CHEMISTRY LETTERS, pp. 177-180, 1991.

Effect of Ti(Oi-Pr)$_4$ on Stereoselectivity of Halocyclization of 2-Substituted 4-Pentenoic Acid and 4-Penten-1-ol

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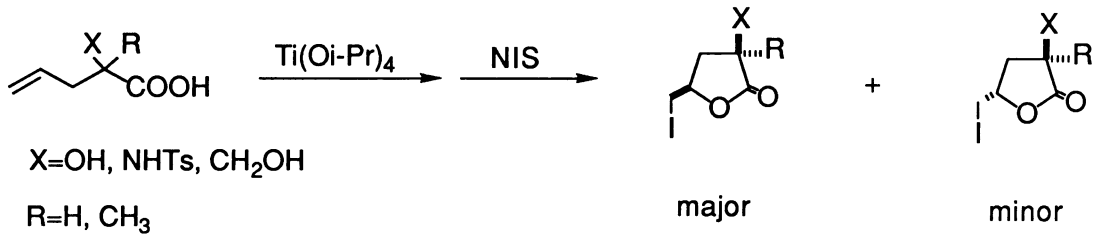
Iodolactonization of 2-substituted (*N*-sulfonylamino, hydroxyl and hydroxymethyl groups)-4-pentenoic acid with NIS or I_2 *in the presence of Ti(Oi-Pr)$_4$* gave the γ-lactone with increased 1,3-cis-selectivity. Stereoselectivity in the haloetherification of 2-hydroxymethyl-4-penten-1-ol was reversed by the *addition of Ti(Oi-Pr)$_4$*.

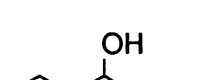
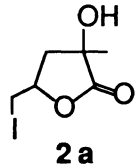
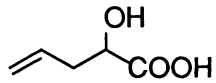
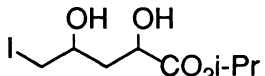
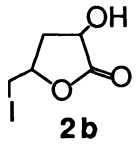
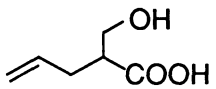
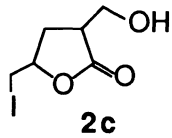
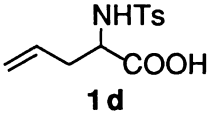
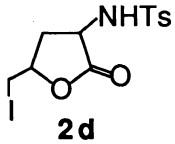
Halocyclization plays an important role in the synthesis of heterocyclic intermediates and functionalization of a double bond, and the exploration of a diastereoselective halolcyclization has been one of the current subjects.[1] A high degree of diastereoselectivity is possible depending on reaction conditions and structure of the substrate. For example, in the cases of δ-lactone formation, 1,2- or 1,3-high asymmetric induction (diastereoselection) usually occurs under thermodynamic control, due to the well-defined chair-like conformation of the six-membered ring.[1] In γ-lactone formation, a 1,2-high asymmetric induction is also observed,[1,2] while 1,3-high asymmetric induction takes place only in cases of 2-alkyl-4-pentenoyl amides[3] or 2-alkyl or aryl-4-pentenoyl thioimidates[4] to give γ-lactones or γ-lactams with the 1,3-trans relationship. 1,3-Cis-favored halolactonizations of 2-amino-4-pentenoic acid derivatives were reported by two groups.[5] It was claimed that halolactonization of 2-hydroxy- and 2-benzyloxy-4-pentenoic acid resulted in the isomeric mixture of γ-lactones in poor yields.[5] In this paper, we report the additive effect of Ti(Oi-Pr)$_4$ on the stereoselectivity of the halocyclization of 4-pentenoic acid and 4-penten-1-ol having polar substituent at C-2 as well as a mechanistic consideration on the selectivity.



Iodolactonization of 2-hydroxy-2-methyl-4-pentenoic acid **1a** under standard conditions brought about the formation of γ-lactone **2a** in low stereoselectivity (I_2/CH_3CN, cis/trans = 1.3; I_2/$NaHCO_3$/THF, cis/trans = 1; NIS/CH_2Cl_2, cis/trans = 1.8). However, when Ti(Oi-Pr)$_4$ (1equiv.) was added to a solution of **1a** prior to the addition of NIS or I_2, stereoselectivity remarkably increased to give cis iodolactone **2a** [I_2 cis/trans = 23 (Table 1, entry 2); NIS cis/trans = 11(Table 1, entry 1)].[6,7] Similar to **1a**, 2-hydroxy-4-pentenoic acid **1b** showed

increased 1,3-cis selectivity by addition of Ti(Oi-Pr)$_4$. In this case, isopropyl 2,4-dihydroxy-5-iodopentanoate **3b** was isolated through ester exchange of the lactone (entry 4). Increase in selectivity was observed not only for α-hydroxy but also both the α-hydroxymethyl carboxylic acid derivative **1c** (entry 6) and α-*N*-sulfonyl amino acid **1d** (entry 8).[8] When the hydroxy group of **1a**,**1b**,and **1c** was protected by methoxymethyl group, NIS-induced cyclization in the presence of Ti(Oi-Pr)$_4$ caused no appreciable 1,3-cis selectivity. These findings along with ^{13}C-NMR spectrum data of 1 : 1 mixture of Ti(Oi-Pr)$_4$ and **1a**[9] may indicate that the bidentate bonding of Ti(IV) with **1** plays an important role to achieve an increased cis-selectivity in the halolactonization.

