Bu_3SnH-Mediated Pinacol Coupling of 1,5- and 1,6-Dicarbonyl Compounds: Synthetic and Mechanistic Studies

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A new method is described for the intramolecular pinacol coupling of 1,5- and 1,6-dicarbonyl compounds, employing Bu_3SnH as the stoichiometric reductant. The key steps in this pinacol cyclization are the addition of a tin ketyl to a carbonyl group and a subsequent intramolecular S_H2 reaction. The isolation of 1,3-dioxa-2-stannolanes, along with other product and labeling studies, provides strong support for the proposed homolytic substitution step, which distinguishes the pinacol cyclization from other reductive cyclizations of tin ketyls, all of which proceed through abstraction of hydrogen from Bu_3SnH in the final step. An interesting consequence of the S_H2 pathway is very high cis selectivity in the cyclization of 1,5-dicarbonyl compounds. Mechanistic studies furnish evidence that the steps that precede homolytic substitution, including C−C bond formation, are reversible under the reaction conditions.

Introduction

The development of radical reactions of Bu_3SnH has been the focus of intense interest in recent years.[1] In some instances, the radical-mediated transformations have no counterpart in heterolytic chemistry, and in other instances they complement heterolytic chemistry with respect to functional group tolerance, diastereoselectivity, and the like.

In 1986, Beckwith established that Bu_3SnH can effect the reductive cyclization of a δ,ϵ-unsaturated aldehyde to form a cyclopentanol (Figure 1).[2,3] Enholm later explored this reaction systematically, developing it into a synthetically useful process for both aldehydes and ketones.[4] We were interested in investigating an analogous reductive cyclization, using a dicarbonyl compound as the substrate (Figure 2).[5] Although a wide array of metals and inorganic metal complexes effect intramolecular pinacol couplings,[6] to the best of our knowledge there have been no reports that metal hydrides can do so.

In comparing the pathway for Bu_3SnH-mediated pinacol coupling that is outlined in Figure 2 with the pathway followed in the Beckwith−Enholm cyclization

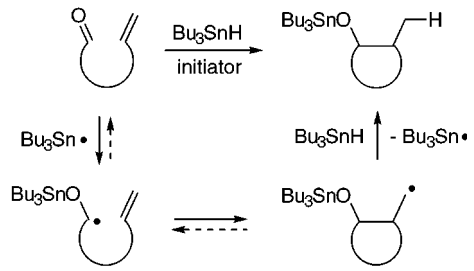

Figure 1. Bu_3SnH-mediated reductive cyclization of enals and enones (Beckwith, Enholm).

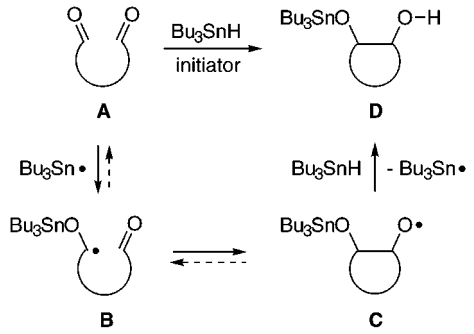

Figure 2. Proposed Bu_3SnH-mediated reductive cyclization of dicarbonyl compounds (intramolecular pinacol coupling).

(Figure 1), from the start it is possible to identify potential pitfalls for the pinacol-coupling reaction. First, whereas the C−C bond-forming step in the Beckwith−Enholm cyclization produces a carbon-centered radical, a higher-energy oxygen-centered radical would be generated in a pinacol coupling (Figure 2, **B** → **C**);[7−9] rather

(1) (a) Neumann, W. P. *Synthesis* **1987**, 665−683. (b) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995. (c) Davies, A. G. *Organotin Chemistry*; VCH: New York, 1997. (d) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987.

(2) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893−5901.

(3) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75−78.

(4) (a) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939−4942. (b) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835−1838.

(5) For Bu_3SnH-mediated reductive cyclizations of carbonyl/oxime ethers, see: (a) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205−2206. (b) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253−256. (c) Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624−626. (d) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201−202.

(6) For a comprehensive review of pinacol couplings, see: Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.6.

(7) We are not aware of any precedent for the addition of a tin ketyl to a carbonyl group.

(8) For discussions concerning the intramolecular addition of a *non*stabilized carbon-centered radical to a carbonyl group, see: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116−2117. Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791−5799. (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 230−234. Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674−2681. (c) Curran, D. P. *Synthesis* **1988**, 417−439.

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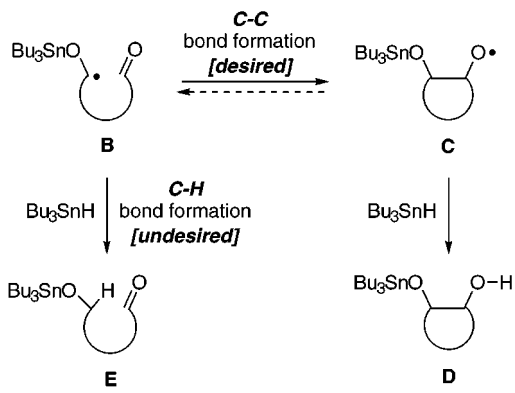
Scheme 1



than form **C**, radical **B** may simply abstract a hydrogen from Bu_3SnH (Scheme 1; **B** → **E**). Second, even if **C** is accessible, the propensity of alkoxy radicals to fragment (e.g., **C** → **B**) could lead to predominant formation of acyclic reduction product (e.g., **E**), rather than desired pinacol product (**D**).[10]

Despite these concerns, we forged ahead with our attempt to develop a Bu_3SnH-mediated pinacol coupling reaction. In this paper, we describe an investigation that has resulted in the discovery of such a process, via an unanticipated mechanistic pathway.[11]

