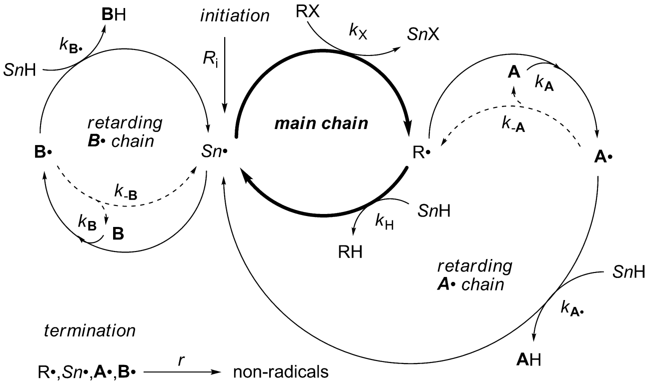
reduction rate

$$v \sim R_{\mathrm{i}}\left(\frac{k_{\mathrm{H}}}{k_{\mathrm{add}}}\right)\frac{[Sn\mathrm{H}]}{[\mathrm{PhH}]} \quad (17)$$

To illustrate, if there is one chain-breaking reaction with solvent per thousand $R^\bullet$ + *Sn*H reactions (0.1%), the observed chain length (v/R_i) cannot be greater than 1000. Thus, if the "ideal" chain length is, e.g., 10000, the observed rate will be only 10% of the ideal rate. Such reactions are not strongly retarded and require a more general treatment that includes second-order termination (vide infra).

4. Kinetic Model. Reduction of an organic halide in a mixture containing species that transfer some radical centers (•) from the main chain to lower reactivity radicals ($R^\bullet + \mathbf{A} \rightarrow \mathbf{A}^\bullet$ and $Sn^\bullet + \mathbf{B} \rightarrow \mathbf{B}^\bullet$) is represented in Scheme 7, in which transfer can be via atom-abstraction or radical-addition. An example of "**B**" would be a halide (e.g., **1**−Br) that reacts with the $Sn^\bullet$ radical to produce a slow- or nonpropagating "$\mathbf{B}^\bullet$" radical (e.g., $\mathbf{1'}^\bullet$); an example of "**A**" would be an arene that adds a propagating $R^\bullet$ radical to produce a slow- or nonpropagating "$\mathbf{A}^\bullet$" radical (the adduct $\mathrm{RArH}^\bullet$).

Scheme 7. Chain-Transfer Degraded-Chain Reduction



In these analyses, it is assumed that all radical−radical reactions,[23] including those involving resonance-stabilized radicals,[24] will be diffusion controlled with rate constants given by eq 9.[25] This simplifies the kinetics greatly compared to polymerization and autoxidation radical chains (where $2k_\mathrm{t}$ can vary over a wide range). Thus, it follows from the normal steady-state assumption, $R_\mathrm{i} = 2k_\mathrm{t}[^\bullet]^2$, that a uniform pseudo-first-order *radical-center termination rate constant* can be assigned to these systems:

$$r = 2k_\mathrm{t}[^\bullet] = (2k_\mathrm{t}R_\mathrm{i})^{1/2} = R_\mathrm{i}/[^\bullet] \quad (18)$$

This is usually in the range 10−30 s^{-1} (for a radical-center turnover time, $\tau_{(\bullet)} = [^\bullet]/R_\mathrm{i} \approx 0.06$ s).

4.1. Reduction without Chain Transfer. Steady-state analysis of the main chain in Scheme 7 yields the maximum or *ideal* stannane-limited reaction rate:

$$v_0 = k_\mathrm{H}[Sn\mathrm{H}][\mathrm{R}^\bullet] = k_\mathrm{H}[Sn\mathrm{H}](R_\mathrm{i}/2k_\mathrm{t})^{1/2}$$

or which the chain length, δ_0, is given by

$$\delta_0 = v_0/R_\mathrm{i} = k_\mathrm{H}[Sn\mathrm{H}]/r \quad (19)$$

A more complete analysis[26] yields the rate equation

$$\frac{v_0}{v} = 1 + \frac{k_\mathrm{H}[Sn\mathrm{H}] + r}{k_\mathrm{X}[\mathrm{RX}]} \quad (20)$$

$$v = \left(\frac{k_\mathrm{X}[\mathrm{RX}]k_\mathrm{H}[Sn\mathrm{H}]}{k_\mathrm{X}[\mathrm{RX}] + k_\mathrm{H}[Sn\mathrm{H}] + r}\right)(R_i/2k_t)^{1/2} \quad (21)$$

The bracketed term in eq 21 is typically within a few percent of unity for an alkyl bromide RX, and *r* is insignificant. The point at which the chain collapses (from dilution or from low reactivity) is where *r* ceases to be insignificant. Thus, e.g., bis-benzylic or 2°-allylic radicals[18] ($k_\mathrm{H} \sim 500\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) are expected to terminate rather than propagate if [*Sn*H] is less than ~10 mM (500 M^{-1} s^{-1} × 0.01 M = 5 s^{-1}), which leads to unsatisfactory yields and annoying mixtures of products.

