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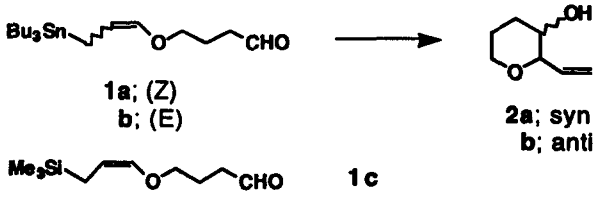
Cyclic Transition State in the Acid Catalyzed Intramolecular Allylstannane-Aldehyde Condensation

Vladimir Gevorgyan[†], **Isao Kadota**, and **Yoshinori Yamamoto***
Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Abstract: Brϕnsted acid catalyzed or Bu_4NF-$TiCl_4$ mediated cyclization of (Z)-ω-stannyl ether aldehyde **1a** gives **2a**, whereas (E)-isomer **1b** affords **2b**. To explain this stereochemical outcome, a push-pull mechanism is proposed.

The allylstannane-aldehyde condensation is one of the most important synthetic methods for regio- and stereoselective C-C bond formation, and its mechanism has been extensively studied during last decade.[1] It is widely accepted that the thermal (80-200°C)[2] or high-pressure reaction (10 Kbar)[3] proceeds through a cyclic transition state and the stereochemical outcome depends upon the double bond geometry of allylstannanes. On the contrary the Lewis Acid induced condensation proceeds through an acyclic transition state which is quite insensitive to the geometry of the allylstannane moiety.[4] In this communication we report that there is the third mechanism yet: the protic acid induced intramolecular reaction proceeds via a cyclic transition state.

As a model was chosen the intramolecular condensation of ω-stannyl ether aldehydes **1a,b**.[5] The results of the cyclization of **1a,b** are summarized in Table 1. The stereochemical outcome of the protic acid induced cyclization depended strongly upon the double bond geometry (entries 3-11, and 17-19); the cyclization of **1a** in the presence of the protic acids predominantly gave **2a**, whereas that of **1b** produced **2b** exclusively.[6] As expected, the Lewis acid induced cyclization afforded predominantly **2b** regardless of the double bond geometry (entries 1-2, and 15-16).

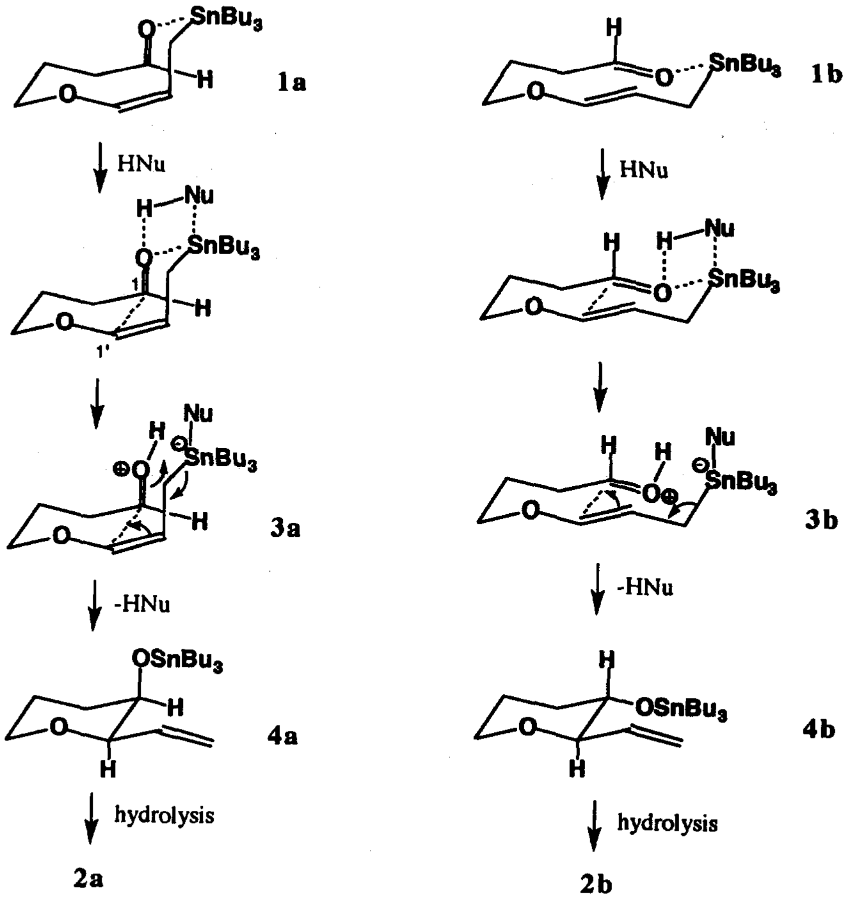


1a; (Z)
b; (E)

