Stereoselective Synthesis of *trans*-2,6-Disubstituted Dihydropyrans through Intramolecular Allylic Transfer Reaction†

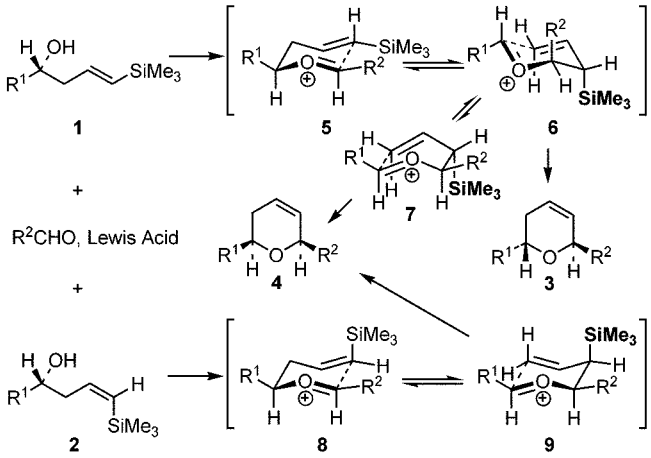
Chan-Mo Yu,* Mi-Sook Shin, and Eun-Young Cho

Department of Chemistry and Laboratory for Metal-Catalyzed Reactions, Sungkyunkwan University, Suwon 440-746, Korea
Received May 18, 2004

Key Words : Cyclization, Dihydropyran, Diastereoselectivity, Lewis acid, Titanium

During the course of our research program aimed at finding new synthetic methods for the stereoselective construction of tetrahydropyran units,[1] we became quite interested in the utilization of **1** as a starting material for the stereoselective synthesis of 2,6-disubstituted *trans*-dihydropyran **2** through a Lewis acid catalyzed allylic transfer reaction as illustrated in Scheme 1. The background behind this current study was the availability of enantiomerically enriched **1** from the method developed by our laboratory.[2] This process related to the well established Prins cyclization reactions of homoallylic alcohols with aldehydes, which provide always *cis*-2,6-disubstituted dihydropyrans preferentially.[3-8] Speckamp and co-workers reported that the oxonium ion **6** of specific aldehyde ($R^2 = CO_2Me$) could be an intermediate for the conversion to *trans*-**3** in moderate diastereoselectivies, 2-5 : 1.[9] Owing to the strong stereoelectronic preference for the trimethylsilyl group to adopt an axial position in the reaction intermediate **6** derived from **5** through oxa-Cope rearrangement that develop carbocationic character at the β-position, it was expected that the conversion could provide the *trans*-2,6-disubstituted dihydropyran **3** in stereoselective manner. However, Roush and co-workers found that the same intermediate **6** from β-hydroxylallylsilanes with normal aldehydes produced *cis*-dihydropyran **4** as a major component rather than *trans*-dihydopyran **3**.[10] Therefore, it was envisaged that the realization of efficient catalytic method for the synthesis of *trans*-2,6-disubstituted dihydropyran **3** from **1** with normal aldehydes under appropriate Lewis acid conditions could be useful because this method might be valuable for the synthesis of bioactive natural products.[11] We report herein our discovery of the diasetreoselective formation of *trans*-2,6-disubstituted dihydropyran **3** from **1** under Lewis acidic conditions with reasonable stereoselectivities.

The first study for preliminary experiments focused on the feasibility of **1** and **2** for the cyclization with achiral aldehydes promoted by a Lewis acid catalyst. To investigate the sequence outlined in Scheme 1, the cyclization began with TMS ethers **1a** and **2a** as starting materials.[12] Initial attempts at the cyclization of **1a** and **2a** with hydrocinnamaldehyde (2 equiv) under TMSOTf (0.5 equiv) at −78 °C in