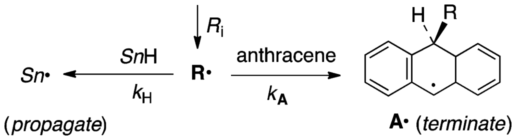
4.2. Reduction with Chain Transfer. Similarly,[26] Scheme 7 affords eq 22 for the ideal rate/observed rate ratio (cf. eq 20). This contains two rate-retarding chain-transfer (C-T) terms: one for transfer of radical centers from $R^\bullet$ to **A** and one for transfer from $Sn^\bullet$ to **B**. Equation 22 is linear, and it is therefore readily applied to various limiting scenarios and can be used to identify reaction mechanisms via simple kinetic tests.

$$\begin{aligned}\frac{\text{ideal rate}}{\text{obsd rate}} &= \frac{v_0}{v} \\ &= 1 + \frac{k_H[SnH] + r}{k_X[RX]} + \frac{k_A[\mathbf{A}]}{k_{\mathbf{A}^\bullet}[SnH] + k_{-\mathbf{A}} + r} \\ &+ \frac{k_H[SnH]}{k_X[RX]}\,\frac{k_B[\mathbf{B}]}{k_{\mathbf{B}^\bullet}[SnH] + k_{-\mathbf{B}} + r} \qquad (22)\end{aligned}$$

Chain transfer changes the radical mixture from one comprising $R^\bullet$ and $Sn^\bullet$ radicals to one dominated by sluggish $\mathbf{A}^\bullet$ (and/or $\mathbf{B}^\bullet$) species (see the Discussion). The **A** and **B** expressions in eq 22 represent the reduction in relative reaction rate, and hence increase in reaction time, induced by the presence, or addition, of the chain-transfer agent. The fact that chain transfer is much slower than propagation means that the resulting retardation is more sensitive to $R^\bullet$ reactivity than is propagation. Accordingly, the more active the $R^\bullet$ radical the *slower* will be the reaction. This is clearly evident from the chain-lengths for reductions in aromatic solvents, which we now examine in more detail.

5. Chain Breaking $R^\bullet$/Arene Addition. Anthracene (An) is a highly reactive arene that can add benzyl, methyl, and other radicals to form adducts ($An^\bullet$) that terminate chains cleanly to produce the expected nonoxidized dimers (An_2).[27] It was chosen as a model for arene addition chain transfer (Scheme 8).

Scheme 8. Chain Length Model for A = Anthracene



Setting $r \gg k_{\mathbf{A}^\bullet}[SnH]$ (no-reinitiation) and generalizing to $R^\bullet$ trapping agents that behave in a manner similar to anthracene by replacing An by **A** allows eq 22 to be written in terms of the kinetic chain length (δ_0 is the ideal chain length, v_0/R_i):

$$\frac{1}{\delta} \approx \left(\frac{k_A}{k_H}\right)\frac{[\mathbf{A}]}{SnH} + \frac{1}{\delta_0} \qquad (23)$$

This has a strong similarity to the Mayo equation for (mean physical) chain length in polymer chemistry.[28] The first term on the right of eq 23 represents first-order (radical-molecule) decay of the propagating radical (rate α R_i), while the second term arises from second-order (radical/radical) decay (rate α $\sqrt{R_i}$). For the purpose of calculating chain-transfer constants ($C_A = k_A/k_H$) from observed rate data; eq 23 may be rearranged to eq 24.

$$\frac{k_A}{k_H} = \frac{[SnH]}{[\mathbf{A}]}\left(\frac{1}{\delta} - \frac{1}{\delta_0}\right) \qquad (24)$$

As an example, a test mixture of anthracene (38 mM), 1-bromoheptane (280 mM), *Sn*H (80 mM), and BONNOB (3 mM, $R_i = 6.0 \times 10^{-8}$ M/s) reacted with first-order kinetics, $k_{obs} = 2.2 \times 10^{-4}$ s^{-1}, and had a chain length, $\delta \approx 250$, versus an unretarded (no anthracene) chain length, $\delta_0 \approx 9{,}000$. These results give the chain-transfer constant k_A/k_H or $C_{An}{}^{heptyl\bullet}$ = (80/38)(1/250−1/9000) = 8 × 10^{-3}. Hence, the rate constant for addition of the hept-1-yl radical to anthracene is $k_{heptyl^\bullet + An}{}^{315\ K} = 0.008 \times (5 \times 10^6)\ M^{-1}\ s^{-1} = 4 \times 10^4\ M^{-1}\ s^{-1}$. This is consistent with the rate constant Fischer calculated from Szwarc's methyl affinity data,[29] viz., $k_{Me^\bullet + An}{}^{315K} = 18 \times 10^4$ M^{-1} s^{-1}, considering methyl/heptyl radical reactivity differences. Other polyaromatics are also likely to be strong **A**-type retarders of *Sn*H reductions of alkyl halides.

The rate retarding effect of benzene solvent (10 M), on the other hand, was mild for alkyl halides, e.g.,

$$\begin{aligned}k_A/k_H &= C_{PhH}{}^{heptyl^\bullet} \\ &= (0.08\ M/10\ M)(1/1930 - 1/9500) \\ &= 4 \times 10^{-6}\end{aligned}$$

Rate retardation increased markedly with increasing thermodynamic reactivity of the $R^\bullet$ radical.

Reactions of aryl and vinyl radicals in benzene were severely retarded. The 315 K chain transfer constants for various solvents with various radicals run under matched conditions are given in Table 4. Benzyl bromide and *tert*-butyl iodide reduction rates were unaffected by benzene.

