Unimolecular Chain Transfer (UMCT) Reactions of Silicon Hydrides: Controlling Relative Configuration in Hydrogen Transfer Reactions of Cyclic Radicals

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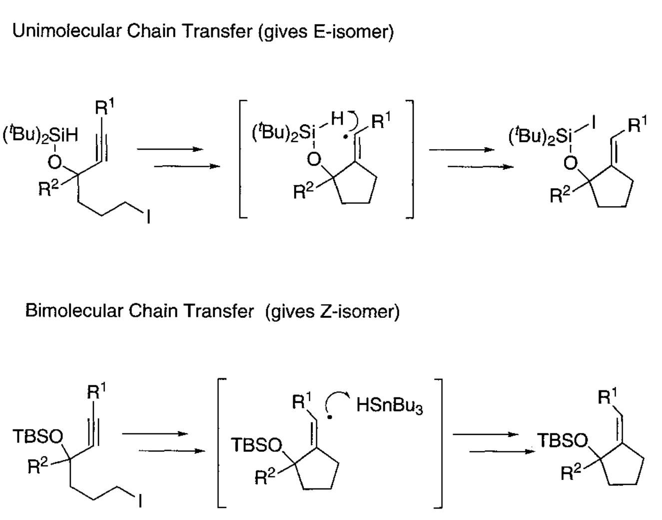
Abstract: UMCT-controlled sequences of radical cyclization followed by 1,5-hydrogen transfer from diphenylsilanes or bis(trimethylsilyl)-silanes are introduced. The later silanes have improved reactivity.

We have recently laid out the features and advantages of conducting radical reactions with chains that have a unimolecular chain transfer (UMCT) step.[1] Fragmentations of β-stannyl and related radicals are the most common types of UMCT reactions, and we are currently studying a new class of reactions based on intramolecular hydrogen transfer reactions of silicon hydrides.[2] Very recently, Studer has demonstrated that intramolecular homolytic substitutions at silicon may offer another general approach with its own set of features.[3]

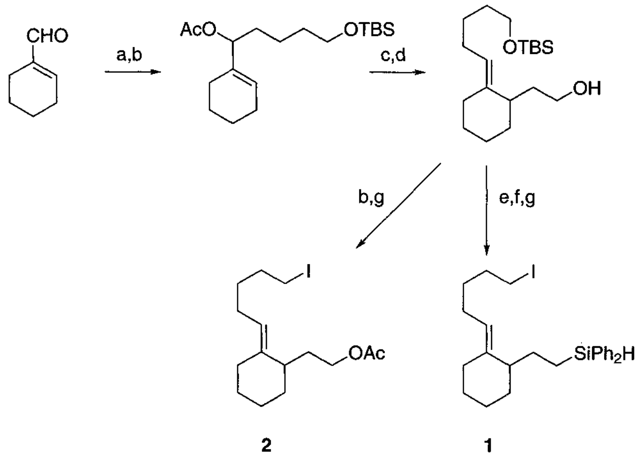
The ability to control relative configuration by intramolecular atom or group transfer is a key feature of UMCT reactions based on homolytic substitution that is not reproduced by UMCT reactions based on β-fragmentation. We have illustrated the possibilities by introducing a series of UMCT reactions of alkynes[2c,d] in which the configuration of the product alkene is controlled by an intramolecular hydrogen transfer reaction to a vinyl radical. In this series, the UMCT reactions are complementary to traditional bimolecular chain transfer reactions, as illustrated by the examples in eq 1.



eq 1

In extending this approach to control the configuration of cyclic compounds and radicals, we have encountered some limitations and made some interesting observations that provide clues for further research. This Letter summarizes these observations.