Results and Discussion

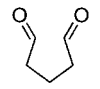
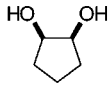
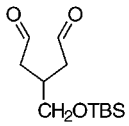
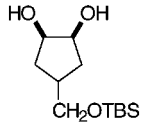
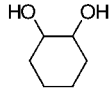
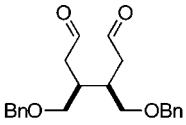
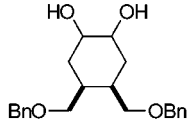
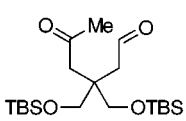
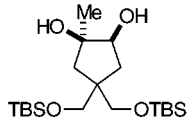
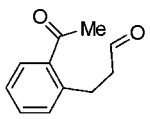
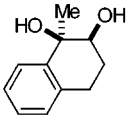
We were pleased to observe that treatment of a range of 1,5- and 1,6-dicarbonyl substrates with Bu_3SnH in refluxing benzene (AIBN as the initiator), followed by a hydrolytic workup, furnishes pinacol coupling products in modest to high yield (Table 1). Both dialdehydes (entries 1−4) and keto aldehydes (entries 5 and 6) undergo cyclization. In the case of glutaraldehyde, the reaction must be run dilute (0.025 M) to afford even a modest yield of cyclopentane-1,2-diol (46%; entry 1); at higher concentrations, 1,2-reduction of the aldehyde predominates. Our preliminary attempts to synthesize larger rings have been unsuccessful.

With Bu_3SnH as the reductant, we have established that dialdehydes cyclize preferentially in the presence of the corresponding keto aldehydes and diketones (Figure 3). The high selectivity is likely a manifestation of *reversible* addition of the Bu_3Sn radical to the carbonyl group (**A** ⇄ **B**, Figure 2). Were addition of the Bu_3Sn radical irreversible for both **1** and **2** (Figure 3), then **1** would be predicted to undergo pinacol cyclization perhaps twice as fast as **2**, rather than more than 10 times as fast.

Inspection of Table 1 reveals that the Bu_3SnH-mediated intramolecular coupling of 1,5-dicarbonyl compounds furnishes cis diols with uniformly high diastereoselectivity (>20:1; Table 1, entries 1, 2, and 5), an observation that stands in sharp contrast to the stereoselection reported for the intramolecular addition of tin ketyls to other unsaturated groups (e.g., olefins and oxime ethers).[2−5] We uncovered a clue to the origin of the cis selectivity when we isolated the prehydrolysis product of the pinacol cyclization of adipaldehyde, which we established to be 1,3-dioxa-2-stannolane **F** (Scheme 2; 60% yield),[12] *not* tin alkoxide **D**.

To determine if tin alkoxide **D** might be an intermediate on the pathway to **F** (Scheme 2), we prepared **D** independently and subjected it to the reaction conditions.

Table 1. Bu_3SnH-Mediated Intramolecular Pinacol Coupling

Entry	Substrate	Product	Stereoselectivity[a,b] (cis : trans)	Yield[a] (%)
1			98 : 1	46[c]
2			>99 : 1[d]	64
3			1 : 2.4	84
4			1 : 1.6[d]	88
5			>20 : 1[e]	62
6			20 : 1	53[f]

[a] Average of two runs. [b] Based on analysis by capillary gas chromatography, except as noted. [c] Isolated by crystallization as the 1,3-dioxa-2-stannolane. [d] ~1:1 mixture of the two diastereomeric cis diols. [e] Based on analysis by ^1H NMR. [f] Isolated as the acetonide.

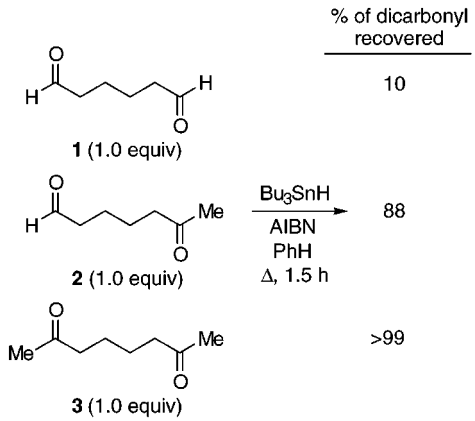


Figure 3. Selective intramolecular pinacol coupling of dialdehydes by Bu_3SnH.

(9) For a recent study of the relative reactivity of oxygen-stabilized versus nonstabilized carbon radicals, see: Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684−1687.

(10) Yeung, B.-W. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1989**, *8*, 413−427.

(11) For a preliminary report, see: Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283−7284.

(12) For reviews of the functionalization of 1,3-dioxa-2-stannolane, see: (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987. (b) Blunden, S. J.; Cusack, P. A.; Smith, P. J. *J. Organomet. Chem.* **1987**, *325*, 141−152. (c) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643−663.

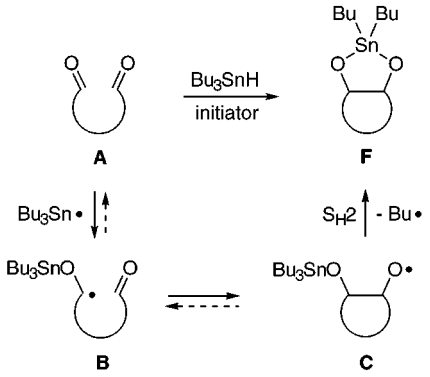
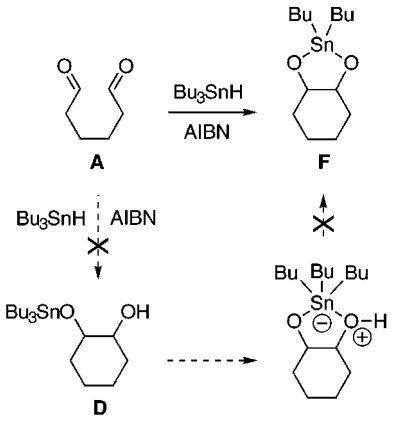


Figure 4. Revised mechanism for the Bu_3SnH-mediated intramolecular pinacol coupling of dicarbonyl compounds.