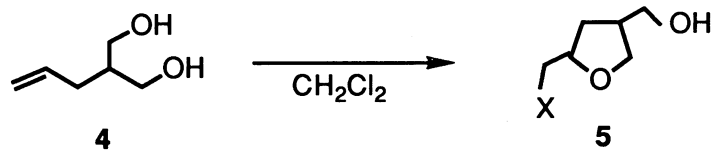
Table 1. Halolactonization of 2-Substituted-4-pentenoic Acid[a]

Entry	Substrate	Additive	Temp/°C	Time/h	Products	cis : trans[b]	Yield/%[c]
1	 **1a**	Ti(Oi-Pr)$_4$	-15	1	 **2a**	11 : 1	87
2		Ti(Oi-Pr)$_4$	0	2		23 : 1[d]	70[d]
3		none	-15	1		1.8 : 1	89
4	 **1b**	Ti(Oi-Pr)$_4$	10	2	 **3b**	9 : 1[e]	52[e]
5		none	0	2	 **2b**	2.4 : 1	45
6	 **1c**	Ti(Oi-Pr)$_4$	0	2	 **2c**	6 : 1	52
7		none	0	2		1.8 : 1	43
8	 **1d**	Ti(Oi-Pr)$_4$	-15	1	 **2d**	12 : 1	86
9		none	-15	1.5		5.2 : 1	88

a) Halolactonization: **1** (1 mmol), NIS (1.3 mmol), CH_2Cl_2 (6-7 ml) b) Determined by 400 MHz ^{1}H-NMR. c) Isolated yield. d) In this case, I_2 was used as the electrophile. A small amount of isopropyl ester also formed (<10%), wihich was nearly quantitatively converted to **2a** by treating with p-TsOH in benzene. e) The ratio and yield were determined after conversion to **2b** by treating **3b** with p-TsOH in benzene.

Ti(Oi-Pr)$_4$ was noted to have remarkable effect on the 1,3-stereoselectivity in the haloetherification of 2-hydroxy-4-penten-1-ol **4**. NIS-induced cyclization of **4** gave the tetrahydrofuran derivative **5**, favouring the 1,3-cis isomer (cis/trans = 2.6), while in the presence of Ti(Oi-Pr)$_4$, similar reaction provided **5** with 1,3-trans selectivity (cis/trans = 1/4.3). It should be pointed out that the latter trans selectivity in etherification of **5** was in a sharp constrast to cis selectivity in the lactonization of **1c**. Further efforts to improve the 1,3-trans selectivity and the yield of **5** revealed that NBS-induced cyclization of **4** in the presence of Ti(Oi-Pr)$_4$ and diisopropyl

tartarate (DIPT) produces **5** in good yield (88%) and increase trans selectivity (trans/cis =7). It is worth mentioning asymmetric induction for the major trans isomer was 25% ee on using (+)-DIPT.



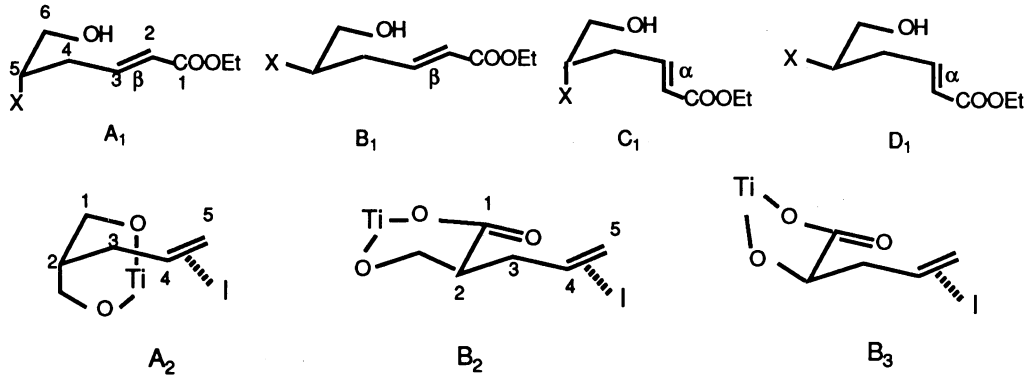
4 **5**

Table 2. Haloetherification of **4**

entry	reagent	Additive	Temp/°C	Time/h	**5** Yield/%[a)]	cis : trans[b)]
1	NIS	none	0	2	84	2.6 : 1
2	NIS	$Ti(Oi\text{-}Pr)_4$	0	2	65	1 : 4.3
3	NIS	$Ti(Oi\text{-}Pr)_4$-DIPT	0	1	78	1 : 4.8
4	NBS	$Ti(Oi\text{-}Pr)_4$-DIPT	-15	2	88	1 : 7

a) Isolated yield. b) Determined by 400 MHz ^{1}H-NMR.

