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

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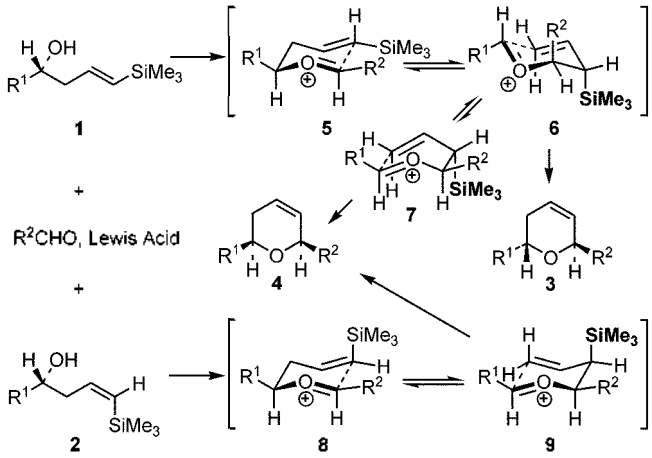
During the course of our research program aimed at finding new synthetic methods for the stereoselective construction of tetrahydropyran units,[1] we became quite interested in the utilization of **1** as a starting material for the stereoselective synthesis of 2,6-disubstituted *trans*-dihydropyran **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

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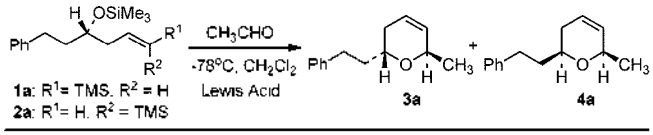
Table 1. Preliminary investigations for intramolecular allylic transfer reactions



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**	$(iPrO)_2Ti(NTf)_2$	5	78 : 22	77
8	**2a**	(30 mol%)	5	1 : >99	75

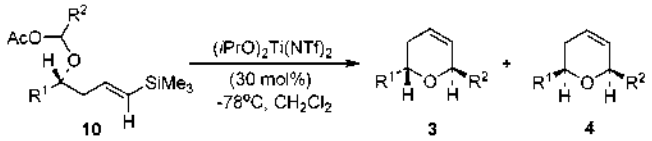
[a]Determined by analysis of 500 MHz ^{1}H NMR spectra. [b]Yields refer to isolated and purified yield.

of $(iPrO)_2Ti(NTf)_2$ 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 $(iPrO)_2Ti(NTf)_2$ 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 $(iPrO)_2Ti(NTf)_2$ (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 $(iPrO)_2Ti(NTf)_2$ 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 $(iPrO)_2Ti(NTf)_2$ 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 $(iPrO)_2Ti(NTf)_2$ 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.

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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.