Scheme 2



Based on our observation that **F** is *not* formed, we have concluded that the Bu_3SnH-mediated intramolecular pinacol coupling of dicarbonyls likely proceeds through the pathway outlined in Figure 4.

The first two steps of the revised mechanism are identical to those in the original pathway (Figure 2). However, when alkoxy radical **C** is produced, rather than abstracting hydrogen from Bu_3SnH in an *inter*molecular reaction, we now believe that the alkoxy radical effects an *intra*molecular homolytic substitution (S_H2) at tin, thereby furnishing 1,3-dioxa-2-stannolane **F** (Figure 4; **C** → **F**).[13–15] The butyl radical that is liberated then propagates the chain through abstraction of hydrogen from Bu_3SnH.

To provide further support for the S_H2 mechanism, as well as to determine if the original hydrogen-abstraction pathway (Figure 2, **C** → **D**) is intervening to any appreciable extent, we quantified the formation of the chain-carrying alkyl radical that is generated upon homolytic substitution (Figure 4, **C** → **F**). For this study, we employed Oct_3SnD, rather than Bu_3SnH, as the stoichiometric reductant; this obviates complications associated with the volatility of butane and allows us to unambiguously establish the fate of the hydrogen (deuterium) initially bound to tin. As illustrated in eq 1, Oct_3SnD-mediated pinacol cyclization of adipaldehyde affords an equal mixture (within experimental error) of pinacol product and Oct-D, a result consistent with a reaction pathway proceeding essentially exclusively according to Figure 4.

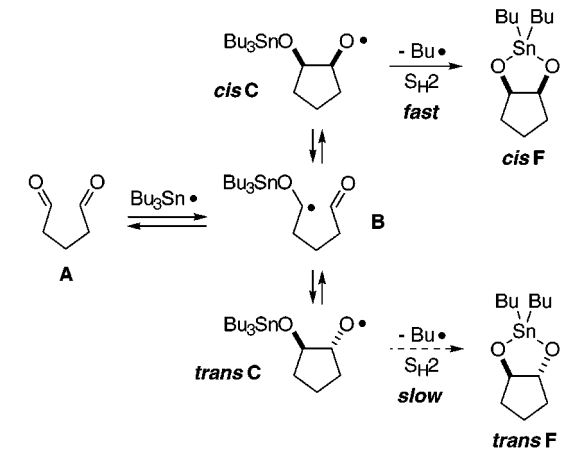
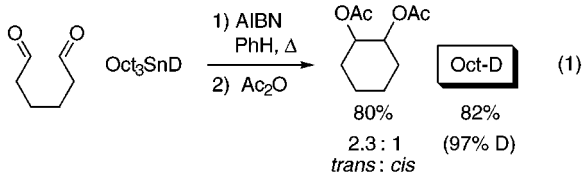


Figure 5. Rationalization of the high cis stereoselectivity that is observed in the Bu_3SnH-mediated intramolecular pinacol coupling of 1,5-dicarbonyl compounds.



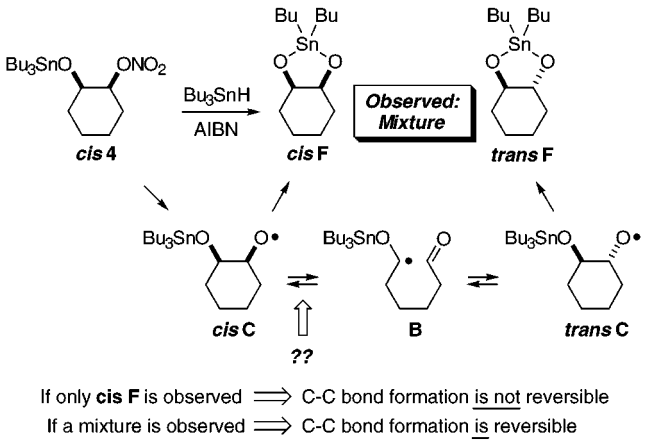
The S_H2 reaction is a favorable process from the standpoints of both entropy and enthalpy (Sn–O bond: ~90 kcal/mol; Sn–C bond: ~65 kcal/mol[1c]). In contrast to the original mechanism, the revised pathway accounts for the observation that reductive cyclizations of 1,5-dicarbonyl substrates afford the pinacol products with high cis diasteroselectivity (Figure 5). Thus, the ketyl radical of **B** can add to the pendant carbonyl group to generate either *cis*-**C** or *trans*-**C**. *cis*-**C** can readily undergo an intramolecular S_H2 reaction to produce a cis [3.3.0] ring system (*cis*-**F**), whereas the analogous reaction of *trans*-**C** is much less facile, since it would furnish a strained trans [3.3.0] ring system (*trans*-**F**). Consequently, *trans*-**C** instead fragments to regenerate **B**, which can in turn provide *cis*-**C** and then *cis*-**F**.

