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Relative Rates and Approximate Rate Constants for Inter- and Intramolecular Hydrogen Transfer Reactions of Polymer-Bound Radicals

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Abstract: Measurements of relative rates and rate constants for inter- and intramolecular hydrogen transfer reactions of polymer-bound radicals are reported. The relative rate of reaction of resin-bound primary alkyl radical with tributyltin hydride is about 2 times slower than that of the benchmark reaction in solution. The data do not reveal whether this is due to a reduced rate constant or a lower concentration of tin hydride in the resin phase. Yet the difference between solid and solution reactions is small enough to be neglected, and it appears that rate constants measured in solution can be applied directly to resin-bound radicals. A resin-bound aryl radical abstracts a hydrogen atom rapidly ($k = 3 \times 10^6\ s^{-1}$) from its own polymer backbone and linker, and a simplified view of the resin as a "solvent" is suggested for predicting such effects with other polymers and linkers. Rapid cyclizations of resin-bound aryl radicals will be possible, but slower cyclizations and most bimolecular reactions will be difficult due to the competing polymer/linker hydrogen transfer.

Introduction

Radical addition and cyclization reactions are established components of the synthetic chemistry reaction kit for building organic molecules in solution.[1] More recently, solid-phase methods have emerged as general tools for small molecule synthesis,[2] and this emergence has generated a need for conducting radical reactions on the solid phase. Representative inter- and intramolecular radical reactions have recently been conducted on polymer-supported radical precursors. These reactions have been mediated by popular solution-phase reagents such as tributyltin hydride,[3] allyltributyltin,[4] triethyl boron,[5] samarium diiodide,[6] and others.[7] Soluble polymers have also been introduced.[8]

The development of reaction conditions by a combination of experience and trial and error is the typical *modus operandi* in solid-phase synthesis, and exisiting radical-based methods fit this mold. In contrast, the "trial and error" approach to developing solution-phase radical reaction conditions is used with increasing rarity. Instead, reagents and conditions for solution-phase radical reactions can usually be selected on the basis of the large body of rate constants and substituent effects known for radical reactions.[1] It follows that a knowledge of relative and absolute rates of reactions of polymer-bound radicals will expedite the development and application of solid-phase radical reactions.

We report herein the first measurements of rates of inter- and intramolecular hydrogen transfer reactions to radicals on the solid phase. The rates are measured by traditional competition kinetics on the basis of intramolecular clock reactions that have been calibrated in the solution phase.[9] Although only two reactions have been timed so far—bimolecular reaction of a primary alkyl radical with tributyltin hydride and intramolecular reaction of an aryl radical with the polymer backbone—the new

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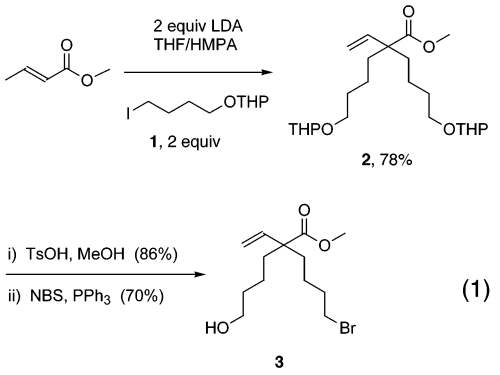
clocks can be readily used to time other reactions. Problems with applying solution-phase competition kinetic methods to solid-phase reactions are discussed.

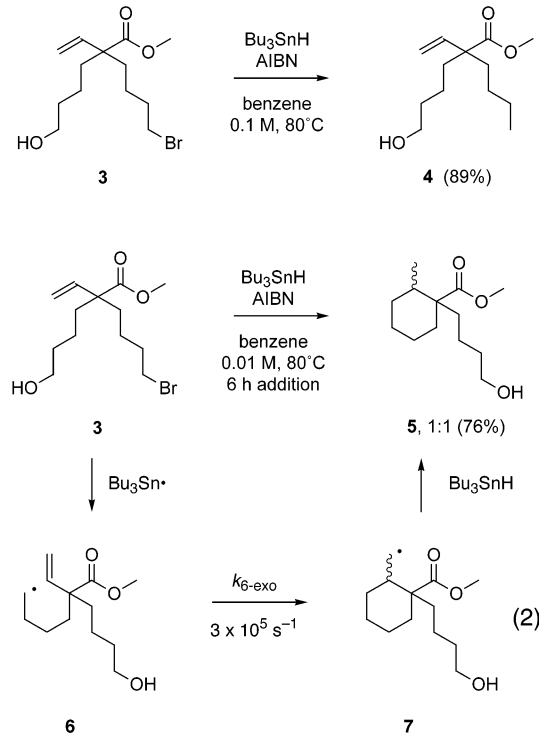
Results and Discussion

Bimolecular Hydrogen Transfer Reactions with Tributyltin Hydride. Although environmental concerns discourage the large-scale, production-oriented use of tributyltin hydride,[10] it remains a popular reagent for small-scale, discovery-oriented synthesis. The large store of absolute and relative rates based on this reagent[11] make it an important touchstone for comparing solid-phase reactions to solution-phase reactions. Accordingly, we set out to measure the rate constant for reaction of a polymer-bound primary alkyl radical with tributyltin hydride in solution. To do this, we designed experiments fashioned after standard solution-phase competition kinetics[9] where a 6-*exo* cyclization of known rate constant competes against hydrogen transfer from tributyltin hydride in solution. It is, at first glance, not at all clear that such experiments based on homogeneous solution-phase kinetics will give meaningful data in the heterogeneous reactions of polymers. Reactions of resin-bound substrates are thought to occur in a gel phase that is separate from the free solution.[12] In the event, a regular "solution-like" dependence of product ratios as a function of tin hydride concentration was observed, and the implications of homogeneous versus heterogeneous kinetics are discussed below.

The radical clock substrate **3** was chosen for the competition reactions with tributyltin hydride. This substrate is readily prepared and has a free alcohol for attachment to the solid phase. The clock reaction is 6-*exo* cyclization, and the substrate has no allylic hydrogens, so intramolecular hydrogen transfer should not compete with bimolecular hydrogen transfer for formation of reduced, noncyclized products. Substrate **3** was assembled in three steps as shown in eq 1. Deconjugative alkylation of methyl crotonate with 2 equiv of iodide **1** and 2 equiv of LDA was conducted sequentially in one flask to provide **2** in 78% isolated yield. Removal of the THP group with tosic acid in methanol provided a diol, which was then reacted with 1 equiv of NBS and triphenylphosphine. Rapid chromatography readily removed the starting diol and the side product dibromide to provide pure **3** in 70% yield.



