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Controlling Radical Chain Reactions by Unimolecular Chain Transfer. Intramolecular Hydrogen Transfer Reactions of Silicon Hydrides

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The benefits of intramolecularity are commonly used in synthesis to form carbon−carbon bonds by radical cyclizations. These cyclizations are usually conducted by methods (metal hydride, atom transfer) that involve bimolecular chain transfer steps.[1] The full potential of bimolecular radical carbon−carbon bond forming reactions has yet to be realized.[2] We now suggest the logical reversal of the standard *modus operandi:* bimolecular radical carbon−carbon bond forming reactions should be conducted with intramolecular chain transfer reactions.[3] We term this class of transformations unimolecular chain transfer (UMCT) reactions.

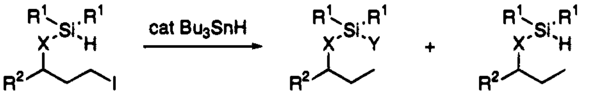
We have initiated our work in this area by studying intramolecular hydrogen transfer reactions because bimolecular hydrogen transfer reactions [for example, from Bu_3SnH and $(TMS)_3SiH$] are the most popular chain transfer reactions for synthetic applications.[1,2] The logical starting point for such an investigation is silicon hydrides.[4,5] Rate constants for bimolecular reactions of alkyl radicals with Et_3SiH fall 1−2 orders of magnitude below the useful limit for bimolecular reactions in solution,[4a,d] so chains based on bimolecular hydrogen transfer of alkyl- and arylsilanes will not generally propagate.[6] However, even a modest rate increase for intramolecularity should allow chains based on UMCT to propagate. Intramolecular hydrogen transfer reactions of carbon−hydrogen bonds are well studied,[7] but there is very little work on their group IVA nuclear analogs (Si, Ge, Sn).[4d,e]

To probe for the possibility for carrying radical chains by UMCT, we prepared a series of silicon hydrides **1a**−**f** by standard silylation of an alcohol or organometallic reagent with the appropriate dialkyl- or diphenylchlorosilane (see eq 1 and Table 1).[5] Chains were initiated by portionwise addition of 5% Bu_3SnH, and reactions were monitored by GC for the formation of rearranged silicon iodide **2** and reduced silicon hydride **3**. In successful experiments, isolated yields were determined by exposing the crude reaction mixture to methanol and triethylamine. This converted the sensitive silicon iodides **2c**−**f** (Y = I) to stable silyl ethers **4d,e** (Y = OMe, X = CH_2) or acetals **4c,f** (Y = OMe, X = O), which were isolated and identified by comparison with authentic samples.

Table 1. Rearrangements of Silicon Hydrides **1a**−**f**

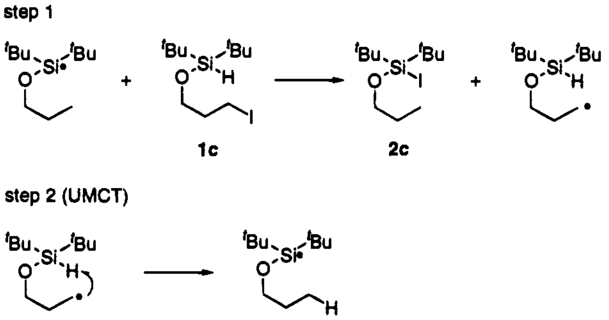
entry	X	R^1	R^2	Bu_3SnH	ratio **2/3**	yield **4** (%)
1a	O	^{i}Pr	H	several	**3a** only	nd[a]
1b	O	$(CH_2)_4$	H	several	**3b** only	nd[a]
1c	O	^{t}Bu	H	5 × 5%	84/16	47
1d	CH_2	^{t}Bu	H	3 × 5%	90/10	72
1e	CH_2	Ph	H	2 × 5%	92/8	84
1f	O	^{t}Bu	Ph	2 × 5%	94/6	71

[a] Not determined since **2** was not formed.



1a - f   **2a - f** Y = I   **4c - f** Y = OMe   **3**   (1)

Reactions with substrates **1a,b** were slow, the silicon iodide (**2a,b**) was not formed in significant amounts, and the yield of the reduced product (**3a,b**) never exceeded the quantity of tin hydride that was added. This suggests that these substrates react only by a normal tin hydride chain; there is no UMCT chain occurring.[8] In contrast, substrates **1c**−**f** were consumed more rapidly, and in significantly greater quantities than the amount of added tin hydride. Substrate **1c** was consumed after addition of 25 mol % Bu_3SnH, **1d** after 15%, and **1e,f** after just 10%. The raw GC ratio of the rearranged silicon iodides **2c,d** to the reduced silicon hydrides **3c,d** showed a rough correlation to the quantity of tin hydride added—less tin hydride translates to a higher **2/3** ratio. These isomerizations can also be conducted by UV irradiation of a benzene solution of **1c**−**f** containing 10% hexabutylditin. For example, reaction of **1c** under these conditions (0.01 M) was complete in 1 h, and **4c** was cleanly produced. The reduced product **3c** did not disappear entirely, although the ratio of **2c** to **3c** increased to 94/6.



