Metal Hydride Mediated Intramolecular Pinacol Coupling of Dialdehydes and Ketoaldehydes

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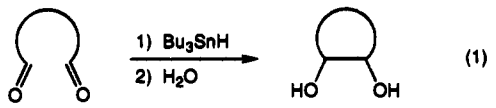
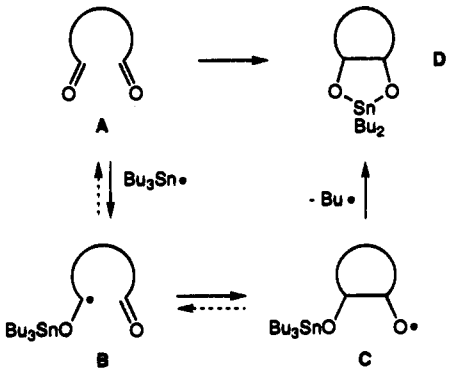
The pinacol coupling of carbonyl groups is a powerful method for constructing carbon–carbon bonds, and it has found widespread application in synthetic organic chemistry.[1-3] To date, efforts to develop new reagents which effect this transformation have focused on metals and inorganic metal complexes.[2] In this communication, we report that a main group organometallic hydride, Bu_3SnH, efficiently mediates the intramolecular pinacol coupling of dialdehydes and ketoaldehydes (eq 1).



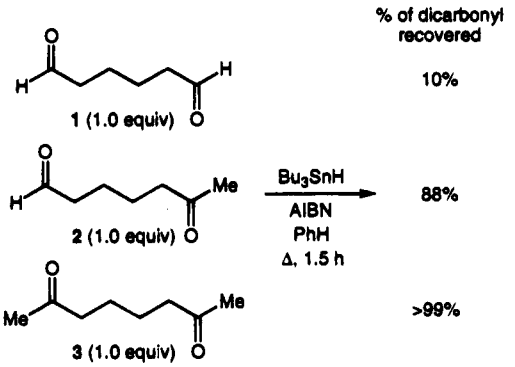
(1)

Building on a foundation laid by others, we postulated that organotin hydrides could effect pinacol coupling reactions via a radical chain process. The capacity of a tributyltin radical to add to a carbonyl group (Scheme 1,[4] **A** → **B**) is well-established.[5] The key step of our pinacol reaction, the addition of the resulting tin ketyl radical to a pendant carbonyl group (**B** → **C**), is not a known process, although several workers have recently reported that tin ketyls add in an intramolecular fashion to olefins.[6-9] 1,3,2-Dioxastannolane **D**,[10] the initial (prehydrolysis) pinacol coupling product,[11] is then generated through homolytic displacement at tin.[12] The butyl radical that is produced propagates the chain process by abstracting a hydrogen atom from Bu_3SnH, thereby generating a new tributyltin radical.

Scheme 1. Proposed Pathway for Tin Hydride Mediated Intramolecular Pinacol Coupling



Scheme 2. Selective Intramolecular Pinacol Coupling of Dialdehydes by Bu_3SnH



We have established that Bu_3SnH does indeed efficiently mediate the intramolecular pinacol coupling of a variety of dialdehydes and ketoaldehydes, providing cyclic 1,2-diols (Table 1). Both 1,5- (entries 1 and 2) and 1,6-dialdehydes (entries 3 and 4) undergo reductive cyclization, as do 1,5- (entry 5) and 1,6-ketoaldehydes (entry 6). All of the 1,5-dicarbonyl compounds studied to date cyclize to generate *cis*-cyclopentane-1,2-diols with high stereoselectivity (entries 1,2, and 5).[13]