Authentic samples of directly reduced and cyclized products derived from **3** were made by reducing it with tributyltin hydride (eq 2). Reduction of **3** at 0.1 M (6 h, 80 °C), followed by KF workup[13] and silica gel chromatography, provided reductively debrominated product **4** in 89% yield (eq 2a). In contrast, dropwise addition of tributyltin hydride at 80 °C over 6 h followed by similar purification provided the cyclized product **5** in 76% isolated yield as an inseparable 1/1 mixture of diastereomers (eq 2b). The product of 7-*endo* cyclization (not shown) was not detected, although its presence in small amounts cannot be ruled out because an authentic sample was not prepared.



Solution-phase kinetic experiments were conducted to determine the rate constant ($k_{6\text{-}exo}$) for 6-*exo* cyclization of radical **6** to **7** (eq 2b). Reduction of **3** in toluene solutions at 80 °C provided a mixture of the reduced product **4** and the cyclized product **5** (1/1 mixture of diastereomers) in ratios that depended on tin hydride concentration. Competition experiments were run in duplicate at constant reaction volume by increasing the amount of tin hydride in steps from 5 to 20 equiv (see Experimental Section). Ratios of **5**/**4** were measured by GC analysis after KF workup to remove most of the tin. The data for this series of experiments are summarized in Table 1. By using standard pseudo-first-order kinetic equations,[14,15] a solution-phase rate constant $k_{6\text{-}exo} = 1.9 \times 10^5\ s^{-1}$ is calculated for the 6-*exo* cyclization of radical **6**. This rate constant is reasonable based on known rate constants for related 6-*exo* cyclizations.[16]

To determine the rate constant for the resin-bound radical, alcohol **3** was grafted to Ellman's THP resin[17] by shaking 5 equiv of **3** and 5 equiv of tosic acid with a suitable amount of

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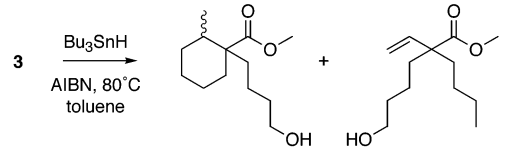
(13) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
(14) The value $6.4 \times 10^6\ M^{-1}\ s^{-1}$ was used for k_H as recommended in ref 11.
(15) Data were analyzed by the following equation: $[RH]/[R'H] = (k_H/k_r)[Bu_3SnH]$. Plots of the ratio of the reduced (RH) to rearranged (R′H) product ratio versus the tin hydride concentration take the form $y = mx + b$, where the slope m is k_H/k_r, and the intercept b is 0. Linear regression analysis gave the following equations: Table 1, $y = 33.6x - 0.1$, $r = 0.9995$; Table 2, $y = 13.8x - 0.1$, $r = 0.9987$; Table 3, $y = 300x - 0.6$, $r = 0.9947$.
(16) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**.
(17) Purchased from NovaBiochem.

Table 1. Solution-Phase Reduction of Bromide **3** with Tributyltin Hydride

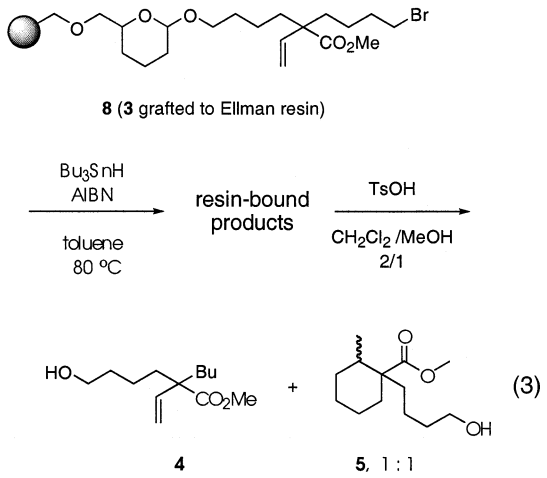


5 **4**

entry	[Bu_3SnH]	ratio **5**/**4**[a,b]
1	0.010	4.26
2	0.014	2.98
3	0.020	1.77
4	0.030	1.13
5	0.040	0.81

[a] Reactions conducted in duplicate; average of two runs. [b] Raw GC peak ratios; **5** is two isomers.

resin in dichloromethane for 3 days. Filtration, washing, and drying provided resin grafted product **8** (eq 3) at 87% of the theoretical loading level (eq 3).

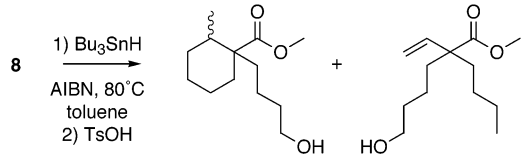


Duplicate sets of kinetic experiments were conducted on the solid phase at five different tin hydride concentrations.[18] Solvent volumes (3−16 mL) were large as compared to the resin quantity (50 mg), so volumes for (apparent) concentrations were obtained simply by using the solvent volume and neglecting the resin entirely. AIBN along with the requisite amount of tributyltin hydride was added to a suspension of **8** in toluene, and the mixture was heated at 80 °C for 20 h. After being cooled, the liquid was separated, and the resin was washed thoroughly to remove the tin to provide resin-bound products (eq 3). The product resin was then treated with tosic acid to detach the mixture of products **5**/**4** (93−97% based on the initial loading level), and the ratio was analyzed by GC as above. Cyclized product **5** was again a 1/1 ratio of stereoisomers. The data for these experiments are shown in Table 2.[15]

Equation 4 shows the partitioning of resin-bound radical **9** between cyclization to **10** and reduction to **11**. Analysis of the data in Table 2 on the basis of relative rates is straightforward, and a standard data plot (not shown) confirms that the relative rate of cyclization of resin-bound radical ($k_{6\text{-}exo}$) to reduction (k_H[Bu_3SnH]) is normal. In other words, the solid-phase reaction of **9** mimics its solution-phase counterpart **6**. For example,

(18) Preliminary experiments showed that about 3 equiv of tin hydride was required for complete consumption of **8**, so 5 equiv was chosen as a minimum amount of tin hydride to ensure that all reactions were complete.

Table 2. Solid-Phase Reduction of Bromide **8** with Tributyltin Hydride

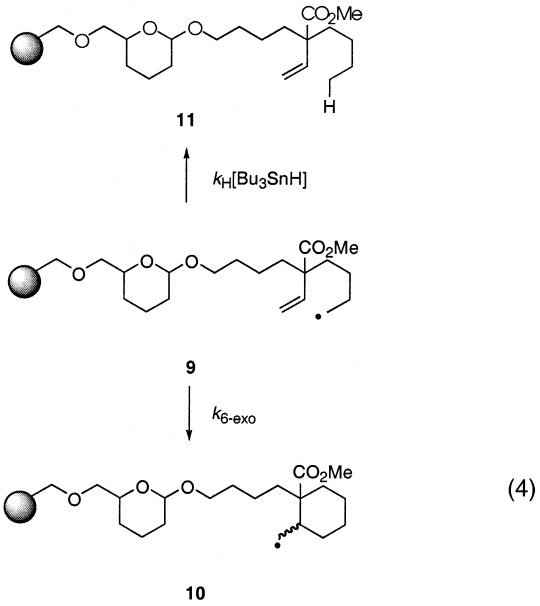


5 **4**

entry	[Bu_3SnH]	ratio **5**/**4**[a,b]
1	0.030	3.15
2	0.040	2.24
3	0.049	1.87
4	0.069	1.21
5	0.097	0.81

[a] Reactions conducted in duplicate; average of two runs. [b] Raw GC peak ratios; **5** is two isomers.

doubling the tin hydride concentration will proportionally increase the amount of reduced product relative to cyclized product.