Table 4. Chain-Transfer Constants (× 10^6) for Some Aromatic Solvents (315 K)[a]

radical[b]	PhH	$PhCH_3$	$PhCF_3$	PhCl
1°-alkyl$^\bullet$	4	7	8	13
2°-alkyl$^\bullet$	2	*c*		6
$CH_3^\bullet$	10			
$C_3H_5^\bullet$	37			85
$Me_2C{=}CH_2^\bullet$	230			
$Ph^\bullet$	400		600	1100

[a] Equation 24 with δ and δ_0 data tabulated in the Supporting Information. [b] RX: 1-bromoheptane; bromocyclohexane; *t*-BuI; CH_3I; C_3H_5I; $Me_2C{=}CHI$ and PhI. [c] Blank = not measured.

Substituted benzenes are more reactive toward radical additions. This reflects the corresponding activation of double bonds to radical addition by alkyl and halogen substituents. Approximate rate constants for addition to benzene can be obtained by multiplying the chain transfer constants by the relevant k_H; i.e.:

Phenyl: $k_{Ph^\bullet + PhH} \approx 2 \times 10^5$ (lit.[30] 4.5×10^5)

Vinyl: $k_{Me2C=CH^\bullet + PhH} \approx 1 \times 10^5$ (lit.[31])

Cyclopropyl: $k_{C3H5^\bullet + PhH} \approx 3 \times 10^3$ (lit.[32] $\leq 3 \times 10^4$)

Methyl: $k_{CH3^\bullet + PhH} \approx 100$ (lit.[29] 120)

1°-Alkyl: $k_{1\text{-heptyl}^\bullet + PhH} \approx 15$.

(Values in M^{-1} s^{-1} at 315K.)

6. *Sn*$^\bullet$ Addition Reactions. These can occur with unsaturated groups, particularly carbonyl groups (the usual "**B**" in Scheme 7). Carbonyls can react with $Sn^\bullet$ to form

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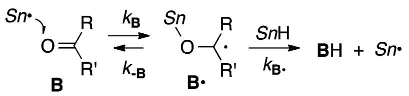
J. Org. Chem. 2015, 80, 1321−1331

stannyloxyalkyl radicals (*Sn*OC$^\bullet$RR′ = **B**$^\bullet$) that may sometimes be reduced by the *Sn*H to yield *Sn*OCHRR′ (**BH**), a hydrostannated ketone,[33] aldehyde,[34] or ester (Scheme 9).[3536]

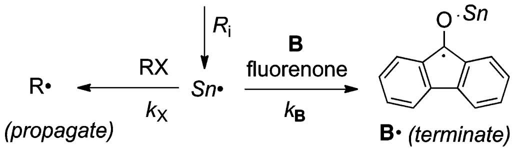
Scheme 9



Alternatively, such **B**$^\bullet$ may undergo β-scission to reform **B** and release the *Sn*$^\bullet$ radical to continue the chain. This back-reaction (rate constant, $k_{-\mathrm{B}}$) means that even very rapid *Sn*$^\bullet$ addition to carbonyls may yield insignificant amounts of the **BH**.

Benzophenone and fluorenone were chosen because their adduct radicals would, for thermodynamic reasons, be unlikely to propagate or undergo β-scission at 315 K.[37,38] Addition of a small amount of either compound strongly retarded the *Sn*H + 1-bromooctane reaction (k_{RBr} [RBr] $\approx 1 \times 10^7$ s^{-1}) in cyclohexane, but only fluorenone blocked the 1-iodooctane reaction (k_{RI} [RI] $\approx 1 \times 10^8$ s^{-1}). The retarded rates were first-order in initiator, zero-order in *Sn*H, and first-order in the substrate halide RX.

Scheme 10. Chain-Length Model for B = Fluorenone



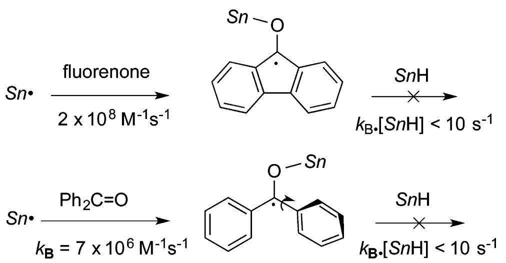
The kinetic competition of Scheme 10 indicates a chain-length, $\delta = k_{\mathrm{X}}[\mathrm{RX}]/k_{\mathrm{B}}[\mathbf{B}]$. More precisely, eq 22 with $r \gg k_{-\mathrm{A}} + k_{\mathrm{A}^\bullet}[Sn\mathrm{H}]$ gives the chain-transfer constant,

$$C_{\mathrm{B}} = \frac{k_{\mathbf{B}}}{k_{\mathrm{X}}} = \frac{[\mathrm{RX}]}{[\mathbf{B}]}\left(\frac{1}{\delta} - \frac{1}{\delta_0}\right) \tag{25}$$

where δ and δ_0 are the observed chain lengths with and without the retarder. The observed chain-transfer constants for 1-bromo- and 1-iodooctane with fluorenone (C_{B} = 5.4 and 0.2) give $k_{\mathrm{Sn}^\bullet\mathrm{+fluorenone}} = 2 \times 10^8$ M^{-1} s^{-1}, in complete agreement with the LFP value.[4b] Similarly, benzophenone yields $k_{\mathrm{Sn}^\bullet\mathrm{+Ph2C{=}O}} = 7 \times 10^6$ M^{-1} s^{-1} (Scheme 11).

The lower rate constant for addition of *Sn*$^\bullet$ to benzophenone, compared with fluorenone, is expected on both entropic and enthalpic grounds because ring rotation must be “frozen” in the transition state for the former ketone, but not for the latter.