The competition experiment that was presented earlier (Figure 3) furnishes evidence that the first step of the Bu_3SnH-mediated intramolecular pinacol coupling process, addition of a Bu_3Sn radical to a carbonyl group, is reversible under the reaction conditions (Figure 4, **A** ⇄ **B**). To investigate the reversibility of the next step of the reaction sequence, C–C bond formation (Figure 4, **B** ⇄ **C**), we synthesized both diastereomers of 1,2-cyclohexanediol derivative **4** (Figure 6). In the presence of Bu_3Sn radicals, nitrate esters undergo addition–frag-

(13) A related process involving a carbon-centered radical has been observed as a minor (≤10%) side reaction in the stannylformylation of 1,6-dienes: Ryu, I.; Kurihara, A.; Muraoka, H.; Tsunoi, S.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 7570–7571 and references therein.

(14) (a) Davies has shown that the presence of electronegative substituents on tin facilitates homolytic displacement of an alkyl group by an alkoxy radical; for an overview, see: *Chemistry of Tin*; Harrison, P. G., Ed.; Chapman and Hall: New York, 1989. (b) For a recent review of free-radical homolytic substitution, see: Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265–13314.

(15) For examples of intramolecular reactions of oxygen-centered radicals with tributyltin alkoxides that lead to Bu_3Sn transfer (rather than cyclization), see the following. (a) 1,5-Bu_3Sn transfer: Davies, A. G.; Tse, M.-W. *J. Organomet. Chem.* **1978**, *155*, 25–30. Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106-5107. (b) 1,6-Bu_3Sn transfer: Kim, S.; Do, J. Y.; Lim, K. M. *Chem. Lett.* **1996**, 669–670.



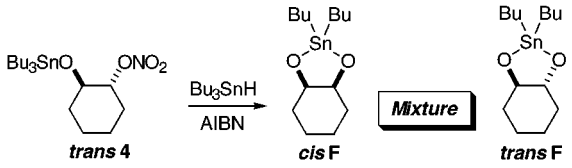
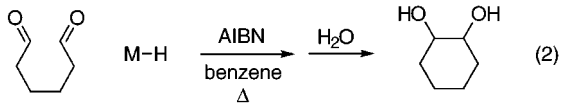


Figure 6. Stereochemical evidence for reversible C−C bond formation under the intramolecular pinacol coupling conditions.

mentation to produce alkoxy radicals (e.g., **C**).[16] Thus, *cis*-**4** and *trans*-**4** provide access to *cis*-**C** and *trans*-**C**, respectively. If the reactions of *cis*-**4** and *trans*-**4** with Bu_3Sn radical each affords diastereomerically pure 1,3-dioxa-2-stannolane **F**, then C−C bond formation in the pinacol coupling proceeds irreversibly; on the other hand, if isomeric mixtures of **F** are produced, then C−C bond formation is reversible. As illustrated in Figure 6, the data strongly support *reversible* C−C bond formation under the pinacol-coupling conditions.

Other group 14 hydrides also effect intramolecular pinacol coupling of dicarbonyl compounds, although they are less efficient than Bu_3SnH (eq 2; yields according to GC).[17,18] Simple 1,2-reduction is the predominant side reaction.



M−H	Yield	*trans*: *cis*
Bu_3SnH	***95%***	2.1 : 1
$(Me_3Si)_3SiH$	***71%***	1.4 : 1
Bu_3GeH	***27%***	2.5 : 1

Summary and Conclusions

We have discovered an interesting new method for the intramolecular pinacol coupling of 1,5- and 1,6-dicarbonyl compounds, employing Bu_3SnH as the stoichiometric reductant. To the best of our knowledge, this is the first example of the use of a metal hydride to effect an intramolecular pinacol reaction. Whereas most methods for pinacol coupling employ 2 equiv of a one-electron reducing agent (Figure 7), this mechanistically distinct Bu_3SnH-mediated process requires just one equivalent of reducing agent (Figure 4).

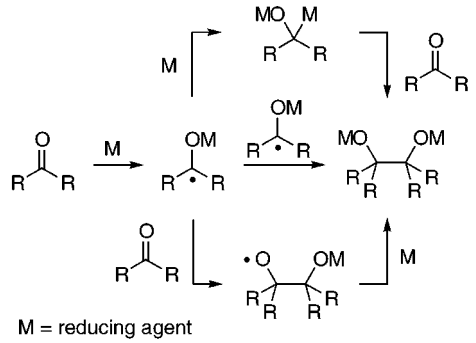


Figure 7. Common mechanisms for pinacol coupling.

The key steps in this pinacol cyclization are an unprecedented addition of a tin ketyl to a carbonyl group (Figure 4, **B** → **C**) and a subsequent intramolecular S_H2 reaction (**C** → **F**). The isolation of 1,3-dioxa-2-stannolanes (**F**), along with other product and labeling studies, provides strong support for the proposed homolytic substitution step, which distinguishes the pinacol cyclization from other reductive cyclizations of tin ketyls, all of which proceed through abstraction of hydrogen from Bu_3SnH in the final step (cf. Figure 2, **C** → **D**).[2−5] An interesting consequence of the S_H2 pathway is very high cis selectivity in the cyclization of 1,5-dicarbonyl compounds. Mechanistic studies furnish persuasive evidence that the steps that precede homolytic substitution, including C−C bond formation, are reversible under the reaction conditions.

Experimental Section

General Methods. AIBN (Eastman) was used without purification. Bu_3SnH (Aldrich) was distilled prior to use. Solvents were distilled from the indicated drying agents: benzene (sodium/benzophenone); toluene (molten sodium); CH_2Cl_2 (calcium hydride).

^{119}Sn chemical shifts are reported in ppm downfield from $SnMe_4$ (neat, external reference, δ scale) and were determined with pulse intervals of 0.3 s; broad-band ^1H NMR decoupling was only applied during acquisition. Coupling constants (J) are given in Hz.