Analysis of the data on the basis of absolute rate constants is more complicated and requires assumptions of variable certainty. First, we assume that the rate constant ($k_{6\text{-}exo}$) for cyclization of **9** to **10** on the solid phase (eq 4) is the same as the measured solution-phase rate constant (1.9×10^5 s^{-1}) for the cyclization of **6** to **7** (eq 2). This assumption seems reasonable because radical cyclization rate constants of this type show small medium effects in solution. However, we are then left with a choice of what to calculate because there are two unknowns—the rate constant for the reaction of the resin-bound radical **9** with tin hydride and the concentration of tin hydride in the resin phase—and only one known—the **5**/**4** ratio. To obtain a value for one of the unknown quantities, we must make an assumption about the other.

On one hand, if we assume that the partition coefficient of the tin hydride on the gel phase is about 1, then the tin hydride concentration in the resin phase equals the concentration of the tin hydride in solution. From this assumption, we can calculate that the rate constant k_H for hydrogen transfer to the resin-bound radical is 2.6×10^6 M^{-1} s^{-1} at 80 °C. This is a little less than

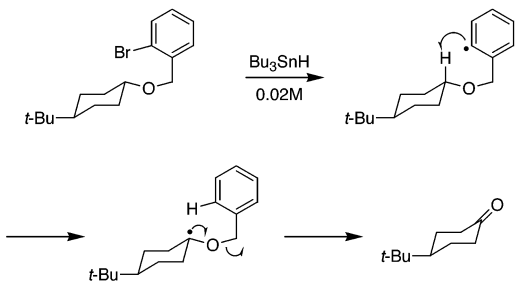


Figure 1. The *o*-bromobenzyl group: cleavage with simultaneous oxidation of the protected substrate.

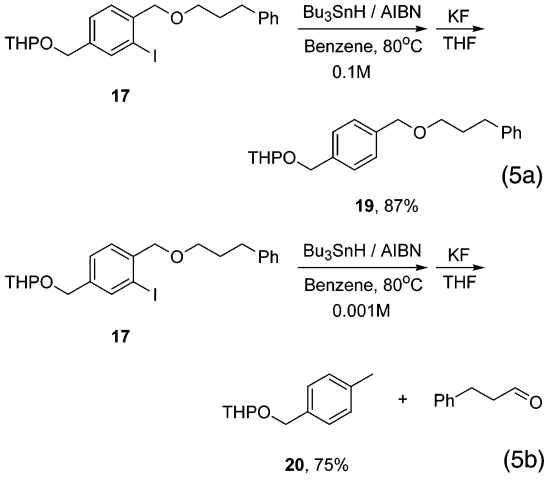
one-half (40%) of the solution rate constant of 6.4×10^6 M^{-1} s^{-1} at this temperature.[11] On the other hand, if we assume that the rate constants k_H for hydrogen transfer in solution and the gel phase are the same, then we can calculate that the concentration of tin hydride in the resin phase is about 40% of that in the solution phase.

The primary conclusion here is that the relative rate of hydrogen transfer in the liquid phase−gel phase reaction is very similar to that in solution. This similarity is likely to arise because both the tin hydride concentration in the resin phase and the rate constant for cyclization in the resin phase are similar to their solution-phase analogues. *This means that solution-phase concentrations and rate constants can be directly applied to radical reactions on the solid phase for the purposes of estimating product ratios.*

Intramolecular Hydrogen Transfer. One of the potential problems with using resin-bound radicals is premature quenching by hydrogen transfer from the polymer backbone. We addressed this problem in the context of proposed development of a new linker based on the *o*-bromobenzyl protecting group for alcohols shown in Figure 1. The unique feature of the *o*-bromobenzyl group is that upon deprotection under reductive conditions, a concomitant oxidation of the substrate occurs to provide an aldehyde or ketone.[19] The suggested mechanism for this oxidative cleavage is radical translocation by 1,5-hydrogen transfer followed by fragmentation. A solid-phase linker fashioned from the *o*-halobenzyl group could be a robust protecting group that could be cleaved under mild, selective conditions. Yet aryl radicals are aggressive hydrogen atom abstractors.[20] Will hydrogen transfer from the polymer compete with fragmentation to prevent the final release of the aldehyde or ketone into solution?

Substrate **18** was selected for comparison kinetics in solution and on the solid phase, and this was readily prepared as shown in Scheme 1. Esterification of 3-bromo-4-methylbenzoic acid **12** provided ester **13** in 86% yield. Radical benzylic bromination gave dibromide **14** (77%), which was reduced with LAH and protected with a THP group to give **15** (74%). Reaction of **15** with hydrocinnamyl alcohol under standard Williamson ether synthesis conditions provided **16** (73%). To provide the best possible radical precursor for the experiments at low concentration, the bromide was then exchanged for an iodide by metalation of **16** and quenching with diiodoethane (75%). Deprotection of iodide **17** afforded the alcohol **18** in 91% yield.

Syntheses of authentic samples of the expected products were accomplished by reducing **18** at extremes of tin hydride concentration, as shown in eq 5. Reduction with tributyltin hydride at high concentration [0.1 M, eq 5a] provided **19** in 87% isolated yield after KF workup and chromatography, while reduction at low concentration [0.001 M, eq 5b] provided **20** in 75% yield. Hydrocinnamaldehyde presumably accompanies **20** in comparable yield, but we made no attempt to isolate this product.