Scheme 11



Acetophenone and methyl benzoate also retarded the *Sn*H + 1-bromooctane reaction but with observed rates that were half-order in initiator and (almost) zero order in *Sn*H. This suggests that these two carbonyls (unlike benzophenone and fluorenone) trap *Sn*$^\bullet$ reversibly. Reinitiation via β-scission (rate constant, $k_{-\mathrm{B}}$, in Scheme 7 and eq 22) yields the initial rate retardation expression.

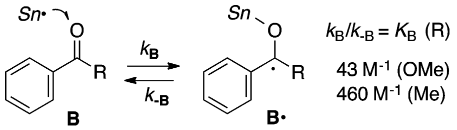
$$\begin{aligned} v_0/v - 1 &= (k_{\mathrm{H}}/k_{\mathrm{X}})k_{\mathrm{B}}[\mathrm{B}]/k_{-\mathrm{B}}[\mathrm{RX}] \\ &= (k_{\mathrm{H}}/k_{\mathrm{X}})K_{\mathrm{B}}[\mathrm{B}]/[\mathrm{RX}] \end{aligned} \tag{26}$$

The value of $(k_{\mathrm{H}}/k_{\mathrm{X}})K_{\mathrm{B}}$ can be calculated from

$$(k_{\mathrm{H}}/k_{\mathrm{X}})K_{\mathrm{B}} = (v_0/v - 1)_{\mathrm{obs}}[\mathbf{B}]/[\mathrm{RX}] \tag{27}$$

Taking $k_{\mathrm{H}}/k_{\mathrm{X}} \approx 0.10$ for a 1-bromoalkane, the observed retarding effects of methyl benzoate and acetophenone gave Scheme 12:

Scheme 12



In these two cases, rate retardation arises because the *Sn*$^\bullet$ radical is reversibly adsorbed onto the C=O group, which diminishes [*Sn*$^\bullet$].[39] Esters are less reactive to addition than ketones because of mesomeric ground-state stabilization. Notably, these two retarded rates were proportional to k_x[RX], implying *that the overall reaction rates might be accelerated up to 10-fold by using iodides rather than bromides* (see below, Figure 1).[40]

7. Retardation by Alkenes: Abstraction of Allylic Hydrogen by R$^\bullet$.

The *Sn*H + 1-bromooctane reaction was strongly retarded in 1-hexene and was fully suppressed in

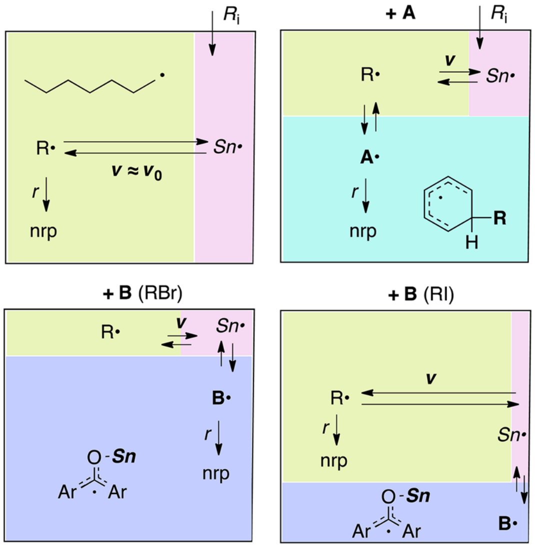


Figure 1. Simplified degraded chain, examples: radical centers flow from R$^\bullet$ (or *Sn*$^\bullet$) to **A** forming delocalized **A**$^\bullet$ (or **B**$^\bullet$) diminishing [R$^\bullet$]$_{\text{steady-state}}$ and retarding reduction. Use of RI diminishes [*Sn*$^\bullet$] and its radical flow to **B**$^\bullet$ ~10-fold, restoring the reduction rate v.

cyclohexene (Table 5). Indeed, the addition of as little as 20 mM cyclohexene to the usual reactant mixture lowered the initial rate by 80%, while the same quantity of 1,4-cyclohexadiene lowered the rate by 97%.

Table 5. Alkene-Retarded Reduction[a]

alkene (M)	$[Sn\mathrm{H}]$[b]	R_i[c]	v_0/v[d]	$k_A/k_{A^\bullet}$
1-hexene (8.4)	0.08	5	6	0.05
1-hexene (8.4)	0.16	5	3[e]	0.04
1-hexene (8.4)	0.08	11	5[e]	0.05_5
c-hexene (0.020)	0.08	5	4.6	18
c-hexene (0.020)	0.08	11	5[e]	20
1,4-CHD (0.02)	0.08	11	30–40[e]	*f*

[a] Relative observed initial rates in matched runs (300 mM Oct-Br) without/with the alkene. [b] M. [c] 10^{-8} M/s. [d] $v_0 = 3.5 \times 10^{-4}$ M/s. [e] $v_0 = 5 \times 10^{-4}$ M/s. [f] For 1,4-cyclohexadiene, $C_A = k_A/k_H = (R_i/v)_{obs}[Sn\mathrm{H}]/[\mathbf{A}] \approx 2\text{–}3 \times 10^{-2}$.

These retarding effects must be due to reactions of $R^\bullet$ (not $Sn^\bullet$) radicals since substantially the same results were found with 1-iodo-octane. Moreover, adding an olefin ($CH_2{=}CHCMe_2CH_2OH$) with no allylic C–Hs had only a small rate-retarding effect.