2a; syn
b; anti

1c

We propose a new "PUSH-PULL"[7] mechanism via cyclic transition state to explain the observed stereochemical results. Because of noticeable Lewis acidity of the tin atom,[2,3,5] there is an interaction between the aldehyde oxygen and tin atom (**1a** or **1b** in Scheme 1). In the presence of protic acid (HNu), proton pulls electrons from the oxygen to produce positively charged carbonyl oxygen, and the nucleophilic part pushes electrons into the tin atom to afford hypervalent tin species (**3a** or **3b**). There is an attractive interaction between the positively charged oxygen and negative tin atom. Accordingly, a new C-C bond formation takes place between C-1 and C-1', to give the alkoxystannane **4a** or **4b** with concomitant elimination of protic acid (HNu). Hydrolysis of **4a** or **4b** gives **2a** or **2b**, respectively.



Scheme 1. "PUSH-PULL" mechanism

Although Lewis acids such as BF_3 and $TiCl_4$ can coordinate the carbonyl oxygen, no pushing group is available and the tin atom remains as tetravalent. Therefore, there is no interaction between the charged oxygen and tin atom, and the reaction proceeds through an acyclic transition state as previously proposed.[8] It is well known that the Lewis acid mediated reaction needs stoichiometric amounts of Lewis acids.[1b,c,4c] In the case of protic acid induced reactions, a catalytic amount of TfOH is quite enough for the conversion of **1a** to **2a** (entry 6). This fact supports the PUSH-PULL mechanism, since HNu is regenerated in the step from **3** to **4**.

To obtain an additional support to the "PUSH-PULL" mechanism, we examined the cyclization with $TfONBu_4$ and Bu_4NF (entries 12, 13). The cyclization did not take place even after a prolonged period of the reaction time.[9] Bu_4N^+ does not coordinate the carbonyl oxygen and only the pushing group (TfO^- or F^-) is available in this case.[9] However, the cyclization occurred smoothly with Bu_4NF-$TiCl_4$ system which possesses both a pushing and pulling group, and the diastereoselectivity was dependent upon the double bond geometry (entry 14 vs 20). At last we examined the reaction of silicon counterpart **1c**.[10] In the presence of Lewis acids,

1c gave **2b** predominantly in high yields (**2a**:**2b**=22:72 with $TiCl_4$, 10:90 with $BF_3 \cdot OEt_2$), and in the presence of CF_3CO_2H **2a** was afforded preferentially in moderate yield (43%) (**2a**:**2b**=80:20). With TfOH no cyclization took place and the starting material was decomposed. These results obviously suggest that the silicon atom is reluctant to form the hypervalent species in comparison with the tin atom. In conclusion, the present findings provide not only a conceptual advance on the mechanism of the allylic tin-aldehyde condensation[11] but also a synthetical useful procedure for the diastereoselective C-C bond formation; rapid reaction at low temperatures and its catalytic property are promising in comparison with the thermal reaction.

Table 1. Intramolecular Cyclization of **1** to **2**[a]

entry	substrate	reagent	ratio [reagent]:[1]	time (min)	temp (°C)	% syn[b] (**2a**)	% anti[b] (**2b**)	yield[b] (%)
1	**1a** (Z)	$TiCl_4$	2:1	30	-70	17	83	86
2		$BF_3 \cdot Et_2O$	2:1	30	-70	32	68	80
3		TfOH	2:1	5	-70	87	13	>95
4		TfOH	c	15	-70	89	11	>95
5		TfOH	c	15	-90	93	7	94
6		TfOH	0.1:1	30	-70	80	20	>95
7		CF_3COOH	2:1	5	-70	90	10	>95
8		CCl_3COOH	2:1	5	-70	89	11	>95
9		$ClCH_2COOH$	2:1	600	0	75	25	>95
10		CH_3COOH	2:1	3600	25	71	29	66
11		HCl	2:1	5	-70	82	18	90
12		$TfONBu_4$	2:1	720	25	-	-	0
13		Bu_4NF	2:1	720	25	-	-	0
14		Bu_4NF-$TiCl_4$[d]	1:1	10	-70	71	29	90
15	**1b** (E)	$TiCl_4$	2:1	30	-70	16	84	>95
16		$BF_3 \cdot Et_2O$	2:1	30	-70	13	87	>95
17		TfOH	2:1	5	-70	0	100	>95
18		CF_3COOH	2:1	5	-70	3	97	>95
19		HCl	2:1	5	-70	3	97	86
20		Bu_4NF-$TiCl_4$[d]	1:1	10	-70	7	93	87

[a] The reactions were carried out with 0.1 M substrate in CH_2Cl_2 under the conditions indicated in the Table, and quenched at -70°C with aqueous sat $NaHCO_3$ solution. [b] Ratios and yields were determined by a capillary GLC analysis. Tetradecane was used as an internal standard. [c] The substrate was added very slowly to the reagent, and thus at the initial stage of reaction [TfOH]:[**1a**]>>2:1. The final ratio was 2:1. [d] Bu_4NF (1M in THF, 1.2 equiv) and $TiCl_4$ (1M in CH_2Cl_2, 1 equiv) were consecutively added to a stirred substrate (1 equiv) at -70°C.