Solution kinetic experiments were conducted as described above for the reduction of **3**. THP-protected iodide **17** was treated with Bu_3SnH at concentrations ranging from 0.005 to 0.02 M. After heating at 80 °C in benzene for 8 h, reaction mixtures were exposed to KF prior to rapid flash chromatography to give mixtures of the reduced product **19** and cleaved product **20** (83−87% combined yields). Ratios of these two products were determined by GC analysis and are shown in Table 3. Rate constants were extracted from these data by assuming the direct partitioning of radical **21a** (eq 6) between 1,5-hydrogen transfer to give **22a** (and ultimately **20**) and hydrogen transfer from tin hydride to give **19**. The rate constant

Scheme 1

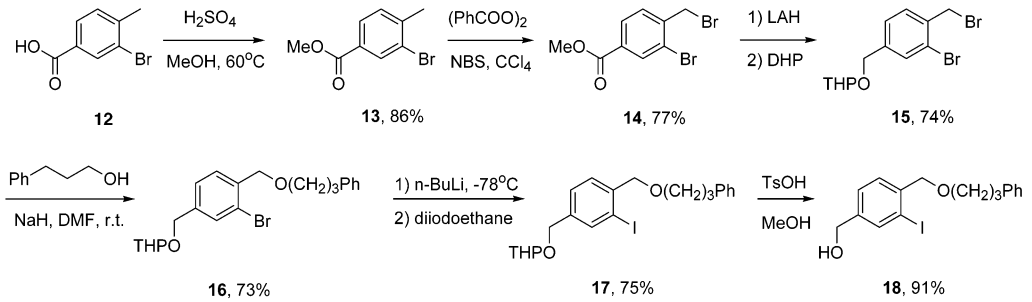
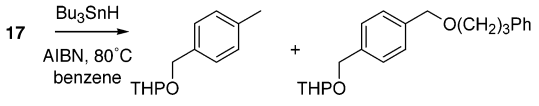


Table 3. Solution-Phase Reduction of Iodide **17** with Tributyltin Hydride

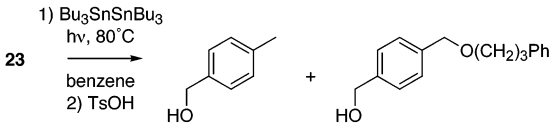


20 **19**

entry	[Bu_3SnH]	ratio **20/19**[a]
1	0.005	0.99
2	0.007	0.63
3	0.011	0.41
4	0.015	0.27
5	0.021	0.17

[a] Raw GC peak ratios.

Table 4. Solid-Phase Photolysis of Iodide **23** with Hexabutylditin

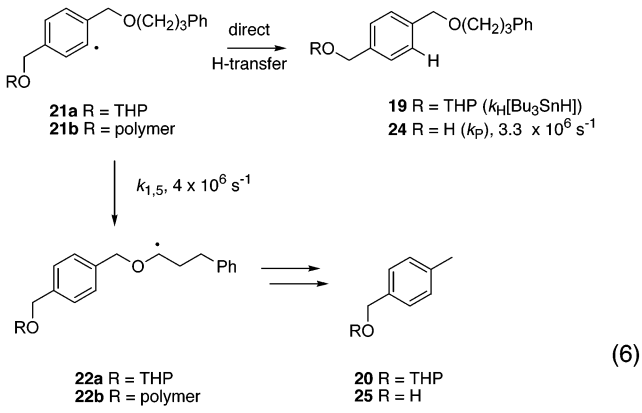


25 **24**

entry	[$(Bu_3Sn)_2$]	ratio **25/24**[a]
1	0.015	1.18
2	0.030	1.33
3	0.060	1.10

[a] Raw GC peak ratios.

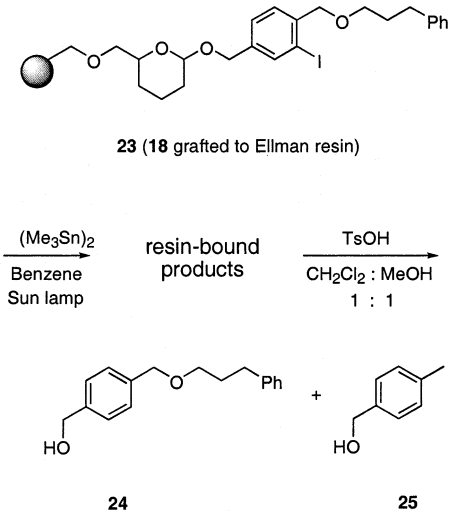
for 1,5-hydrogen transfer ($k_{1,5}$) is 4×10^6 s^{-1}.[21]



(6)

THP series; direct hydrogen transfer is from Bu_3SnH in solution
Polymer series; direct hydrogen transfer is from the polymer backbone and/or linker

Alcohol **18** was then grafted to the Ellman resin (90% loading level) for the solid-phase kinetic experiments (eq 7). Interpretation of kinetic experiments with this resin-bound substrate is straightforward. The two hydrogen transfer reactions of radical **21b** (eq 6)—1,5-hydrogen transfer and abstraction from the polymer backbone—are competing intramolecular reactions. No tin hydride is needed. We assume that fragmentation of **22b** rapidly succeeds 1,5-hydrogen transfer of **21b**, and it follows that the ratio of ether **24** to cleaved toluene **25** is a measure of the ratio hydrogen transfer from the polymer backbone (k_P) to the aryl radical to 1,5-hydrogen transfer ($k_{1,5}$). We assume that ($k_{1,5}$) for the resin-bound radical **21b** is the same as that for soluble radical **21a**.



(7)

Hexamethylditin (3 equiv) was added to a suspension of polymer **23** in benzene at three different concentrations (Table 4), and the mixtures were irradiated with a sunlamp for 20 h. After thorough washing, the products **24** and **25** were released from the resin by treatment with methanolic tosic acid (91−93% yields), and their ratios were measured by GC. As expected from competing intramolecular reactions, the ratios were all about the same, and an average rate constant of $k_P = 3.3 \times 10^6$ s^{-1} is calculated for the hydrogen transfer from the polymer to the aryl radical.

In addition to the usual errors in competition kinetics, the main source of error in this measurement is the neglect of competing 1,6- and 1,7-hydrogen transfer. We know that these reactions occur in related systems,[17,22] and, if they occur here, that would bolster the apparent rate constant for hydrogen transfer from the polymer. The 75% isolated yield of the fragmentation product **20** (eq 6) sets an upper limit to these side reactions of 25%.

Preparatively, almost one-half of the resin-bound aryl radicals **21b** are reduced by hydrogen transfer from the polymer prior to 1,5-hydrogen transfer. This limits the cleavage yield of a bound substrate from the resin by radical fragmentation to just over 50%. Accordingly, we conclude that the *o*-halobenzyl group will not be an especially useful linker, at least with Ellman resin, because the cleavage efficiency is too low. Either a linker with more rapid 1,5-hydrogen transfer or a polymer/linker combination with poorer hydrogen donating ability is needed.

A simple but useful way to view the hydrogen transfer from the polymer is as an effect of a solvent.[23] Resin-bound radicals **22b** are surrounded in the gel phase by alkyl, benzylic, ether, and acetal C−H bonds from the polymer and the linker. The measured rate constant for hydrogen abstraction from the polymer (k_P) is an aggregate of individual rate constants of all of these C−H bonds, and it is in the same range as pseudo-first-order rate constants for solvents with related C−H bonds.[23] As already shown in the literature,[6] rapid aryl radical cyclizations can surpass polymer hydrogen transfer reactions, and cyclization products can be formed in high yields. Yet the high rate constant measured here for polymer hydrogen transfer suggests that

(19) Curran, D. P.; Yu, H. S. *Synthesis* **1992**, 123.
(20) (a) Yu, T.; Lin, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 4371. (b) Hanson, P.; Hammond, R. C.; Goodacre, P. R.; Purcell, J.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 691. (c) Yu, T.; Lin, M. C. *J. Phys. Chem.* **1995**, *99*, 8599.
(21) The value 1.2×10^9 M^{-1} s^{-1} was used for k_H at 80 °C on the basis of the value of 7.8×10^8 M^{-1} s^{-1} recommended as the 20 °C rate constant in ref 11.

slower cyclizations and most bimolecular reactions of aryl radicals will be difficult to conduct.