The retarded rates were consistent with the kinetic equation for the abstraction-degraded chain

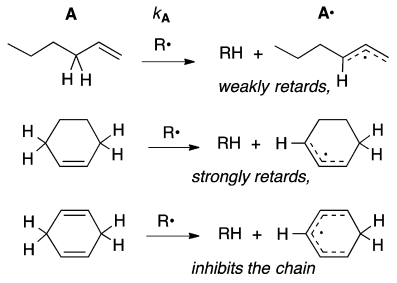
$$v_0/v - 1 = k_{\mathbf{A}}[\mathbf{A}]/k_{\mathbf{A}^\bullet}[Sn\mathrm{H}] \tag{28}$$

which yielded $k_A/k_{A^\bullet}$ (Table 5). Substitution with $k_{A^\bullet}$ from Table 2 ($k_{\text{c-hex-2-enyl}^\bullet/Sn\mathrm{H}}$ and $k_{\mathrm{H3CH{=}CHCH2}^\bullet/Sn\mathrm{H}}$) then affords k_A, the H-abstraction rate constants for the alkenes:

$$k_{\text{1-octyl}^\bullet/c\text{-hexene}} \approx 9000 \text{ and } k_{\text{1-octyl}^\bullet/\text{1-hexene}} \approx 400\ \mathrm{M^{-1}\ s^{-1}}$$

Thus, the 300-fold difference in the retarding effect of cyclohexene versus that of 1-hexene comprises a ~20-fold faster chain transfer and a ~15-fold slower chain return. Retardation is even greater with 1,4-CHD because the chain transfer is ~10-fold faster again and the $\mathbf{A}^\bullet$ radical terminates. Confirming this picture, our observed chain constant ($C_A = k_A/k_H \sim 0.02\text{–}0.03$) is consistent with that for the $R^\bullet$ = hex-5-enyl radical clock:[41] $C_A = k_{R^\bullet/1,4\text{-CHD}}/k_{R^\bullet/Sn\mathrm{H}} = 2 \times 10^5\ \mathrm{M^{-1}\ s^{-1}}/5 \times 10^6\ \mathrm{M^{-1}\ s^{-1}} = 0.04$ (323 K).[42] The situation for the tested species is summed up in Scheme 13.

Scheme 13. Rate Effect of Allylic CHs



Substrates containing these or related groups are expected to suffer a large degree of autoinhibition.

DISCUSSION

Tributyltin hydride reduction of organic halides has been the most frequently used and well-developed[2] method of free-radical synthesis for close on half a century,[1,2i] but little quantitative attention has been paid to its radical chain kinetics under typical laboratory conditions. This is surprising because most reported reduction rates are one or more orders of magnitude slower than those predicted from the propagation rate constants[43] and from those measured[3] for simple organic halides in a nonaromatic solvent. The sheer size of these discrepancies has long cried out for explanation.

One source of sluggish reaction rates, radical addition to arenes, was identified by the Beckwith group[44] while examining the synthetically promising but extremely slow reductions of **1**–Br and **2**–I for which the rates were up to 5,000 times slower than calculated because intramolecular cyclization onto an arene group produced highly stabilized radicals that could not continue the chain (e.g., Schemes 4). It was soon realized that this rate-retarding effect extended to intermolecular *Sn*H/RX radical reactions, particularly in aromatic solvents (see Scheme 6).

Kinetic measurements showed that the *Sn*H dehalogenations of **1**–Br and **2**–I were *not* chain reactions under standard conditions[44−46] and that the addition of small amounts of **1**–Br or **2**–I to a *Sn*H + alkyl halide reaction strongly retarded its rate. Indeed, the more reactive iodide (**2**–I) completely suppressed the reduction of neat 1-bromoheptane until all of the **2**–I had been consumed by $Sn^\bullet$-radicals generated from *Sn*H by the initiator radicals. The kinetics of these retarded coreductions were consistent with the breaking of the radical chains (Scheme 4).

Likewise, radical addition to arenes, e.g., benzene solvent or when the substrate is aromatic, $R^\bullet + ArH \rightarrow RArH^\bullet$ (Scheme 6), transfers some radical centers from the main (fast) chain to slower chains (or nonchains) and retards the reaction (as represented by the $\mathbf{A}/\mathbf{A}^\bullet$ loop in Scheme 4). The $RArH^\bullet$ radicals may then terminate with each other either directly or revert or transfer their radical centers onto the initiator,[44−46] depending on reaction conditions.[26] In the kinetics experiments, addition of $R^\bullet$ to an aromatic solvent is a very minor (but rate-retarding) side reaction. In homolytic arylation,[45] it is reduction of the $R^\bullet$ radical that is the undesired side reaction. In either case, an optimal chain is desired for optimal yields (cf. Remedies, below).