Scheme 1

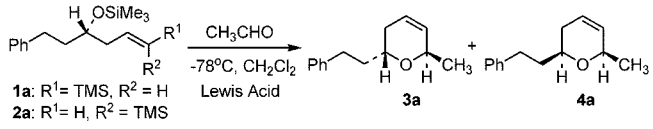
CH_2Cl_2 indicated that the conversion into the dihydropyran could be realized, but the reaction produced the same *cis*-dihydropyran **4a** as a major component with good diastereoselectivity in moderate chemical yields as indicated in Table 1. The preferential formation of the *cis*-dihydropyran **4a** from **1a** can be explained by the favour of boat-like stereochemical model **7** over chair-like model **6** mainly due to the steric bias as depicted in Scheme 1. We subsequently speculated that bigger counter anion in intermediates **6** and **7** might be a control factor to regulate stereochemical pathways.[1] Attempts to develop more efficient Lewis acids by modification of the triflate ion with the more bulky and electron withdrawing counter anion such as bis(trifluoromethylsulfonyl)amide [$MN(SO_2CF_3)_2$, $MNTf_2$][13] afforded encouraging but only marginal results-- although compound **2a** afforded *cis*-dihydropyran **4a** almost exclusively, compound **1a** produced a 1 : 3 mixture of the diastereomers as shown in Table 1 (entries 3 and 4).

In order to improve reaction conditions in terms of chemical conversion and stereoselectivity, an intramolecular reaction of the α-acetoxy acetal **10** was considered immediately. The α-acetoxy acetals **10** were prepared by the method described by Rychnovsky for in situ acylation of the tetrahedral intermediates generated by DIBAL reduction of corresponding esters.[14] Compound **10a** ($R^1 = PhCH_2CH_2$, $R^2 = CH_3$) was chosen as a model compound. After surveying numerous conditions with a variety of Lewis acids, several key findings were emerged: i) reaction of **10a** in the presence

†Dedicated to Professor Yong Hae Kim in admiration of his contributions to organic chemistry

*Corresponding Author: Tel: +82-31-290-7067; Fax: +82-31-290-7075; e-mail: cmyu@chem.skku.ac.kr

Table 1. Preliminary investigations for intramolecular allylic transfer reactions



Entry	**1a** or **2a**	Lewis acid	Time, h	dr (**3a**:**4a**)[a]	Yield (%)[b]
1	**1a**	TMSOTf	8	4 : 96	44
2	**2a**	(50 mol%)	8	3 : 97	53
3	**1a**	$TMSNTf_2$	8	24 : 74	67
4	**2a**	(30 mol%)	8	1 : >99	72
5	**1a**	Me_2AlNTf_2	6	44 : 56	71
6	**2a**	(30 mol%)	6	1 : >99	78
7	**1a**	$(i\text{PrO})_2\text{Ti}(\text{NTf})_2$	5	78 : 22	77
8	**2a**	(30 mol%)	5	1 : >99	75

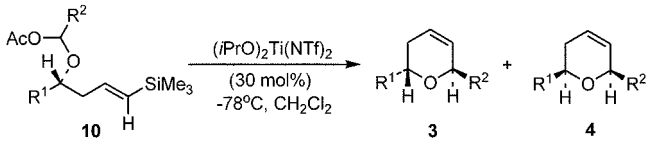
[a]Determined by analysis of 500 MHz ^{1}H NMR spectra. [b]Yields refer to isolated and purified yield.

of $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ occurred readily at −78 °C: this Lewis acid was generally superior to other Lewis aicds such as $SnCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf, $TMSNTf_2$, and Me_2AlNTf_2; ii) 30 mol% of $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ required for optimal conditions in terms of chemical yields and reaction rates; iii) reaction performed at −78 °C in CH_2Cl_2 resulted in the best chemical yields and stereoselectivities in comparison with other solvents such as toluene, THF, and $PhCF_3$; iv) diastereomeric ratio turned out to be 91 : 9 as determined by the analysis of ^{1}H NMR of crude products. Under optimal conditions (entry 1 in Table 2), the reaction was conducted by dropwise addition of $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ (30 mol%) in CH_2Cl_2 at −78 °C to a stirred solution of **10a** in CH_2Cl_2. After 5 h at −78 °C, usual work up and chromatography gave **3a** along with **4a** in 81% yield.