(1) Fittig, R. *Justus Liebigs Ann. Chem.* **1859**, *110*, 17–22.
(2) For a comprehensive review, see: Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.6.
(3) For example, a McMurry pinacol coupling reaction (McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524) is a key step in Nicolaou's recent total synthesis of taxol: Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634.
(4) We have evidence that one or more of the steps illustrated in Scheme 1 are reversible for certain substrates (Scheme 2 and unpublished results). We believe that the final, product-generating step (**C** → **D**) is irreversible.
(5) (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987. (b) Neumann, W. P. *Synthesis* **1987**, 665–683. (c) Omae, I. *Organotin Chemistry*; Elsevier: New York, 1989. (d) *Chemistry of Tin*; Harrison, P. G., Ed.; Chapman and Hall: New York, 1989.
(6) (a) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893–5901. (b) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75–78. (c) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939–4942. (d) Enholm, E. J.; Kinter, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 7784–7785. (e) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835–1838. (f) Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129–132. (g) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1383–1384.
(7) While our study was in progress, the intramolecular addition of tin ketyls to oximes was reported: (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.
(8) For a report of radical–radical coupling of tin ketyls, see: Hillgartner, H.; Neumann, W. P.; Schroeder, B. *Justus Liebigs Ann. Chem.* **1975**, 586–599. See also ref 6c.
(9) For a recent study of the relative reactivity of oxygen-substituted versus unsubstituted carbon radicals, see: Johnson, C. C.; Horner, J. H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684–1687.
(10) For reviews of the functionalization of 1,3,2-dioxastannolanes, see: (a) Reference 5a. (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.
(11) We have isolated by crystallization a 60% yield of the 1,3,2-dioxastannolane formed from the pinacol cyclization of adipaldehyde (see supporting information). See also entry 1 of Table 1.
(12) A related process has been observed as a minor (≤10%) side reaction in the stannylformylation of 1,6-dienes. See: Ryu, I.; Kurihara, A.; Muraoka, H.; Tsunoi, S.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 7570–7571 and references cited therein. 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 ref 5d, Chapter 9.
(13) In contrast, other cyclization reactions of tin ketyls generally proceed with low levels of stereoselectivity (refs 6 and 7). Possible explanations for the high cis selectivity of the intramolecular pinacol coupling of 1,5-dicarbonyl compounds include the following: (a) **B** → **C** proceeds irreversibly with a strong preference for formation of *cis*-C; (b) **B** → **C** proceeds reversibly to generate both *cis*- and *trans*-C, but only *cis*-C proceeds to **D**; (c) the carbonyl oxygen of **B** binds to tin prior to carbon–carbon bond formation (C is not an intermediate).
(14) Sample experimental details (Table 1, entry 2): A solution of the dialdehyde (218 mg, 0.89 mmol, 1.0 equiv), Bu_3SnH (311 mg, 1.07 mmol, 1.2 equiv), and AIBN (15 mg, 0.089 mmol) in benzene (36 mL) was heated to reflux in an oil bath. Additional AIBN (15 mg, 0.089 mmol) was added at 3-h intervals. After 12 h, the reaction mixture was concentrated to a cloudy, colorless oil and purified by flash chromatography, which provided 147 mg (67%) of the cyclopentane-1,2-diol derivative as a colorless oil. GC analysis of an acetylated aliquot of the unpurified reaction mixture revealed >99:1 cis:trans stereoselectivity. The two diastereomeric cis diols were present in equal (1.0:1) quantities.

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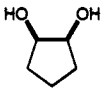
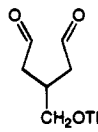
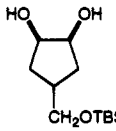
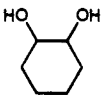
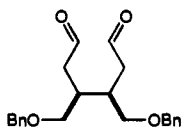
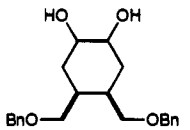
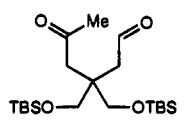
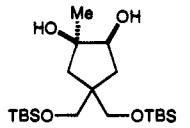
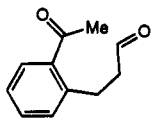
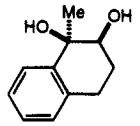
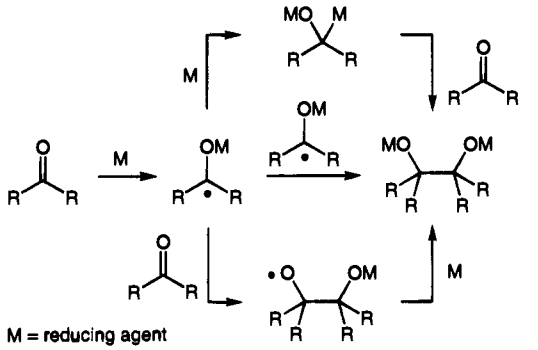
Table 1. Metal Hydride Mediated Intramolecular Pinacol Coupling[14]