(2)

We suggest that substrates **1c**−**f** isomerize by a UMCT mechanism. Interestingly, for reactions involving intramolecular atom (or group) transfer, two different chains can be envisioned, as illustrated in eqs 2 and 3 for the conversion of **1c** to **2c**. One chain (eq 2) features intermolecular iodine transfer (step 1) and intramolecular hydrogen transfer (step 2), while the other (eq 3) features intramolecular iodine transfer (step 1) and intermolecular hydrogen transfer (step 2). Although the closed shell precursors and products are the same in these two chains, they

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(1) (a) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715. (c) Ref 1b, p 779. (d) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986.

(2) For example, in natural products applications, strategies involving radical cyclizations significantly outnumber those involving radical additions. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(3) The benefits of intramolecularity have been recognized for fragmentation reactions (which are unimolecular by definition), but not for other types of radical chain transfer reactions (which can be either unimolecular or bimolecular). See refs 1c, 2, and the following: (a) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. *Chemtracts−Org. Chem.* **1993**, *6*, 147. (b) Feldman, K. S.; Lee, Y. B. *J. Am. Chem. Soc.* **1987**, *109*, 5850. (c) Curran, D. P.; Van, E. P. A. *Tetrahedron Lett.* **1989**, *30*, 2501.

(4) (a) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* **1993**, *58*, 249. (b) Chatgilialoglu, C. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht: 1989; p 215. (c) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246. (d) Chatgilialoglu, C. *Chem. Rev.*, in press. (e) Clive, D.; Contin, M. *J. Chem. Soc., Chem. Commun.* **1995**, 319.

(5) Ionic intramolecular hydrosilylations can be promoted with Lewis acids or transition metals. Leading references: (a) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541. (b) Colvin, E. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 645. (c) Hiyama, T.; Kusumoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 788. (d) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121.

(6) Significant exceptions: Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1993**, *49*, 2793. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1993**, *49*, 7193.

(7) Recent leading reference: Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

(8) Control experiments with tributyltin deuteride (see supplementary material) suggest that 1,6- and 1,7-hydrogen transfer reactions from C−H bonds break the chain.

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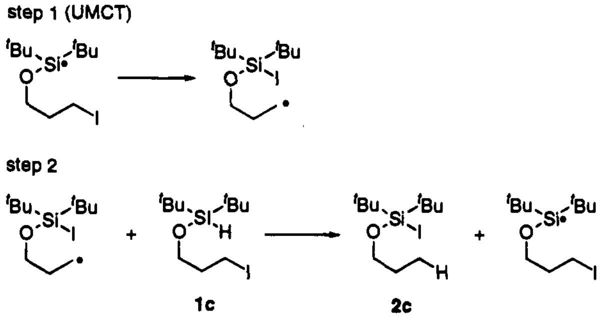
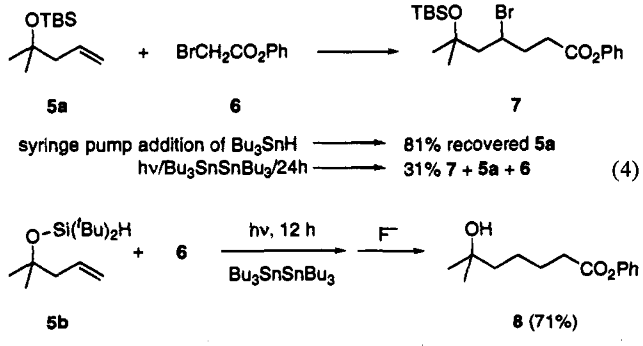


(3)

share no common radical intermediates. We term these "orthogonal chains". Literature precedent suggests that the bimolecular hydrogen transfer step (eq 3, step 2) is too slow to propagate a chain,[4a,c] so most of the product must come through the chain that features intramolecular hydrogen transfer, eq 2. This conclusion is also supported by control experiments.[9] No tin radical (or tin hydride) is consumed in these chains; the tin hydride and distannane presumably serve primarily as initiators.