Benzene has been the most widely used solvent for free-radical syntheses because of its chemical compatibility, stability, low polarity, negligible H-donor reactivity, and low radical-addition reactivity. However, despite its popularity among free-radical synthetic chemists, there was plenty of prior evidence from polymer chemistry that, as a solvent, benzene retards the rates of organic-radical chain reactions and that it does so by introducing kinetically first-order chain termination.[47] The addition of various $R^\bullet$ radicals to benzene solvent strongly retards the *Sn*H reductions of aryl, vinyl, and cyclopropyl halides, and it even retards the reductions of 1°- and 2°-alkyl bromides and iodides, especially in dilute *Sn*H solutions (Table 4). Unsurprisingly, given their greater methyl affinities,[29] substituted benzenes retard more than benzene (in the order: chlorobenzene > $CF_3C_6H_5$ > toluene > benzene). However, aromatic solvents did not affect the rates of *Sn*H reactions involving tertiary (*tert*-butyl•) and delocalized (benzyl•) radicals.[48]

Clearly, aromatic solvents should be avoided for *Sn*H reactions that involve aryl or vinyl radicals, and even 1°- and 2°-alkyl radicals, if low [*Sn*H] is required to effect the desired transformation. The standard procedure for working at low

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J. Org. Chem. 2015, 80, 1321−1331

[*Sn*H] is to slowly add the *Sn*H to a dilute reaction mixture in benzene via a motorized syringe pump. The *Sn*H concentration reaches a steady state defined by the addition rate, *P*, the chain-transfer constant, *C*, the initiation rate, and the benzene concentration:

$$[SnH]_{\text{steady-state}} \approx C(P/R_i) \times 10\ \text{M} \tag{29}$$

Thus, benzene solvent might raise $[SnH]_{\text{steady-state}}$ by a factor of 10 over that in an unreactive solvent: i.e., eq 29 with $P = 3 \times 10^{-6}$ M/s, $C = 3 \times 10^{-6}$, and $R_i = 3 \times 10^{-8}$ M/s gives $[SnH]_{\text{steady-state}} = 3$ mM for benzene versus the 0.3 mM calculated for a nonaromatic solvent. This situation is much worse for aryl and other σ-radicals.[49]

The reduction of aryl halides is, of course, strongly self-retarded: $Ar^\bullet + ArX \rightarrow Ar{-}ArX^\bullet$ (terminating). Under the standard conditions, iodobenzene reacted ~40 times more slowly than did 1-bromoheptane in cyclohexane solvent.[26] Since the chain length is proportional to the mole ratio *Sn*H/ArX, the reduction of aryl halides might be optimized by keeping the *Sn*H in a large excess and, naturally, by using a nonarene solvent.

More generally, our findings indicate most substrates and products of any synthetic interest will contain chain-transfer groups that retard the *Sn*H chain. These include allylic CHs, conjugated double bonds, and aryl or bis-aryl C═O groups.[26] Regardless of whether the transfer is from the organic or the stannyl radical, via abstraction or addition, the result is the transfer of most radical centers into a pool of "slow" or dead-end species, such as delocalized radicals $\mathbf{A}^\bullet$ or $\mathbf{B}^\bullet$. The result is a slower reaction and a longer reaction time, as quantified by eq 22. The effect of chain transfer is depicted in Figure 1, where relative areas represent relative radical concentrations (totaling $[^\bullet] = \sqrt{(R_i/2k_t)} \sim 15$ nM), down-arrows are chain transfer or termination, up-arrows are chain return, and horizontal arrows represent propagation in the main chain (i.e., v_0 and $v = -d[\text{RX}]/dt$).

Steady-state radical concentrations are determined by relative reactivities, with the most highly reactive radicals being present at the lowest concentrations. Thus, in spite of benzene's low reactivity toward alkyl radicals ($k_{\text{RCH2}^\bullet\text{+PhH}} \approx 15\ \text{M}^{-1}\ \text{s}^{-1}$), around 80% of the C-centered radicals in the 1-heptyl bromide + *Sn*H reaction in solvent benzene are delocalized radicals and only 20% are heptyl$^\bullet$. When $R^\bullet$ is an aryl radical, $Ar^\bullet$, the ratio of terminating $\mathbf{A}^\bullet$ ($ArPhH^\bullet$) to propagating $R^\bullet$ ($Ar^\bullet$) radicals climbs to 90 or 95%, with the rate falling to just 5−10% of its value in cyclohexane solvent.[26] (ArX, being aromatic, will be both substrate and product inhibited).

However, the "plumbing" of Figure 1 means that increasing the flow of radical centers back from $\mathbf{A}^\bullet$ or $\mathbf{B}^\bullet$ to the main chain will increase $[R^\bullet]$ and $[Sn^\bullet]$, thus accelerating the reaction.

Known and Potential Remedies for Slow Tin Hydride Reactions. Crich et al.[50] have developed a clever remedy by the addition of PhSeH (or a source thereof). This compound is a highly reactive H atom donor, which enhances the desired chain as shown below:

$$\text{RArH}\bullet + \text{PhSeH} \rightarrow \text{RArH}_2 + \text{PhSe}\bullet \tag{30}$$

$$\text{PhSe}\bullet + Sn\text{H} \rightarrow \text{PhSeH} + Sn\bullet \tag{31}$$

$$\text{RArH}\bullet + \text{PhSeH} + Sn\text{H} \rightarrow \text{RArH}_2 + \text{PhSeH} + Sn\bullet \tag{32}$$

This "chain return" process replaces the reduction by $\text{RArH}^\bullet$ of AIBN[45] with a chain-propagating pathway. This repair of the reaction chain eliminates the need for heroic amounts of "initiator" and (in cyclizations) reduces the ipso-addition[26] radicals that may otherwise form dimers.