Conclusions

The measurements reported in this paper take the first step toward a detailed kinetic understanding of inter- and intramolecular hydrogen transfer reactions of resin-bound radicals. Despite the potential complications imposed by biphasic reaction conditions, the reductions of primary radical **9** (eq 4) showed clean solution-like behavior, and the estimated rate constant for hydrogen transfer from Bu_3SnH ($1.9 \times 10^6\ M^{-1}\ s^{-1}$) was within a factor of 2.5 of the solution rate constant ($6.4 \times 10^6\ M^{-1}\ s^{-1}$). Given all of the possible complications and assumptions with the resin number, these rate constants are probably not different outside experimental error. So, as a first step, all of the complications of the solid phase should be ignored, and reactions of polymer-bound radicals mediated by tin hydride should be planned as if they were solution-phase reactions. This convenient simplification may only apply under conditions where the tin hydride is used in excess as in our competition experiments. However, the use of excess reagents in solid-phase reactions is common, so this is not a serious limitation.

Experiments with resin-bound aryl radical precursor **23** suggest that the Ellman resin behaves roughly like a solvent with relatively reactive C−H bonds. As such, reactions of its resin-bound aryl radicals will be limited to the fastest intramolecular classes; slower intramolecular and bimolecular reactions will suffer from competing hydrogen transfer. While it would be worthwhile to test other linkers, we suspect that much of the damage is done by the polymer itself. We suggest that a simple, first-order way to view this problem is as a solvent effect; rates of polymer hydrogen transfer reactions can be estimated from pseudo-first-order rate constants for hydrogen abstraction for related solvents. For example, ethyl benzene can be used as a model for H-transfer reactions of polystyrene, and dimethoxyethane or even diethyl ether are models for estimating how fast radicals might abstract hydrogen from Tentagel polymers.

Despite potential problems, solution-phase competition kinetics can be readily adapted to the solid phase to provide useful information about relative and absolute rates of resin-bound radicals. The substrates introduced in this paper can be applied to clock other solution- or solid-phase reactions. The method can be used to time new clocks and to build a horlogerie of solid-phase radical clocks to complement the large selection of solution-phase radical clocks. Better calibration of the solid-phase clocks is of little importance for synthetic planning but will be needed in due course to allow more accurate comparisons of rates and substituent effects of resin-bound radicals.

Experimental Section

2,2-Bis-[4-(tetrahydropyran-2-yloxy)butyl]but-3-enoic Acid Methyl Ester (2). To a stirred solution of LDA (1.6 M, 1.3 mL, 2.1 mmol) and HMPA (0.7 mL, 4 mmol) in THF (20 mL) was added methyl crotonate (0.2 mL, 2 mmol) under nitrogen atmosphere at −78 °C. After 1 h, iodo-THP ether **1** (0.57 g, 2 mmol) was added, and the mixture was stirred at −78 °C for 1 h. The mixture was warmed to room temperature, stirred for 1 h, and cooled to −78 °C. Additional LDA (1.6 M, 1.3 mL, 2.1 mmol) was added. After 1 h, additional iodo-THP ether **1** (0.57 g, 2 mmol) was added. The mixture was stirred for 1 h at −78 °C, and then warmed to room temperature, and stirred for 2 h. The reaction mixture was quenched with aqueous NH_4Cl at 0 °C, diluted with diethyl ether at room temperature, and extracted with diethyl ether. The organic layer was dried and concentrated under reduced pressure. The residue was chomatographed on silica gel column to give **1** (0.64 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22−1.29 (4H, m), 1.52−1.63 (12H, m), 1.69−1.74 (6H, m), 1.80−1.82 (2H, m), 3.35−3.41 (2H, m), 3.48−3.52 (2H, m), 3.68 (3H, s), 3.69−3.76 (2H, m), 3.82−3.86 (2H, m), 4.55−4.58 (2H, m), 5.05−5.20 (2H, dd, J = 11.0 Hz, 17.8 Hz), 5.94−6.04 (1H, dd, J = 11.0 Hz, 17.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 21.0, 25.4, 30.1, 30.7, 35.9, 51.8, 52.3, 62.3, 67.2, 98.8, 114.4, 139.9, 175.9. IR (neat): 2943, 1729, 1033. LRMS: m/z 327, 311, 227, 85. HRMS (ESI) calcd for $C_{23}H_{41}O_6$ [M + H] 413.2903, found 413.2892.

2,2-Bis-(4-hydroxybutyl)but-3-enoic Acid Methyl Ester. A catalytic amount of TsOH (49.3 mg) was added to a stirred solution of **2** (5.6 g, 13.6 mmol) in MeOH (5 mL) at room temperature. After 2 h, the reaction mixture was quenched with aqueous $NaHCO_3$, diluted with diethyl ether, and extracted with diethyl ether. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the diol (2.9 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23−1.30 (4H, m), 1.51−1.60 (4H, m), 1.64 (2H, s), 1.69−1.75 (4H, m), 3.64 (4H, t, J = 6.4 Hz), 3.69 (3H, s), 5.06−5.21 (2H, dd, J = 10.8 Hz, 17.6 Hz), 5.93−6.02 (1H, dd, J = 10.9 Hz, 17.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 32.8, 35.3, 51.8, 52.3, 62.1, 114.5, 139.9, 176.0. IR (neat): 3044 (br), 2940, 1729. LRMS: m/z 244, 171, 140. HRMS (ESI) calcd for $C_{13}H_{24}O$ 244.1675, found 244.1681.

2-(4-Bromobutyl)-2-(4-hydroxybutyl)but-3-enoic Acid Methyl Ester (3). To a stirred solution of the above diol (2.4 g, 9.8 mmol) and PPh_3 (2.6 g, 9.8 mmol) in anhydrous CH_2Cl_2 was added NBS (*N*-bromosuccinimide, 1.7 g, 9.8 mmol) portionwise at 0 °C. After 3 h, the reaction mixture was concentrated and filtered through a short silica gel column to obtain **3** (2.1 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25−1.37 (4H, m), 1.52−1.57 (2H, m), 1.61 (1H, s), 1.68−1.74 (4H, m), 1.81−1.86 (2H, m), 3.39 (2H, t, J = 6.8 Hz), 3.63 (2H, t, J = 6.5 Hz), 3.69 (3H, s), 5.05−5.21 (2H, dd, J = 10.7 Hz, 17.6 Hz), 5.92−6.02 (1H, dd, J = 11.0 Hz, 17.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 22.9, 33.0, 33.3, 35.0, 35.7, 51.8, 52.0, 52.3, 62.5, 114.7, 139.7, 175.7. IR (neat): 3384 (br), 2949, 2866, 1729. LRMS: m/z 307, 289, 233, 171. HRMS (ESI) calcd for $C_{13}H_{23}O_3Br$ 306.0831, found 306.0846.