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated.

Note: The data reported below for intramolecular pinacol-coupling reactions may differ slightly from the data reported in the text, since the latter are the average of two runs.

Table 1, Entry 1. Commercially available glutaric dialdehyde (50 wt % solution; Aldrich; 5−6 mL) was dissolved in benzene (75 mL) and dried with $MgSO_4$. After filtration and concentration, the resulting viscous, colorless oil was distilled bulb-to-bulb to afford the anhydrous dialdehyde as a clear, colorless oil that remained predominantly monomeric for at least 48 h.

A solution of the dialdehyde (200 mg, 2.00 mmol), Bu_3SnH (699 mg, 2.40 mmol), and AIBN (33 mg, 0.20 mmol) in benzene (80 mL) was heated to reflux. Additional AIBN (33 mg, 0.20

(16) Vite, G. D.; Fraser-Reid, B. *Synth. Commun.* **1988**, *18*, 1339−1342.

(17) (a) For a report of a triplet ketone reacting with $(Me_3Si)_4Si$ via an S_H2 pathway, see: Alberti, A.; Dellonte, S.; Paradisi, C.; Roffia, S.; Pedulli, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 1123−1129. (b) For related work, see: Kulicke, K. J.; Chatgilialoglu, C.; Kopping, B.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 935−939. Miura, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1992**, 2477−2478.

(18) In the reaction of $(Me_3Si)_3SiH$ with adipaldehyde, more than one molecule of the pinacol coupling product is generated for each molecule of $(Me_3Si)_3SiH$ that is consumed (see Experimental Section). We believe that this is attributable to the preference of the Me_3Si radical, generated upon S_H2 cyclization, for effecting pinacol coupling of adipaldehyde rather than hydrogen atom abstraction from $(Me_3Si)_3SiH$.

mmol) was added every 3 h. After 12 h, the reaction mixture was cooled to room temperature, and an aliquot was removed for GC analysis (acetylated and analyzed as the bisacetate derivative; 98:1 cis/trans; comparison with authentic cis and trans diols from Aldrich). The reaction mixture was concentrated, and the resulting white solid was washed with ice-cold toluene (3 × 5 mL) and dried, affording 313 mg (47%) of the 1,3-dioxa-2-stannolane as a white solid. The ^{1}H NMR spectrum was identical to the published spectrum.[19]

Table 1, Entry 2. A solution of the dialdehyde (218 mg, 0.890 mmol), Bu_3SnH (311 mg, 1.07 mmol), and AIBN (15 mg, 0.089 mmol) in benzene (36 mL) was heated to reflux. Additional AIBN (15 mg, 0.089 mmol) was added at 3 h intervals. After 12 h, the reaction mixture was cooled to room temperature, concentrated, and purified by flash chromatography, which afforded 147 mg (67%) of a mixture of diastereomeric cis diols as a clear, colorless oil. Less polar diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (br t, 2H), 3.54 (d, 2H, J = 3.0), 3.25 or 2.80 (br s, 2H), 2.24 (m, 1H), 2.03 (m, 2H), 1.49 (dt, 2H, J_1 = 14.3, J_2 = 5.5), 0.93 (s, 9H), 0.09 (s, 6H). More polar diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 2H), 3.43 (d, 2H, J = 5.1) 3.25 or 2.80 (br s, 2H), 2.42 (m, 1H), 1.77 (m, 2H), 1.64 (m, 2H), 0.09 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.2, 74.0, 66.6, 66.4, 36.8, 35.8, 34.1, 33.4, 25.8, 18.3, 18.2, −5.4, −5.5; IR (neat) 3383; HRMS calcd for $C_{12}H_{27}O_3Si$ $[M + H]^+$ 247.1729, found: 247.1727.

GC analysis of an acetylated aliquot of the unpurified reaction mixture revealed a ratio of 1.0:1 for the diastereomeric cis diols and a ratio of >99:1 for cis/trans diols (comparison with authentic products prepared by dihydroxylation of 4-[(*tert*-butyldimethylsilyl)oxymethyl]cyclopentene).

Table 1, Entry 3. A solution of the dialdehyde (114 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (10 mL) was heated to reflux for 1 h. Upon cooling to room temperature, the 1,3-dioxa-2-stannolane precipitated as a white solid. CH_2Cl_2 was added until the reaction mixture was homogeneous, and an aliquot was then removed for GC analysis. The reaction mixture was concentrated to a white solid/colorless oil and purified by flash chromatography, which provided 97 mg (84%) of a mixture of cis and trans diols as a white solid. GC analysis of the acetylated aliquot revealed a 1:2.4 (cis/trans) mixture of diols (comparison with authentic cis and trans diols from Aldrich).

Table 1, Entry 4. A solution of the dialdehyde (172 mg, 0.486 mmol), Bu_3SnH (170 mg, 0.583 mmol), and AIBN (16 mg, 0.097 mmol) in benzene (4.9 mL) was heated to reflux. After 3 h, AIBN (8 mg, 0.05 mmol) was added, and the reaction was refluxed for an additional 1 h. The reaction mixture was concentrated to a cloudy, colorless oil and purified by flash chromatography, which provided 152 mg (88%) of diols as a colorless oil that solidified on standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 10H), 4.45−4.39 (m, 4H), 3.90−3.31 (m, 6H), 3.15 (br s, OH), 2.85 (br s, OH), 2.60 (br s, OH), 2.34−1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.3, 138.2, 137.4, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.65, 127.60, 127.5, 75.1, 73.4, 73.1, 73.08, 73.02, 72.2, 71.9, 71.8, 70.7, 69.6, 69.2, 68.5, 37.9, 35.1, 34.4, 33.4, 31.9, 30.6; IR (neat) 3385; HRMS calcd for $C_{22}H_{29}O_4$ $[M + H]^+$ 357.2066, found 357.2068.