Curran and Keller[51a] have devised another neat remedy using oxygen to rearomatize arene adduct radicals.[51] The radical center is returned to the main chain via the hydroperoxyl radical, $\text{HOO}^\bullet$:

$$\text{RArH}\bullet + \text{O}_2 \rightarrow \text{RAr} + \text{HOO}\bullet \tag{33}$$

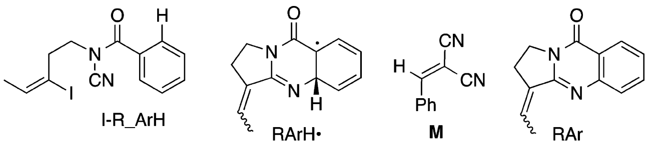
$$\text{HOO}\bullet + Sn\text{H} \rightarrow \text{HOOH} + Sn\bullet \tag{34}$$

$$\text{RArH}\bullet + \text{O}_2 + Sn\text{H} \rightarrow \text{RAr} + \text{H}_2\text{O}_2 + Sn\bullet \tag{35}$$

This procedure worked well for cyclizations and arene additions,[26] especially with iodide precursors, iodine as initiator, and the silane, TMS_3SiH.

Another potential remedy is suggested by the studies of Larauffie et al.[52] In a series of intricate label-crossover experiments they established that a conjugated terminal olefin is a more active bimolecular trap ($H^\bullet$-acceptor) for the labile hydrogen in the adduct ($\text{RArH}^\bullet$) than is the AIBN initiator.[44] Inclusion of an even better $H^\bullet$-trap, the electron deficient olefin **M**, as a "sacrificial" bimolecular oxidant afforded near-quantitative yields of both the oxidized arylation product, RAr,[53] and reduced **M** ($\mathbf{MH}_2 = \text{PhCH}_2\text{CH(CN)}_2$) (Scheme 14).

Scheme 14



Product analysis showed that one H came from the arene and one from the *Sn*H,[53] i.e.

$$\text{RArH}^\bullet + \mathbf{M} \rightarrow {}^\bullet\mathbf{MH} + \text{RAr} \tag{36}$$

$${}^\bullet\mathbf{MH} + Sn\text{H} \rightarrow \mathbf{MH}_2 + Sn^\bullet \tag{37}$$

Thus, a third way to convert chain-blocking arene-adduct $\mathbf{A}^\bullet$ radicals into propagating species may be to add an electron-deficient unsaturated compound as a $\text{RArH}^\bullet$ oxidant:

$$\mathbf{A}^\bullet + \mathbf{M} + Sn\text{H} \rightarrow \rightarrow \mathbf{A}(-\text{H}) + \mathbf{MH}_2 + Sn^\bullet \tag{38}$$

A nonterminal **M** is indicated, but even a simple monomer like methyl acrylate might work.

As for remedies for allylic $\mathbf{A}^\bullet$ radicals, Crich et al.[18a] have shown that catalytic PhSeH can accelerate reactions and eliminate dimers in *Sn*H reductions that are retarded or blocked by allylic species.

$$\mathbf{A}^\bullet + \text{PhSeH}_{\text{cat}} + Sn\text{H} \rightarrow \rightarrow \text{AH} + \text{PhSeH}_{\text{cat}} + Sn^\bullet \tag{39}$$

For benzylic $\mathbf{A}^\bullet$ radicals, Ford et al.[50d] have shown PhSeH improves the kinetics and yields in the radical-chain hydrostannation of styrenes, $Sn^\bullet + \text{CH}_2{=}\text{C(X)Ph} \rightarrow Sn\text{CH}_2{-}\text{C}^\bullet\text{(X)Ph}$ ($\mathbf{A}^\bullet$).

Alternatively, if "trickier" to implement, a well-judged flux of oxygen (O_2) could serve to convert allylic or other delocalized

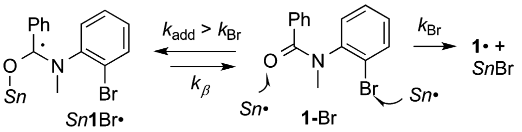
A$^\bullet$ radicals into fast-propagating organic peroxyl radicals (AOO$^\bullet$), returning radical centers to the chain and hastening the overall reduction.

$$\mathbf{A}^\bullet + O_2 + Sn\mathrm{H} \rightarrow \rightarrow \mathbf{A}\mathrm{OOH} + Sn^\bullet \qquad (40)$$

The problem here is that $i^\bullet$, R$^\bullet$, and $Sn^\bullet$ radicals all undergo diffusion-controlled reactions with O_2.[54] Even so, from eq 22 (Scheme 7) we calculate substantial rate acceleration at low O_2 concentrations ($[O_2] < 10^{-4}$ M) from the removal of **A**$^\bullet$ provided, that is, the formation of the retarding SnOO$^\bullet$ radical[55] is minimized by using an iodide rather than bromide substrate.[26]

Iodides also minimize retardation by carbonyls, since, unlike R$^\bullet$ radicals, $Sn^\bullet$ radicals do not abstract hydrogen but they can undergo rate-retarding reversible additions (see Figure 1). That said, the benefit of reversibility is that even fast addition does not preclude high yields from slower irreversible reactions. For instance, addition to the activated carbonyl in **1**−Br (forming Sn**1**Br$^\bullet$) would likely be faster than the bromine abstraction ($k_{Br} = 2 \times 10^6$ M^{-1} s^{-1}) and yet products arise only from the bromine abstraction (via **1**$^\bullet$). Build-up of adduct Sn**1**Br$^\bullet$ may slow the reduction rate but does not divert the reaction because it undergoes β-scission more rapidly than it reacts with the *Sn*H: $k_\beta \gg k_{Sn1Br^\bullet/SnH}$ [*Sn*H] (Scheme 15).