In regard to homoallylic chiral induction in the halocyclization of the substrate having a polar substituent such as hydroxyl or amino group at homoallylic position, possible mechanisms have been reported by two groups.[5,10)] The transition-structure model for kinetic haloetherification of ethyl 5,6-dihydroxy-2-hexenoate proposed by Labelle et al. may possibly suffice as explanation for the present results.[10)] They explained the trans selectivity on the basis of four chair type models (A_1-D_1), which separately consider the two ends of the molecule (C_2-C_3 olefin part and C_5-C_6 stereogenic part). By AM-1 calculation, preferred orientation of olefinic moiety is postulated to be β corresponding to model A_1 and B_1. It would thus follow that homoallylic chiral induction is controlled through the conformational preferrence of the substituent X. That is, the axial conformer (A_1) causes the formation of the 1,3-trans isomer.[11)] Applying this model to the present study, 1,3-trans selectivity in the haloetherification of **4** in the presence of $Ti(Oi\text{-}Pr)_4$ may be explained by transition-structure model A_2, in which Ti(IV) is bound to two oxygen atoms and the hydroxymethyl group at C-2 is in the axial position.[12)] In the case of lactonizations , the observed 1,3-cis selectivity may be explained by model B_2 and B_3 in which the preferred orientation of the substituent at C-2 is equatrial by the bidentate coordination of Ti(IV).



The present reaction is the first example of halocyclization in which a Lewis acid is used, causing remarkable effect on the stereoselectivity. Further application to other systems is currently carried out.

References

1) For example, see: P. A. Bartlett and J. Myerson, *Tetrahedron*, **40**, 2377(1984); G. Cardillo and M. Orena, *ibid.*, **46**, 3321(1990).
2) H. J. Gunther, E. Gunturm, and V. Jager, *Annalen.*, **1984**, 15; A. R. Chamberlin, M. Dezube, P. Dussault, and M. C. McMills, *J. Am. Chem. Soc.*, **105**, 1079(1983).
3) Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K, Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **106**, 1079(1984); K. Fuji, M. Node, Y. Naniwa, and T. Kawabata, *Tetrahedron Lett.*, **31**, 3175(1990).
4) H. Takahata, T. Takamatsu, M. Mozumi, Y. Chen, T. Yamazaki, and K. Aoe, *J. Chem. Soc., Chem. Commun.*, **1987**, 1627.
5) N. Izumiya and B. Witkop, *J. Am. Chem. Soc.*, **85**, 1835(1963); Y. Ohfune, K. Hori, and M. Sakaitani, *Tetrahedron Lett.*, **27**, 6079(1986) and references cited therein.
6) The stereochemistry of **2a** was determined by X-ray crystallographic analysis of trans-**2a.**
7) Addition of 0.5 equiv. of Ti(Oi-Pr)$_4$ brought about selectivity comparable to that of 1equiv. of Ti(Oi-Pr)$_4$, while the decrease in selectivity was obserbed when 0.1 equiv. of Ti(Oi-Pr)$_4$ was used. High 1,3-cis selectivity was also observed on using Et_2Zn instead of Ti(Oi-Pr)$_4$ (**2a**, cis/trans = 9).
8) Since the yield and diastereoselectivity of γ-lactone prepared by I_2 or NBS-induced reaction were slightly lower than those by NIS, we carried out the reactions using NIS except for **1a.**
9) The ^{13}C-NMR spectrum of the 1:1 mixture of **1a** and Ti(Oi-Pr)$_4$ in $CDCl_3$ at room temperature was comprised of the two new sets of sharp signals, and the signals of free **1a** completely disappeared. These two set signals were characterized that C_2 carbon of **1a** (remarkably) moved 18.47 and 18.29 ppm downfield and the carbonyl carbon (C_1) 0.34 and 0.41ppm downfield, respectively as compared with those of the 1:2 mixture of **1a** and i-PrOH in $CDCl_3$.
10) M. Labelle, H. E. Morton, Y. Guindon, and J. P. Springer, *J. Am. Chem. Soc.*, **110**, 4533(1988).
11) By AM1 calculation, the preferred orientation of the substituent X in the transition state model is postulated axial for polar substituents, while for nonpolar substituents such as a methyl group, the energy levels of both axial and equatrial conformer are postulated very similar. In the former case, the importance of hydrogen bond between X and hydroxyl at C-6 for stabilization of axial conformer is considerablly significant.
12) The effect of Ti(Oi-Pr)$_4$ on the stereoselectivity of haloetherification of 2-hydroxy and 2-*N*-sulfonylamino-4-penten-1-ol was quite little; presumably the five membered ring structure including Ti(IV) can not be involved in the transition state.

(Received October 20, 1990)