GC analysis of an acetylated aliquot of the unpurified reaction mixture indicated that a 20:17:63 (cis/cis/trans) mixture of diols was obtained (comparison with authentic products prepared by dihydroxylation of *meso*-4,5-bis(benzyloxymethyl)cyclohexene and acid-induced ring opening of *meso*-4,5-bis(benzyloxymethyl)cyclohexene oxide).

Table 1, Entry 5. A solution of Bu_3SnH (218 mg, 0.750 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (1 mL) was added via syringe pump over 36 h to a refluxing solution of the keto aldehyde (101 mg, 0.250 mmol) in benzene (0.50 mL). The reaction mixture was cooled to room temperature, and an aliquot was passed through a plug of silica gel and analyzed by ^{1}H NMR (no trans diol was detectable ⇒ >20:1 cis/trans; comparison with authentic cis product prepared by dihydroxylation of 4,4-bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-methylcyclopentene). The reaction mixture was concentrated to a pale yellow oil and purified by flash chromatography, which afforded 64 mg (63%) of the cis diol as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (s, 1H), 3.64 (m, 1H), 3.42 (s, 2H), 3.28 (s, 2H), 2.68 (d, 1H, J = 10.8), 1.88 (dd, 1H, J_1 = 13.7, J_2 = 7.4), 1.72 (d, 1H, J = 14.4), 1.65 (d, 1H, J = 14.1), 1.59 (dd, 1H, J_1 = 13.4, J_2 = 8.9), 1.22 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.10 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.1, 77.7, 69.0, 68.5, 45.2, 43.4, 37.2, 25.9, 25.7, 23.4, 18.4, 18.1, −5.61, −5.64; IR (neat) 3412; HRMS calcd for $C_{20}H_{45}O_4Si_2$ $[M + H]^+$ 405.2856, found 405.2845.

Table 1, Entry 6. A solution of the keto aldehyde (176 mg, 1.00 mmol), Bu_3SnH (437 mg, 1.50 mmol), and AIBN (33 mg, 0.20 mmol) in benzene (100 mL) was heated to reflux in an oil bath. Additional AIBN (33 mg, 0.20 mmol) was added at 3 h intervals. After 9 h, the reaction mixture was cooled to room temperature, concentrated to a yellow oil, and passed through a pad of silica gel. Treatment of the crude diol with 2,2-dimethoxypropane (1.0 g, 10 mmol) and catalytic PPTS, followed by aqueous workup and flash chromatography, afforded 116 mg (53%) of the acetonide as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J_1 = 7.4, J_2 = 1.4), 7.24−7.13 (m, 2H), 7.06 (d, 1H, J = 7.1), 4.17 (dd, 1H, J_1 = 4.2, J_2 = 2.1), 3.06 (ddd, 1H, J_1 = 17.1, J_2 = 12.7, J_3 = 5.4), 2.62 (ddd, 1H, J_1 = 16.5, J_2 = 5.4, J_3 = 2.4), 2.31−2.22 (m, 1H), 2.01−1.89 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 134.9, 127.8, 127.7, 126.8, 126.4, 107.9, 79.04, 79.00, 27.5, 27.2, 27.1, 24.1, 23.6; IR (neat) 2982, 2931, 2870; HRMS calcd for $C_{14}H_{19}O_2$ $[M + H]^+$ 219.1385, found 219.1378.

An aliquot of the unpurified reaction mixture was passed through a plug of silica gel and analyzed by GC, which revealed a 20:1 (cis/trans) ratio of diastereomers (comparison with authentic cis product prepared by dihydroxylation of 4-methyl-1,2-dihydronaphthalene).

Competition Experiment (Figure 3). A solution containing the dialdehyde (114 mg, 1.00 mmol), keto aldehyde (128 mg, 1.00 mmol), diketone (142 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and tetradecane (65 μL; internal standard) in benzene (10 mL) was prepared and analyzed by GC. AIBN (16 mg, 0.10 mmol) was added, and then the solution was heated to reflux for 90 min. Upon cooling to room temperature, a white precipitate formed. The reaction mixture was made homogeneous by the addition of CH_2Cl_2, and it was then analyzed by GC. The amount of each dicarbonyl compound that remained, as a percentage of its original amount, follows: dialdehyde (9%); keto aldehyde (87%); diketone (100%).

Isolation of a 1,3-Dioxa-2-stannolane (Scheme 2). A solution of adipaldehyde (114 mg, 1.00 mmol), Bu_3SnH (349 mg, 1.20 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (10 mL) was heated to reflux for 1 h. Stirring was then stopped, and the reaction mixture was permitted to slowly cool to room temperature, thereby allowing the 1,3-dioxa-2-stannolane to crystallize as white needles. After 34 h, the solvent was removed, and the crystals were washed with cold benzene (three times) and dried under vacuum (199 mg, 60%; ^{1}H NMR spectrum identical to the published spectrum[20]).

Examination of the Chemical Competence of D → F (Scheme 2). Bu_3SnOEt (3.35 g, 10.0 mmol) was added to a suspension of *trans*-1,2-cyclohexanediol (1.16 g, 10.0 mmol) in benzene (10 mL). The reaction was stirred under vacuum until no ethoxy peaks remained in the ^{1}H NMR spectrum. The spectrum revealed that a mixture of tin alkoxides was present. AIBN (1.0 mg, 0.0080 mmol) and Bu_3SnH (27.9 mg, 0.096 mmol) were added to a solution of the tin alkoxide mixture (32.4 mg, 0.0800 mmol) in C_6D_6 (800 μL) in a J. Young tube. After 2.5 h in an oil bath maintained at 80 °C, the reaction mixture was examined by ^{1}H NMR, which indicated that no

(19) *Gmelin Handbook of Inorganic Chemistry, Organotin Compounds*, 8th ed.; Kruerke, U., Ed.; Springer-Verlag: Berlin, 1988; Vol. 15, p 52.