With the notion that this approach might lead to a general and efficient method for the synthesis of *trans*-2,6-dihydropyran **3**, we set out to determine the substituent effects with several **10** to produce structurally various products. Indeed, the method is successful with **10** to yield the *trans*-2,6-disubstituted pyrans **3**, in moderate to high diastereoselectivities as it can be seen in Table 2. We observed that better diastereoselectivities and chemical yields were obtained with less hindered substituents of R^2 in **10** compared to more hindered substituents. It is worthy note that the enantiomerically enriched starting compound (**10a**, 93%ee) produced the optically active product (**3a**, 92%ee) without loosing optical purity as judged by HPLC analysis using chiral column (Chiracel, OJ-H).

In summary this paper describes a novel procedure for the stereoselective synthesis of *trans*-2,6-disubstituted pyrans **3** from the α-acetoxy acetal **10** catalyzed by $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ in a general and efficient way, which promises to be widely useful. The chemical transformation involves the oxa-Cope rearrangement and subsequent imtramolecular allylic transfer reaction into the oxonium ion. Further studies including synthetic applications and more detail mechanistic pathway are in progress.

Table 2. Cyclization of **10** with $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ to *trans*-dihydropyran **3a**[a]



Entry	compound	R^1	R^2	dr (**3**:**4**)[b]	Yield (%)[c]
1	**a**	$PhCH_2CH_2$	CH_3	91 : 9	81
2	**b**		$PhCH_2CH_2$	88 : 12	78
3	**c**		$CH_2CH(CH_3)_2$	81 : 19	64
4	**d**	Ph	CH_3	93 : 7	77
5	**e**		$PhCH_2CH_2$	84 : 14	67
6	**f**		$CH_2CH(CH_3)_2$	88 : 12	58
7	**g**	nC_6H_{13}	CH_3	91 : 9	73
8	**h**		$PhCH_2CH_2$	83 : 17	81
9	**i**		$CH_2CH(CH_3)_2$	78 : 22	71

[a]All reactions were carried out with 30 mol% of $(i\text{PrO})_2\text{Ti}(\text{NTf})_2$ at −78 °C for 5 h in CH_2Cl_2. [b]Determined by the analysis of 500 MHz ^{1}H NMR spectra. [c]Yields refer to isolated and purified yield.

Acknowledgment. Generous financial support by grants from the Korea Ministry of Science and Technology through the National Research Laboratory program and the Center for Molecular Design & Synthesis (CMDS: KOSEF SRC) at KAIST is gratefully acknowledged.

References and Notes

1. Yu, C.-M.; Lee, J.-Y.; So, B.; Hong, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 161.
2. Yu, C.-M.: Kim, J.-M.; Shin, M.-S.; Yoon, M.-O. *Chem. Commun.* **2003**, 1744.
3. Viswanathan, G. S.; Yang, J.; Li, C.-J. *Organic Lett.* **1999**, *1*, 933.
4. Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1091.
5. Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.
6. Marko, I.; Chelle, F. *Tetrahedron Lett.* **1997**, *38*, 2895.
7. (a) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (b) Marko, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259.
8. Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911.
9. (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (b) Lolkema, L. D. M.; Semeyn, C.; Asheek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129.
10. Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 956.
11. (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Organic Lett.* **1999**, *1*, 87. (b) Rychnovsky, S. D.; Thomas, C. R. *Organic Lett.* **2000**, *2*, 1217.
12. Compound **2** was prepared from the corresponding homo propargyl alcohol by two step sequence: 1) i) *n*BuLi (2.2 quiv), THF, −78 °C ii) TMSCl (2.2 euiv) iii) H_3O^+ 2) Ni-B, H_2, see: Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *Chem. Commun.* **1997**, 763.
13. (a) Marx, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 178. (b) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497. (c) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, M.; Maruta, M. *Synlett* **1996**, 171.
14. Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.