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]

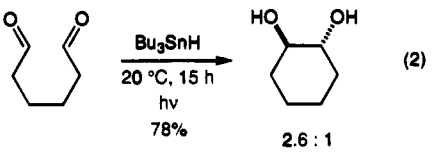
[a] Average of two runs. [b] Based on analysis by capillary gas chromatography, except as noted. [c] Isolated by crystallization as the 1,3,2-dioxastannolane. [d] ~1:1 mixture of the two diastereomeric cis diols. [e] Based on analysis by ^{1}H NMR. [f] Isolated as the acetonide.

Selective pinacol cyclization of a dialdehyde in the presence of a ketoaldehyde or a diketone can be accomplished when Bu_3SnH is used as the reducing agent (Scheme 2). We believe that the high selectivity of the Bu_3SnH-mediated reaction is a consequence of the *reversibility* of tributyltin radical addition to the carbonyl group (**A** ⇌ **B**, Scheme 1). The product distribution is therefore guided not simply by the relative ease of formation of the tin ketyl (**A** → **B**) but by the relative facility with which the ketyl radical adds to the pendant carbonyl (**B** → **C**). The slower the latter reaction (e.g., due to steric effects), the more likely that **B** will fragment to starting material (**B** → **A**) rather than proceed toward product (**B** → **C**).

Scheme 3. Typical Mechanisms for Pinacol Coupling



Other main group metal hydrides (e.g., Ph_3SnH, $(TMS)_3SiH$,[15] and Bu_3GeH) also effect the intramolecular pinacol coupling of dicarbonyl compounds, although they are somewhat less efficient than Bu_3SnH. Initiation by ultraviolet irradiation at 20 °C (eq 2)[16] affords results comparable to thermal initiation with AIBN (entry 4, Table 1).[17]



The most common mechanisms for pinacol coupling reactions are illustrated in Scheme 3.[2] Each of these pathways requires 2 mol of reducing agent/mol of product generated. The tin hydride mediated pinacol cyclization proceeds smoothly with 1.2 equiv of Bu_3SnH, an observation which is consistent with the mechanism proposed in Scheme 1, but not with any of the pathways illustrated in Scheme 3.

We have discovered a mechanistically novel variant of the pinacol coupling reaction, the metal hydride mediated pinacol cyclization of 1,5- and 1,6-dicarbonyl compounds. The well-defined nature of the intermediates in this process renders it amenable to investigation of the origin of the observed diastereoselectivity, as well as to the design of chiral organotin hydrides which may provide control of absolute stereochemistry. Further studies of this reaction are underway.

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Supporting Information Available: Listing of experimental procedures and compound characterization data (26 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.

JA9511836

(15) For a review, see: Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194.

(16) We have isolated by crystallization a 74% yield of the prehydrolysis product of this reaction, the 1,3,2-dioxastannolane (see supporting information). For a related, but mechanistically distinct, photochemical coupling process, see: Hammond, G. S.; Leermakers, P. A. *J. Am. Chem. Soc.* **1962**, *84*, 207–211.

(17) The other methods of initiation that we have explored [e.g., ultrasound (Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849–6850) or BEt_3/O_2 (Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549)] have proved to be inferior to thermal initiation with AIBN.