(20) (a) Reference 19. (b) See also: Grindley, T. B.; Thangarasa, R. *J. Am. Chem. Soc.* **1990**, *112*, 1364−1373.

1,3-dioxa-2-stannolane had formed. $PhSiH_3$ (9 mg, 0.08 mmol) was then added to the reaction mixture; after 105 min at room temperature, no Bu_2SnH_2 was observed ($PhSiH_3$ reacts rapidly at room temperature with $R_2Sn(OR)_2$ to form R_2SnH_2), verifying that no 1,3-dioxa-2-stannolane was present.

Synthesis of Oct_3SnD. A solution of Oct_3SnCl (948 mg, 1.92 mmol) in Et_2O (4 mL) at 0 °C was added to a solution of $LiAlD_4$ (80.6 mg, 1.92 mmol; Aldrich, 98% D) in Et_2O (2 mL). After the mixture was stirred at room temperature for 90 min, the Oct_3SnD was isolated under an atmosphere of nitrogen by filtering, concentrating, passing through Celite (benzene washes), concentrating, filtering through an Acrodisc, and then concentrating. This procedure furnished Oct_3SnD as a slightly cloudy, colorless oil. No Oct_3Sn**H** was detectable by ^1H NMR: ^1H NMR (300 MHz, C_6D_6) δ 1.68 (m, 6H), 1.43−1.52 (m, 30H), 1.04 (m, 6H), 0.94−0.90 (m, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 35.0, 32.8, 30.2, 30.1, 28.6, 23.5, 14.7, 9.1. ^{119}Sn NMR (111.9 MHz, C_6D_6) δ −90.5 (t, J = 243); ^2H NMR (46 MHz, C_6H_6) δ 5.14 (s, ^1J ($^{119}Sn/^2H$) = 243, ^1J ($^{117}Sn/^2H$) = 232); IR (neat) 2918, 2850, 1465, 1378, 1340, 1300.

Pinacol Cyclization of Adipaldehyde with Oct_3SnD (Eq 1). Oct_3SnD (613 mg, 1.33 mmol), nonane (142 mg, 1.11 mmol; internal GC standard), and tetradecane (220 mg, 1.11 mmol; second internal GC standard) were added to a solution of adipaldehyde (127 mg, 1.11 mmol) and AIBN (18 mg, 0.11 mmol) in benzene (11 mL). The resulting reaction mixture was heated to reflux for 75 min. An aliquot was then analyzed by GC, which revealed an 82% yield of octane. Analysis by GCMS indicated that the octane was 97% deuterated. GC analysis of an acetylated aliquot revealed an 80% yield of acetylated pinacol products (2.3:1 trans/cis).

***trans*-1,2-Cyclohexanediol Mononitrate.**[21] A solution of fuming HNO_3 (2.52 g, 40.0 mmol) in Ac_2O (5 mL) was added to a suspension of *trans*-1,2-cyclohexanediol (4.64 g, 40.0 mmol) in Ac_2O (25 mL) at 0 °C. The reaction was allowed to warm to room temperature over 2.5 h, and then the Ac_2O was destroyed by slow addition of saturated $NaHCO_3$ (700 mL) at 0 °C. After the mixture was stirred at room temperature for 24 h, the product was extracted from the aqueous layer with Et_2O, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography, followed by bulb-to-bulb distillation, which afforded *trans*-1,2-cyclohexanediol mononitrate as a white solid. The ^1H and ^{13}C NMR spectra were identical to published spectra.

***cis*-1,2-Cyclohexanediol Mononitrate.**[22] This material was prepared as above from *cis*-1,2-cyclohexanediol (667 mg, 5.74 mmol) and fuming HNO_3 (362 mg, 5.74 mmol) in Ac_2O (20 mL). Flash chromatography afforded *cis*-1,2-cyclohexanediol mononitrate as a clear, colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (m, 1H), 4.03 (m, 1H), 2.05−1.98 (m, 1H), 1.83−1.65 (m, 6H), 1.46−1.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.4, 68.0, 30.7, 25.5, 22.0, 20.6.

Synthesis of *trans*-4. Bu_3SnOEt (1.41 g, 4.19 mmol) was added to a solution of *trans*-1,2-cyclohexanediol mononitrate (676 mg, 4.19 mmol) in pentane (4 mL). The reaction mixture was stirred under vacuum until no ethoxy peaks remained in the ^1H NMR spectrum: ^1H NMR (300 MHz, C_6D_6) δ 4.87 (m, 1H), 3.58 (m, 1H), 1.90−1.80 (m, 2H), 1.64−1.56 (m, 6H), 1.40−1.28 (m, 9H), 1.13−0.90 (m, 18H); ^{13}C NMR (75 MHz, C_6D_6) δ 89.1, 74.1, 37.0, 29.0, 28.6, 27.8, 24.4, 24.1, 15.5, 14.2; ^{119}Sn NMR (112 MHz) δ 100.2.