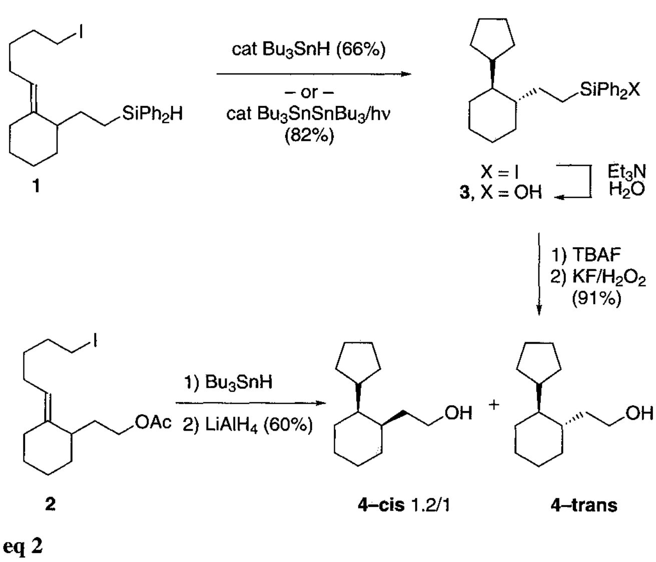
We prepared substrates **1** and **2** to probe the potential for using UMCT reactions of silicon hydrides to control relative configuration in the reactions of cyclic radicals. The syntheses of **1** and **2** were straightforward, as outlined in Scheme 1.[4] Interestingly, the best way to introduce the diphenylsilane substituent was by an unusual (but well precedented[5]) homolytic substitution of hydride from Ph_2SiH_2.



a) $I(CH_2)_4OTBS$, *t*-BuLi, (56%); b) Ac_2O (92%, 98%);
c) LDA, TBSCl, then 65°C; d) LAH (60% overall);
e) MsCl, then NaI (79%); f) *t*-BuLi, then Ph_2SiH_2 (88%);
g) DPPE, Br_2, then NaI (92%, 88%)

Scheme 1

The reactions of the UMCT substrate **1** and the control **2** are summarized in eq 2. Initiation of the isomerization of **1** was relatively inefficient with tributyltin hydride, but the starting material was finally consumed after addition of 5-7 portions of 5% Bu_3SnH. The reaction mixture was treated with triethylamine and water to hydrolyze the expected silicon iodide product, and the silanol **3** was isolated as a single stereoisomer in 66% yield. Photolytic initiation with 10% $Bu_3SnSnBu_3$ was more efficient (in this case Et_3N and water were present in the reaction mixture), and provided **3** in 82% yield.[6] The control experiments (see below) show that the hydrogen transfer in this reaction is intramolecular, and the relative configuration of **3** is accordingly assigned as trans.

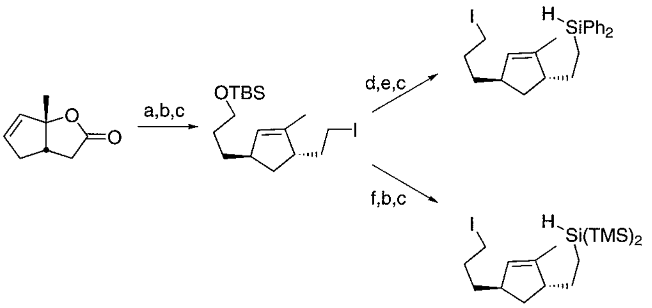


eq 2

Standard reductive cyclization of **2** with Bu_3SnH provided an inseparable mixture of acetates that was directly reduced with $LiAlH_4$.

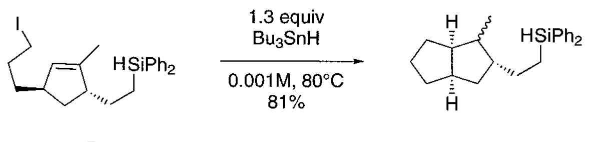
This provided a 1.2/1 mixture of alcohols **4-cis/4-trans**. The correlation was completed by conducting a Tamao-Fleming[7] oxidation of **3**, which provided exclusively the minor alcohol **4-trans**. Thus, the bimolecular hydrogen transfer reaction provides a slight selectivity in favor of the cis isomer while the intramolecular hydrogen transfer reaction is highly trans selective.