2-Butyl-2-(4-hydroxybutyl)but-3-enoic Acid Methyl Ester (4). To a solution of **3** (37.2 mg, 0.121 mmol) and AIBN (6.0 mg, 0.3 equiv) in benzene (1.21 mL, 0.1 M) was added Bu_3SnH (36 μL, 0.134 mmol). The mixture was degassed for 30 min by slow bubbling of deoxygenated nitrogen at room temperature. After being heated for 6 h at 80 °C, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in THF (2.0 mL), and aqueous KF (2.0 mL) was added with stirring. After 2 h, the mixture was concentrated and filtered through a short silica gel pad. The crude product was purified by silica gel column chromatography to give **4** (24.6 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz), 1.14−1.32 (5H, m), 1.50−1.57 (4H, m), 1.65−1.74 (4H, m), 3.64 (2H, t, J = 6.5 Hz), 3.68 (3H, s), 5.05−5.19 (2H, dd, J = 10.6 Hz, 18.0 Hz), 5.94−6.03 (1H, dd, J = 11.0 Hz, 17.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 20.7, 23.2, 26.6, 33.1, 35.7, 36.0, 52.0, 52.4, 62.7, 114.5, 140.1, 176.2. IR (neat): 3437 (br), 2937, 1729. LRMS: m/z 228, 211, 196, 109, 95. HRMS (ESI) calcd for $C_{13}H_{24}O_3$ 228.1725, found 228.1725.

1-(4-Hydroxybutyl)-2-methylcyclohexanecarboxylic Acid Methyl Ester (5, Cis/Trans Mixture). A solution of **3** (32.5 mg, 0.106 mmol)

(22) (a) Curran, D. P.; Somayajula, K. V.; Yu, H. S. *Tetrahedron Lett.* **1992**, *33*, 2295. (b) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (c) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.
(23) For a table of some representative rate constants, see: Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.

in benzene (10.6 mL, 0.01 M) and a solution of Bu_3SnH (34 μL, 0.126 mmol) and AIBN (5.2 mg, 0.3 equiv) in benzene (10.0 mL) were each degassed for 30 min by slow bubbling of deoxygenated nitrogen at room temperature. The degassed benzene solution of Bu_3SnH and AIBN was added dropwise to the refluxing benzene solution of **3** over 6 h by syringe pump under nitrogen atmosphere at 80 °C. Heating was continued for 1 h, and the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in THF (2.0 mL), and aqueous KF (2.0 mL) was added. After 2 h, the mixture was concentrated and filtered through a short silica gel pad. The crude product was purified by silica gel column chromatography to afford the 1:1 cis/trans mixture of cyclized product **5** (18.4 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81−0.84 (1.5H, d, J = 7.1 Hz), 0.92−0.94 (1.5H, d, J = 7.0 Hz), 1.20−1.65 (14H, m), 2.05−2.10 (2H, m), 3.60−3.91 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.7, 20.3, 21.1, 22.1, 23.3, 23.6, 30.1, 30.2, 30.4, 33.1, 33.2, 35.3, 36.3, 40.6, 49.9, 50.0, 51.6, 51.7, 62.6, 62.8, 177.9, 178.6. IR (neat): 3439, 2936, 1725.9. LRMS: *m*/*z* 228, 196, 156, 95. HRMS (ESI) calcd for $C_{13}H_{24}O_3$ 228.1725, found 228.1731.

Solution-Phase Kinetic Experiments with 3. Bromide **3** (61.5 mg, 0.20 mmol) and AIBN (16.4 mg) were added into a 100 mL volumetric flask. This was purged with dried nitrogen gas for 10 min at room temperature. To make a 0.002 M solution, about 100 mL of degassed toluene was added to the volumetric flask. A suitable volume of the mixture (8 mL, first trial; 10 mL, second trial) was added to five tubes, and a different amount of Bu_3SnH was added to each of the five tubes to obtain the concentrations listed in Table 1. The tubes were sealed and heated for 8 h at 80 °C, cooled, and concentrated under reduced pressure. The residue was dissolved in THF (3.0 mL), and aqueous KF (2.0 mL) was added. After 2 h, each mixture was concentrated and filtered through a short silica gel pad. The crude products were purified by flash column chromatography to give mixtures of **4** and **5** (84−87%). The ratio of **4** and **5** was analyzed with GC, as shown in Table 1.

Resin-Bound Cyclization Substrate 8. To a mixture of Ellman resin (0.98 mmol/g, 495.5 mg) and TsOH (434.7 mg, 4.7 equiv) in anhydrous CH_2Cl_2 (2.0 mL) was added **3** (871.3 mg, 5.8 equiv) at 0 °C. After being shook for 3 days, the resin was washed with CH_2Cl_2 (10 mL × 3), acetone (10 mL × 3), and anhydrous CH_2Cl_2 (10 mL × 3) and dried under high vacuum for 5 h to afford **8** (625.4 mg, loading level = 87%, 0.68 mmol/g).

Solid-Phase Kinetic Experiments with 8. A suitable amount of Bu_3SnH (42−134 μL) was added to a mixture of **8** (50−52 mg) and AIBN (about 3 mg, 0.5 equiv) in degassed toluene (3.2 mL for 5−10 equiv experiments, and 16.6 mL for 15 and 20 equiv experiments). After being heated for 20 h at 80 °C with gentle stirring, the mixtures were cooled to room temperature and washed with CH_2Cl_2 (10 mL × 3), hexane (10 mL × 3), and anhydrous CH_2Cl_2 (10 mL × 3). The resin-bound product was detached with TsOH (10 mg) for 10 h at room temperature to give mixtures of **4** and **5** (93−98%). The ratio of **4** and **5** was analyzed by GC, and the results are shown in Table 2.

3-Bromo-4-methylbenzoic Acid Methyl Ester (13). 3-Bromo-4-methylbenzoic acid **12** (2.51 g, 11.63 mmol) was dissolved in MeOH (10 mL), 5 drops of H_2SO_4 were added, and the mixture was heated to 60 °C for 10 h. The solvent was removed, and the residue was diluted with Et_2O and water and extracted with diethyl ether. The brown oil obtained after concentration was purified with silica gel column chromatography to give **13** (2.29 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (3H, s), 3.91 (3H, s), 7.30 (1H, d, J = 7.9 Hz), 7.87 (1H, d, J = 7.8 Hz), 8.20 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): 23.2. 52.2, 124.7, 128.3, 129.4, 130.7, 133.4, 143.3, 165.8. IR (neat): 3063.9, 1725. LRMS: *m*/*z* 230, 228, 197, 89. HRMS (ESI) calcd for $C_9H_9O_2Br$ 227.9786, found 227.9786.