References and Notes

† JSPS Foundation postdoctoral fellow

1. For recent overviews see: (a) Yamamoto, Y. *Aldrichim. Acta*, **1987**, 20, 45. (b) Roush, W. R. In Comprehensive Organic Synthesis, Vol. 2, Trost, ed., *Pergamon Press*: Oxford, **1991**, 1. (c) Fleming I. ibid. 563. (d) Marshall, J. A. *Chemtracts*, **1992**, 5, 75.
2. See for example: (a) Hull, C.; Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.*, **1987**, 5343. (b) Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *ibid.* **1987**, 527.
3. Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.*, **1983**, 489.

4. (a) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. ***Tetrahedron*, 1984**, 40, 2239. (b) Yamamoto, Y. *Chemtracts-Org. Chem.*, **1991**, 255. (c) Pereyre, M.; Quintard, J-P.; Rahm, A. *Tin in Organic Synthesis*, Butterworths: London, **1987**, pp.211-230.
5. Recently this type of cyclization has been succesfully used for medium sized ring construction in the synthesis of natural policyclic ether fragments: Yamamoto, Y.; Yamada, J.; Kadota, I. *Tetrahedron Lett.*, **1991**, 7069.
6. Denmark investigated the stereochemical outcome on the intramolecular cyclization of certain cyclic systems in the presence of CF$_3$CO$_2$H. However invariability of the double bond geometry (cis-double bond in the cyclic substrate) led to the same stereochemical outcome as in the case of Lewis Acids (CF$_3$COOH, syn/anti : 99/1; FeCl$_3$: 98/2; SnCl$_4$: 93:7), which did not allow the authors to find an essential difference between protic- and Lewis acids mediated reactions. (a) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.*, **1984**, 106, 7970. (b) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron*, **1989**, 45, 1053.
7. We denote a PUSH-PULL mechanism in the sense of electron density. Lewis acids and/or proton pull electrons from the aldehyde oxygen, leading to an oxocarbenium cation. Nucleophiles are able to push electrons to the tin atom of Bu$_3$Sn, affording a charged hypervalent tin species. See: (1b, c), (4c). When both processes proceed simultaneously or just consecutively we call this mechanism "PUSH-PULL".
8. Formation of both syn- and anti- cyclic products from a synclinal transition state was evidently demonstrated for the Lewis Acids mediated intramolecular condensation for ω-stannyl ether acetals and aldehydes : (a) Yamada, J.; Asano, T.; Kadota, I.; Yamamoto, Y. *J. Org. Chem.*, **1990**, 55, 6066. (b) ref 5.
9. Assistance of Bu$_4$NF in the allylstannane-aldehyde condensations is known, however more strong reaction conditions (reflux in THF) are normally required. (a) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.*, **1976**, 188. (b) Trost, B. M.; Remuson, R. *Tetrahedron Lett.*, **1983**, 1129. (c) Denmark, S. E.; Weber, E. J. *Helv. Chem. Acta*, **1983**, 66, 1655.
10. The intramolecular allylsilane-aldehyde condensation in the presence of protic acids was reported previously. The authors attempted to explain the stereochemical outcome by acyclic models : Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.*, **1979**, 1783.
11. The TfOH mediated intermolecular reaction of (E) and (Z)-crotyltins with benzaldehyde gave the syn-adduct predominantly, although the syn-selectivity significantly decreased in the case of the (E)-isomer. The reversal of diastereoselectivity, which was observed in **1a** and **1b**, did not take place.

General procedure. All reactions were carried out in a 1 mL Pierce-microreactor. To a stirred solution of **1a** or **1b** (0.025 mmol) in CH$_2$Cl$_2$ (250 μl) under Ar at a suitable temperature (see Table 1) was added a reagent in one portion. The reaction was monitored by TLC, and quenched with sat aqueous NaHCO$_3$ solution (100 μl). The reaction mixture was filtered through a short silica gel column (10 mm length), and the silica gel was washed with AcOEt until total volume of filtrate reaches to 1 mL. Tetradecane (10 μl) as an internal standard was added to the filtrate, and the mixture was analyzed by a capillary GC (CBP 20-M25-025, Shimazu).

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