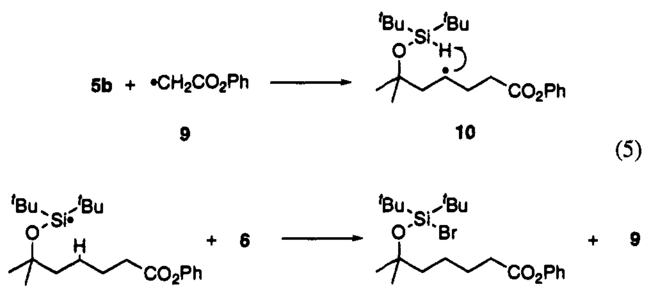
The mechanism in eq 2 provides a framework for interpreting the observations in Table 1. The increased efficiency of the chain and the increased **2**/**3** ratio suggest the following trend in increasing rate of intramolecular 1,5-hydrogen transfer from the silicon hydride: RPh$_2$SiH > R(^{t}Bu)$_2$SiH > RO(^{t}Bu)$_2$SiH. Preliminary competition experiments with allyltributylstannane[10] suggest that the rate constant for 1,5-hydrogen transfer in eq 2, step 2 is about 1 × 10^4 M^{-1} s^{-1}. Radicals derived from **1d**–**f** rearrange with transfer rate constants of about 2.5 × 10^4 M^{-1} s^{-1}. No bimolecular rate constants are known for hydrogen transfer reactions of alkoxysilanes, but by using the rate constant for triethylsilane, we can estimate an effective molarity of their rearrangements at about 2–20 M. Because the base rate constant for radical allylation is not known with high accuracy, these numbers should serve only as estimates until more accurate rate constants are measured.

Although they are interesting for the study of mechanism and substituent effects, simple UMCT-based chains like these have little preparative value. The real value of these chains will be in mediating slow bimolecular reactions. To demonstrate this potential value, we conducted the three reactions shown in eq 4. Silicon hydride **5a,b** was chosen on the basis of the anticipation that the geminal dimethyl substituent would accelerate the 1,5-hydrogen transfer by a Thorpe–Ingold effect. TBS ether **5a** mirrors **5b** in its radical acceptor ability, but intramolecular hydrogen transfer is not possible. In each reaction, alkene **5** and bromophenyl acetate **6** were used in 1/1.2 ratio. Additions to the TBS ether **5a** were attempted by the "tin hydride" and "atom transfer" methods.[1] Syringe pump addition of tributyltin hydride to **5a** and **6** provided recovered **5a** (81% isolated yield) and reduced phenyl acetate. The atom transfer reaction provided a slow, inefficient conversion to γ-bromo ester **7**. After 1 day at 60 °C, much unreacted **5a** and **6** remained, and the isolated yield of **7** was 31%. In contrast, silicon hydride **5b** was smoothly consumed over 12 h at 25 °C in the UMCT reaction (UV irradiation, 5% hexabutylditin). The intermediate silicon bromide was desilylated in situ, and hydroxy ester **8** was isolated in 71% yield after flash chromatography.



(4)

Equation 5 shows the suggested mechanism for the UMCT addition of **6** to **5b**. In this reaction, radical **9** has a long lifetime because bimolecular hydrogen transfer from the silicon hydride is slow. But the adduct radical **10** undergoes efficient intramolecular chain transfer. The tin hydride method fails because reduction of **9** is faster than addition under these conditions. In the atom transfer method, radical **9** has a fair chance of adding to the alkene, but the subsequent bromine transfer step is slow,[11] so the chain is not efficient. Were the atom transfer step endothermic, such an atom transfer chain would not propagate at all. The advantage of the reaction of **5b** is quite simply that the chain transfer step is unimolecular.



(5)

These preliminary results suggest that UMCT reactions of silicon hydrides have significant potential for expanding the scope and practicality of bimolecular radical reactions. By using known rate and substituent trends in radical additions, it should now be possible to introduce new classes of reagents in which the silicon hydride is placed either in the radical acceptor (as in eq 5) or in the radical precursor. Relative to the currently used reagents [Bu$_3$SnH and (TMS)$_3$SiH], the new class of hydrides must be connected by a bond to one of the reactant partners. In return for the extra steps of attachment and detachment, one gains all of the advantages of the UMCT method as well as a number of practical ones—the types of silicon hydride that are used are inexpensive and readily available, the products can be converted into protecting groups (providing a dual use for the silicon), and the introduction and cleavage of silanes, silyl ethers, and related functional groups is well known. The results with UMCT-based hydrogen transfer chains suggest that the "unimolecularization" of other radical chain transfer reactions is a worthwhile endeavor. Finally, all UMCT chains should be especially useful for tandem radical reactions[1d,3] because they will allow strict control of the timing of the chain transfer step in complex settings.

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Supplementary Material Available: Summary of control experiments showing that chains based on bimolecular hydrogen transfer will not propagate (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Details of control experiments are provided in the supplementary material.

(10) Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1990**, *31*, 2861.

(11) (a) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826. (b) Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* **1994**, *35*, 2763.