3-Bromo-4-bromomethylbenzoic Acid Methyl Ester (14). A solution of 3-bromo-4-methylbenzoic acid methyl ester **13** (2.28 mg, 9.95 mmol) in anhydrous CCl_4 (2 mL) was added to a solution of NBS (1.86 g, 10.45 mmol) and benzoyl peroxide (482 mg, 1.99 mmol) in anhydrous CCl_4 (3 mL) at room temperature. The reaction mixture was refluxed for 10 h at 80 °C under nitrogen atmosphere, cooled to room temperature, and extracted with CH_2Cl_2 (10 mL × 3), aqueous $NaHCO_3$ (5 mL), and H_2O (10 mL × 3). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was subjected to column chromatography to afford an inseparable mixture of **13** and **14** (2.36 g, 77%, 1:8.5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (3H, s), 4.61 (2H, s), 7.54 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 8.0 Hz), 8.25 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.2, 52.5, 124.3, 128.9, 131.1, 131.7, 134.4, 141.7, 165.2. IR (CH_2Cl_2): 3055.95, 1725. LRMS: *m*/*z* 308, 277, 227, 89. HRMS (ESI) calcd for $C_9H_8O_2Br_2$ 305.8891, found 305.8879.

2-(3-Bromo-4-bromomethylbenzyloxy)tetrahydropyran (15). LAH (284 mg, 7.47 mmol) was added to the above product mixture (2.30 g, 7.47 mmol) in anhydrous ether (20 mL) at 0 °C, and the suspension was vigorously stirred for 30 min at 0 °C. The mixture was diluted with ether (10 mL) and extracted with aqueous 10% HCl (10 mL) and ether (20 mL × 3). After drying ($MgSO_4$) and evaporation of the solvents, a white solid was obtained. To the crude white solid were added anhydrous CH_2Cl_2 (10 mL), DHP (680 μL, 7.47 mmol), and a catalytic amount of TsOH (47 mg) at 0 °C. After 30 min at 0 °C, the mixture was extracted with CH_2Cl_2 (10 mL × 3), aqueous $NaHCO_3$ (5 mL), and H_2O (10 mL × 3) and dried. The residue obtained after evaporation of solvents was purified with column chromatography to afford **15** (2.01 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46−1.91 (6H, m), 3.51−3.62 (1H, m), 3.85−3.96 (1H, m), 4.47 (1H, d, J = 12.6 Hz), 4.61 (2H, s), 4.71 (1H, m), 4.76 (1H, d, J = 12.6 Hz), 7.29 (1H, d, J = 7.8 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.60 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 25.5, 30.6, 33.4, 62.3, 67.6, 98.1, 124.6, 127.2, 131.3, 132.4, 136.1, 141.1. IR (neat): 3050.9, 2955.3, 1605.9, 1036.9. LRMS: *m*/*z* 363, 346, 283, 263, 182, 85. HRMS (ESI) calcd for $C_{13}H_{16}O_2Br_2$ 363.9497, found 363.9507.

2-[3-Bromo-4-(3-phenylpropoxymethyl)benzyloxy]tetrahydropyran (16). 60% NaH in mineral oil (435 mg, 10.88 mmol) was added to a solution of 3-phenyl-1-propanol (1.48 g, 10.88 mmol) in anhydrous DMF (10 mL) at 0 °C under nitrogen. After 1 h at room temperature, **15** (1.98 mg, 5.44 mmol) was added, and the mixture was stirred for 10 h at room temperature. The final mixture was poured into brine (10 mL), extracted with aqueous NH_4Cl and ether (10 mL × 3), and dried with $MgSO_4$. The residue obtained after evaporation of solvents was subjected to flash chromatography to give **16** (1.67 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54−1.95 (6H, m), 1.96−2.01 (2H, m), 2.76 (2H, t, J = 7.4 Hz), 3.53−3.59 (3H, m), 3.88−3.92 (1H, m), 4.48 (1H, d, J = 12.3 Hz), 4.57 (2H, s), 4.70−4.72 (1H, m), 4.76 (1H, d, J = 12.3 Hz), 7.17−7.33 (6H, m), 7.46 (1H, d, J = 7.8 Hz), 7.58 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 25.6, 30.7, 31.5, 32.5, 62.3, 67.9, 70.1, 72.1, 97.9, 122.8, 125.9, 126.9, 128.5, 128.6, 129.1, 131.8, 137.2, 139.6, 142.1. IR (neat): 3021.9, 2945.9, 1608, 1563, 1037. LRMS: *m*/*z* 318, 289, 105. HRMS (ESI) calcd for (M-THPOH) $C_{17}H_{17}OBr$ 318.0442, found 318.0431.

2-[3-Iodo-4-(3-phenylpropoxymethyl)benzyloxy]tetrahydropyran (17). First, 1.6 N BuLi in hexane (4.56 mL, 7.30 mmol) was added to a solution of **16** (1.53 g, 3.65 mmol) in anhydrous THF (10 mL) at −78 °C under nitrogen. After 1 h, a solution of 1,2-diiodoethane (2.06 g, 7.31 mmol) in THF (3 mL) was added. The mixture was allowed to warm slowly to room temperature (1 h), poured into 5% Na_2SO_3 (10 mL), and extracted with ether (10 mL × 3). The organic layer was dried with $MgSO_4$, and the residue obtained after removal of solvents was subjected to column chromatography to provide **17** (1.28 g, 75%). δ 1.55−1.91 (6H, m), 1.96−2.01 (2H, m), 2.77 (2H, t, J = 7.4 Hz), 3.53−3.60 (3H, m), 3.88−3.94 (1H, m), 4.46 (1H, d, J = 12.4 Hz), 4.48 (2H, s), 4.69−4.70 (1H, m), 4.74 (1H, d, J = 12.4 Hz), 7.17−7.43 (7H, m), 7.85 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 25.5, 30.6, 31.4, 32.5, 62.2, 67.6, 70.1, 76.4, 97.8, 125.8, 127.7, 128.4, 128.6, 138.4, 139.6, 140.0, 142.0. IR (neat): 3058, 3025, 2945, 2855, 1602.

LRMS: *m*/*z* 466, 448, 382, 230, 135, 91. HRMS (ESI) calcd for $C_{22}H_{26}O_3I$ 465.0927, found 465.0932.