This success was contrasted by a clear failure in the related system **5**, which was prepared as shown in Scheme 2. Reactions of **5** with either portions of tin hydride under thermal conditions or ditin under photolytic conditions did not result in clean transformations. In general, the reactions quickly turned red (I_2?), and large amounts of starting material were recovered. That the reason for these failures was the intramolecular hydrogen transfer reaction was demonstrated by conducting a standard cyclization of **5** with 1.3 equiv of tributyltin hydride at low concentration. This provided an 89% yield of **6-endo/6-exo** in a ratio of 3.6/1 (eq 3). In this reaction, the diphenylsilane group is nothing but a spectator.



a) $I(CH_2)_3OTBS$, *t*-BuLi, CuBr; b) LAH (79%, 71% overall); c) MsCl, then NaI (81%, 95%, 92%); d) *t*-BuLi, Ph_2SiH_2 (96%);

Scheme 2

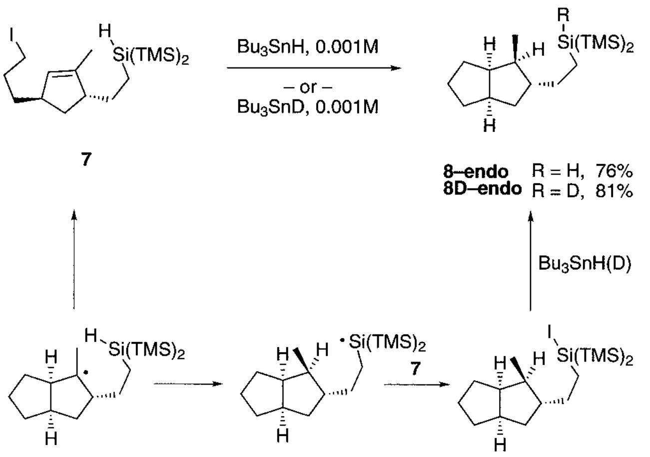


5 **6–endo/6–exo**, 3.6/1

eq 3

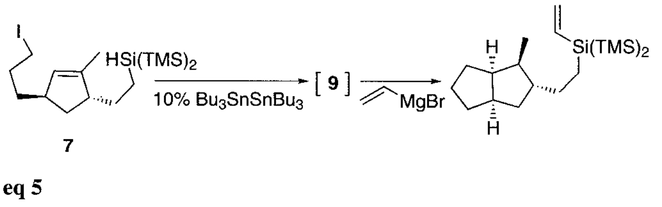
Although the reasons why **1** participates in a UMCT process and **5** does not are not clear, the failure with **5** is not unique.[8] These and related failures with tertiary and resonance stabilized radicals raise the possibility that dialkyl- and diphenylsilanes are not sufficiently reactive to transfer hydrogen to more stabilized radicals, even though the hydrogen transfer reactions do succeed in some cases.[2b]

The strength of Si–H bonds can be significantly weakened by adjacent silyl substituents,[9] so we prepared the substrate **7** (Scheme 2) to test for improved performance with the bis(trimethylsilyl)silane group. First results (eq 4) were discouraging. Attempts to isomerize **7** by portionwise addition of tin hydride were not successful. As with **5**, a red color was quickly produced and little conversion was observed. However, the control experiment with 1.3 equiv of tin hydride provided a surprise: the expected reduced product was formed in good yield but as a single stereoisomer **8-endo**.[10] The contrast of this result with the mixture formed in eq 3 suggested that the intramolecular hydrogen transfer reaction had now succeeded. This was confirmed by a labeling experiment with tin deuteride: the deuterium label was not adjacent to the methyl group but was instead on the silicon (**8D-endo**).