Scheme 15



The chain-transfer kinetic analysis demonstrated here is readily adapted to nonstannyl reagents, as well as to the optimization of mixed reagents like triethylsilane + thiol/selenol.[26,56]

■ CONCLUSION

The rates of *Sn*H reductions of RX under laboratory conditions are frequently determined by chain-transfer side reactions of the $Sn^\bullet$ or R$^\bullet$ radical with solvent, substrate, and product. These side processes can lead to much slower overall reactions and greatly extended reaction times. Such retarded reactions can be accelerated, and reaction times therefore reduced, by catalyzing the transfer of less reactive, and even unreactive, radical centers back to the main chain. Chain transfer in the industrially important fields of polymer[57] and autoxidation[58] chemistry has been the subject of intense research interest, whereas *Sn*H reductions have been restricted (thanks to the perceived toxicity of organotin compounds) to small-scale work in research laboratories.[2] Nonetheless, organostannane radical chain reduction is a powerful synthetic tool that continues to be developed and published at an undiminished rate. It is hoped that the findings and ideas presented here, including the use of faster nontoxic solvents in place of benzene, and strategies to either minimize or utilize chain transfer will help to further refine experimental procedures.

■ EXPERIMENTAL SECTION

Reduction Velocity (*v*). The rates of tri-*n*-butylstannane (*Sn*H) reductions can be erratic owing to the effects of residual oxygen, reagent, and solvent impurities (notably radical-generating peroxide impurities in ethers and rate-retarding olefin impurities in organic halides). These factors were minimized by using freshly purified, alumina-filtered, and argon-sparged solvents and reagents and by excluding oxygen and light. Typically, a cyclohexane solution of RX and the initiator was degassed using a slow stream of argon delivered via a fine glass capillary inside a syringe needle inserted through the septum of a small glass ampule warmed to 42 ± 1 °C. Vacuum distilled *Sn*H (0.2–0.5 equiv) was then injected (and rapidly mixed by the argon stream). Samples from the reaction mixture were quenched by addition to 10 volumes of argon-sparged CCl_4, warmed for a few minutes (or for up to 2 h for strongly retarded reactions), and analyzed by capillary GC (25 m × 0.32 mm BP1 column and FID). Reaction rates were calculated from the product ratio $\alpha = (Sn\mathrm{Br}/Sn\mathrm{Cl})_{gc}$ (the chloride being formed from reaction of the remaining *Sn*H with the CCl_4). This afforded the observed first-order reaction rate constant ($k_{obs} = [\ln(1 + \alpha)]/t$) and initial reaction velocity, $(v)_0 = -(d[Sn\mathrm{H}]/dt)_0 = [Sn\mathrm{H}]_0[\ln(1 + \alpha)]/t$, which was averaged over eligible time points. The initiator BONNOB has a half-life of 25 h at 42 °C, so R_i was taken to be constant for reaction periods of up to 6 h. GC product ratios were reproducible to ±4% (1 SD) and repeat reactions exhibited a further ±5% superposed random variation.

Competition Kinetics. Competition kinetics were used to determine the halogen-atom abstraction rate constants for **1**−Br and **2**−I. Where the stannane is consumed by a large excess of a mixture of halides RX and R′Y (X ≠ Y), the *pseudo-first-order rate* equation $k_X/k_Y \approx (Sn\mathrm{X}/Sn\mathrm{Y})_{gc}\ (\mathrm{R'Y/RX})_0$ gave reasonably accurate rate ratios (where the use of stannyl halide yield ratios obviated the need to quantify the injection-port-labile rearranging halides). Thus, a freeze−pump−thaw degassed cyclohexane solution of **1**−Br (100 mM), benzyl chloride (100 mM), *Sn*H (20 mM), and BONNOB (8 mM) was warmed to 42 °C for 15 h in a sealed glass ampule and then analyzed, and the relative rate constants were calculated from the yield ratio $k_{1\text{-}Br}/k_{PhCH2Cl} \approx (Sn\mathrm{Br}/Sn\mathrm{Cl})_{gc} = 1.7 \pm 0.2$. Likewise, for **2**−I with benzyl bromide as the competitor: $k_{2\text{-}I}/k_{PhCH2Br} \approx (Sn\mathrm{I}/Sn\mathrm{Br})_{gc} = 1.3 \pm 0.2$. Another measurement for **2**-I (0.10 M) in 1-bromoheptane solvent (8.0 M) afforded a confirming rate constant: $k_{Sn^\bullet/2I} \approx 81 \text{ x } k_{Sn^\bullet/1\text{-}HepBr} = 2 \times 10^9$ M^{-1} s^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Kinetic derivations; radical-flow figures; reversible benzene addition; 1-hexene + $Sn^\bullet$ reversible addition equilibrium data; arene addition mechanism; selenol-assisted arene cyclization mechanism; O_2-assisted arene addition; kinetic competition equations; Table showing 1-Br/bromoheptane coreduction. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ DEDICATION

In grateful memory of Professor Athel Beckwith for initating and supporting this investigation.

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$$(1/\varepsilon)i_2\mathrm{N}_2 + Sn\mathrm{H} + \mathrm{RX} + \mathrm{ArH} \rightarrow 2i\mathrm{H} + Sn\mathrm{X} + \mathrm{RAr} + (1/\varepsilon)\mathrm{N}_2$$

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