[3-Iodo-4-(3-phenylpropoxymethyl)phenyl]methanol (18). A catalytic amount of TsOH (52 mg) was added to a stirred solution of **17** (989 mg, 2.12 mmol) in MeOH (5 mL) at room temperature. After 2 h, the mixture was quenched with aqueous $NaHCO_3$, diluted with ether (5 mL), and extracted with H_2O (10 mL × 3) and ether (10 mL × 3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then subjected to column chromatography to afford **18** (737 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (1H, s), 1.94−2.04 (2H, m), 2.77 (2H, t, J = 7.3 Hz), 3.58 (2H, t, J = 6.3 Hz), 4.49 (2H, s), 4.67 (2H, s), 7.20−7.44 (7H, m), 7.86 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 32.5, 64.2, 70.1, 76.4, 97.9, 125.9, 126.8, 128.4, 128.6, 128.8, 137.6, 140.0, 142.0. IR (neat): 3387 (br), 2916, 2856, 1601, 1452. LRMS: *m*/*z* 382, 364, 307, 135, 105, 91. HRMS (ESI) calcd for $C_{17}H_{19}O_2I$ 382.0430, found 382.0414.

2-[4-(3-Phenylpropoxymethyl)benzyloxy]tetrahydropyran (19). Bu_3SnH (23 μL, 0.085 mmol) was added to a solution of **18** (32.9 mg, 0.071 mmol) and AIBN (3.5 mg, 0.3 equiv) in benzene (710 μL, 0.1 M), and the mixture was degassed for 5 min by slowly bubbling deoxygenated nitrogen at room temperature. The mixture was refluxed for 2 h at 80 °C, cooled to room temperature, and concentrated under reduced pressure. The residue was dissolved in THF (2.0 mL), and aqueous KF (2.0 mL) was added. After 2 h, the mixture was concentrated and filtered through a short silica gel pad. The crude product was purified by silica gel column chromatography to give the reduced product **7** (21.0 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47−1.85 (6H, m), 1.86−2.00 (2H, m), 2.73 (2H, t, J = 7.4 Hz), 3.50 (2H, t, J = 6.4 Hz), 3.52−3.58 (1H, m), 3.88−3.99 (1H, m), 4.50−4.54 (3H, m), 4.71−4.73 (1H, m), 4.80 (1H, d, J = 12.0 Hz), 7.17−7.39 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 25.6, 30.7, 31.5, 32.5, 62.2, 68.7, 69.5, 72.7, 97.7, 125.8, 127.8, 128.0, 128.4, 128.6, 138.4, 137.7, 138.0, 142.1. IR (neat): 3063, 3028, 2944, 2855, 1603. LRMS: *m*/*z* 340, 281, 239, 105, 91. HRMS (ESI) calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2043.

2-(4-Methylbenzyloxy)tetrahydropyran (20). To a solution of **18** (47.3 mg, 0.10 mmol) and AIBN (4.9 mg, 0.3 equiv) in degassed benzene (101 mL, 0.001 M) was added Bu_3SnH (29 μL, 0.11 mmol). After being heated for 6 h at 80 °C, the mixture was cooled to room temperature and concentrated. The residue was dissolved in THF (2.0 mL), and aqueous KF (2.0 mL) was added. The mixture obtained after 2 h was concentrated and filtered through a short silica gel pad. The crude product was purified by silica gel column chromatography to afford **20** (15.6 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55−1.90 (6H, m), 2.38 (3H, s), 3.55−3.60 (1H, m), 3.93−4.00 (1H, m), 4.50 (1H, d, J = 11.8 Hz), 4.73−4.75 (1H, m), 4.79 (1H, d, J = 11.8 Hz), 7.19 (2H, d, J = 7.8 Hz), 7.30 (2H, d, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 21.3, 25.6, 30.7, 62.2, 68.8, 97.6, 128.0, 129.1, 135.3, 137.3.

Solution-Phase Kinetic Experiments with 17. Radical precursor **17** (35.0 mg, 0.075 mmol) and AIBN (4.9 mg) were added into a 25 mL or 100 mL volumetric flask, which was then purged with dried nitrogen gas for 10 min at room temperature. To make 30 mM or 0.75 mM solutions, about 25 mL or 100 mL of degassed benzene was added to the volumetric flask. The reaction mixture (7 mL or 20 mL) was added to five tubes, and different amounts of Bu_3SnH were added to each tube (see Table 3). The five tubes were sealed and heated for 8 h at 80 °C. After being cooled and concentrated under reduced pressure, the residues were dissolved in THF (2.0 mL), and aqueous KF (2.0 mL) was added. After 2 h, the mixtures were concentrated and filtered through a short silica gel pad. The crude products were purified by flash chromatography to give mixtures of **19** and **20** (87−93%). The ratios of **19** and **20** were analyzed by GC.

Resin-Bound Radical Precursor 23. To a mixture of Ellman resin (0.98 mmol/g, 615.3 mg, 0.603 mmol) and **18** (693 mg, 1.81 mmol, 3.0 equiv) in anhydrous CH_2Cl_2 (3.0 mL) was added TsOH (344 mg, 1.81 mmol, 3.0 equiv) at 0 °C. The resulting mixture was shaken for 3 days at room temperature. The reaction mixture was washed with CH_2Cl_2 (10 mL × 3), acetone (10 mL × 3), and anhydrous CH_2Cl_2 (10 mL × 3) and dried under high vacuum for 10 h to afford **23** (822.7 mg, loading level = 90%, 0.660 mmol/g).

Radical Reaction of Resin-Bound Substrate 23. Hexamethylditin (3.0 equiv) was added to a suspension of **23** in degassed benzene under nitrogen at room temperature. The reaction mixture was irradiated at 80 °C with a 275 W GE sunlamp for 20 h with gentle stirring. After being cooled to room temperature, the mixture was washed with CH_2Cl_2 (10 mL × 3), hexane (10 mL × 3), and anhydrous CH_2Cl_2 (10 mL × 3). TsOH was then added to the suspension in CH_2Cl_2/MeOH (1:1) at room temperature. After 10 h at room temperature, the resin was filtered and washed, and the solvent was removed to provide a mixture of **24** and **25** (91−93%). The ratio of **24** and **25** was analyzed by GC.

[4-(3-Phenylpropoxymethyl)phenyl]-methanol (24). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (1H, s), 1.92−2.00 (2H, m), 2.73 (2H, t, J = 7.4 Hz), 3.50 (2H, t, J = 6.4 Hz), 4.52 (2H, s), 4.71 (2H, s), 7.17−7.21 (3H, m), 7.27−7.31 (2H, m), 7.36 (4H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 32.4, 65.3, 69.6, 72.7, 114.7, 125.8, 127.2, 128.0, 128.4, 128.5, 138.2, 140.3, 142.0.

***p*-Tolylmethanol (25).** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (1H, s), 2.37 (3H, s), 4.65 (2H, s), 7.19 (2H, d, J = 7.9 Hz), 7.27 (2H, d, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 65.1, 127.2, 129.3, 137.4, 138.0.

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