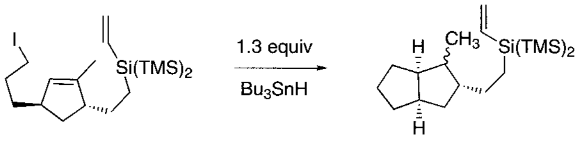
eq 4

Eq 4 outlines a likely mechanism for the formation of **8-endo**. This mechanism suggests that the initiation by portionwise addition of tin hydride fails because the isomerized silicon iodide **9** consumed the tin hydride. This was confirmed by two different experiments. First, isomerization of **7** to **9** did succeed by the photolytic method in the presence of ditin. The silyl iodide **9** was trapped by addition of vinyl magnesium bromide to provide **10-endo** as a single isomer in 79% yield (eq 5). Second, a control experiment showed *bis*(trimethylsilyl)silicon iodides rapidly react with Bu_3SnH. In a ^1H NMR experiment, reaction of $C_6H_{13}(TMS)_2SiH$ with adamantyl iodide (AIBN, C_6D_6, 80°C) provided $C_6H_{13}(TMS)_2SiI$. Addition of 1.5 equiv of Bu_3SnH to this mixture rapidly converted the silicon iodide back to the starting silane with concomitant formation of Bu_3SnI.



eq 5

Finally, the expected selectivity in an authentic bimolecular hydrogen transfer reaction was confirmed by the reduction of vinyl silane **10** with 1.3 equiv of Bu_3SnH (eq 6). This provided an 86% yield of a 3.5/1 mixture of **11-endo** and **11-exo**. This ratio is identical within experimental error to that observed in eq 3.



10 **11** 3.5/1

eq 6

These results have a number of implications for the development of UMCT chains based on hydrogen transfer reactions of silicon hydrides. The failures suggest that the current generation of silicon hydrides bearing diphenyl and di-*t*-butyl substituents may have limited utility. While reactions with more reactive vinyl and alkyl radicals have tended to succeed, those with less reactive alkyl radicals have tended to fail and the reason for failure can in several cases be traced directly to the hydrogen transfer step itself. A possible solution to this problem is to use more reactive hydrogen donors such as the bis(trimethylsilyl)silane introduced herein. This approach warrants further investigation although it must always be kept in mind that when the hydrogen donor becomes too good, bimolecular hydrogen transfer reactions can compete and the unique features of the UMCT process are lost. Finally, the use of tin hydride as a UMCT initiator is clearly not possible whenever the UMCT product reacts with tin hydride. This is not a major limitation since the photolytic ditin procedures generally gives better yields anyway.

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References and Notes

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6. $Bu_3SnSnBu_3$ (8.10 µL, 0.015 mmol) was added to a solution of **1** (0.060 g, 0.161 mmol) and Et_3N (0.02 mL, 0.15 mmol) in *t*-BuOH (1.6 mL) containing 2% H_20 (32 µL) at 80°C. After 12 h, the reaction was concentrated and the residue was purified by flash chromatography (Hexanes:EtOAc = 7:1) to afford **3** as a single diastereoisomer (0.050 g, 82%): ^1H NMR δ 7.62 (m, 4 H), 7.42 (m, 6 H), 2.13 (s, 1 H), 2.02 (m, 1 H), 1.47 (m, 2 H), 1.12 (m, 10 H); ^{13}C NMR δ 136.5, 136.4, 134.2 129.9, 127.9, 42.9, 41.7, 39.9, 30.2, 29.8, 27.2, 25.6, 25.3, 25.2, 11.2; IR 3474, 2998, 2925, 2858, 1725, 1447, 1422, 1286, 1118, 848, 835, 736, 699, MS *m/e* 300, 222, 199, 149, 129, 71; HRMS calcd for $C_{19}H_{28}OSi$ ($M-C_6H_6$) 300.1909, Found 300.1897.
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10. ^1H NMR δ 3.02 (t, *J* = 4.4 Hz, 1 H), 2.36 (m, 2 H), 1.89-1.01 (m, 12 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.90-0.61 (m, 2 H), 0.10 (s, 18 H); ^{13}C NMR δ 48.9, 46.4 42.5, 40.5, 39.5, 35.7, 32.1, 29.8, 28.4, 27.7, 15.5, 13.9, 0.4, 0.3; IR 2950, 2864, 2057, 1452, 1241, 833, 692 613; MS *m/e* 326, 311, 252, 178, 161, 155, 131, 117, 102, 73, 59; HRMS calcd for $C_{17}H_{38}Si_3$ (M) 326.2281, Found 326.2279.