Synthesis of *cis*-4. This material was prepared as above from *cis*-1,2-cyclohexanediol mononitrate (161 mg, 1.00 mmol) and Bu_3SnOEt (335 mg, 1.00 mmol): ^1H NMR (300 MHz, C_6D_6) δ 4.76 (m, 1H), 3.98 (m, 1H), 2.01−1.95 (m, 1H), 1.78−1.53 (m, 8H), 1.45−1.26 (m, 8H), 1.13−0.89 (m, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ 86.5, 70.5, 34.8, 28.6, 27.8, 25.4, 23.9, 20.7, 15.5, 14.3.

Note: Nitrate esters are known to afford oxygen-centered radicals when treated with Bu_3SnH under free-radical conditions.[16] Unfortunately, these reactions are slow, and they do not always proceed cleanly.[23] In the following stereochemical tests for reversible C−C bond formation, we regard the observation that both cis and trans diol acetates are formed (following acetylation), as well as *cis*- and *trans*-1,3-dioxa-2-stannolanes, to be strong evidence for reversibility. However, due to side reactions of the starting material under the reaction conditions, we believe that the ratio of diol acetates that we measure may be biased toward the starting isomer.

Reaction of *cis*-4 (Figure 6). Bu_3SnH (29.1 mg, 0.100 mmol) and methyl butyl ether (internal ^1H NMR standard) were added to a solution of *cis*-**4** (37.4 mg, 0.0830 mmol) and AIBN (1.3 mg, 0.0080 mmol) in C_6D_6 (800 μL) in a J. Young tube. The reaction was heated for 4 h in an oil bath maintained at 80 °C, at which time 73% of *cis*-**4** remained, as determined by integration versus the internal standard. GC analysis of an acetylated aliquot revealed a 1.3:1 (trans:cis) mixture of bisacetates of *trans*- and *cis*-1,2-cyclohexanediol. The NMR tube was immersed in an ice bath, resulting in the precipitation of a white solid, which was washed with benzene (1 × 1 mL) and dried. The white solid was then dissolved in $CDCl_3$ and examined by ^1H and ^{119}Sn NMR, which revealed that both *cis*- and *trans*-1,3-dioxa-2-stannolanes were present.

Reaction of *trans*-4 (Figure 6). Bu_3SnH (349 mg, 1.20 mmol) was added to a solution of *trans*-**4** (450 mg, 1.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (10 mL). The reaction mixture was heated to reflux for 5.5 h. Then, more AIBN (16 mg, 0.10 mmol) was added, and the reaction was refluxed for 7 h. GC analysis of an acetylated aliquot revealed a 3.9:1 trans/cis mixture of bisacetates of 1,2-cyclohexanediol. The bulk reaction mixture was concentrated to a white solid/colorless oil. The solid was washed with pentane (3 × 1 mL), dried, and analyzed by ^1H and ^{119}Sn NMR, which revealed that both *cis*- and *trans*-1,3-dioxa-2-stannolanes were present.

Pinacol Cyclization of Adipaldehyde with Bu_3SnH (Eq 2). A solution of adipaldehyde (228 mg, 2.00 mmol), Bu_3SnH (699 mg, 2.40 mmol), AIBN (33 mg, 0.20 mmol), and tetradecane (198 mg, 1.00 mmol; internal GC standard) in benzene (20 mL) was heated to reflux for 1 h, at which time GC analysis indicated that 8% of the dialdehyde remained. The reaction was refluxed for an additional 1.75 h, cooled to room temperature, and made homogeneous by the addition of CH_2Cl_2 (20 mL). GC analysis of an acetylated aliquot revealed that the bisacetate of 1,2-cyclohexanediol was present in 95% yield (2.1:1 trans/cis by GC and by ^1H NMR) and that 6-acetoxyhexanal was present in 3% yield.

Pinacol Cyclization of Adipaldehyde with TTMS (Eq 2). A solution of adipaldehyde (228 mg, 2.00 mmol), TTMS (597 mg, 2.40 mmol), AIBN (33 mg, 0.20 mmol), and tetradecane (198 mg, 1.00 mmol; internal GC standard) in benzene (20 mL) was heated to reflux for 3 h. GC analysis of the reaction mixture indicated that 5% of adipaldehyde remained and that 1.11 mmol of the TTMS had been consumed. ^1H NMR analysis revealed polymeric material in the carbinol, aliphatic, and TMS regions. An aliquot was treated with excess TBAF, acetylated, and analyzed by GC. The bisacetate of 1,2-cyclohexanediol was found to be present in 71% yield (1.4:1 trans/cis), as determined by integration versus the internal standard, along with 4% of acetylated acyclic 1,2-reduction products (corrected for 5% adipaldehyde).

Pinacol Cyclization of Adipaldehyde with Bu_3GeH (Eq 2). A solution of adipaldehyde (9.1 mg, 0.080 mmol), Bu_3GeH (23.5 mg, 0.0960 mmol), AIBN (1.5 mg, 0.010 mmol), *n*-butyl methyl ether (1.20 mg, 0.0133 mmol; from stock solution; internal ^1H NMR standard), and tetradecane (8.0 mg, 0.040 mmol; internal GC standard) in C_6D_6 (0.800 mL) was heated to 80 °C in a J. Young tube. The reaction was monitored by ^1H NMR. Additional AIBN (2 mg) was added after 9.3 and 24.3 h (total time). After 35 h, 10% of the dialdehyde remained. The reaction mixture was acetylated and analyzed by GC, which revealed a 27% yield (2.5:1 trans/cis) of the

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(22) Cristol, S. J.; Franzus, B. *J. Am. Chem. Soc.* **1957**, *79*, 2488−2489.

(23) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415−4416.

bisacetate of 1,2-cyclohexanediol, along with 16% and 21% of acetylated 1,6-hexanediol and 6-hydroxyhexanal, respectively.

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Supporting Information Available: ^1H NMR spectra of the reaction products illustrated in Table 1 (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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