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Highly stereocontrolled synthesis of fluorinated 2,6-*trans* dihydropyrans via Prins cyclization

Hai-Qing Luo, Xu-Hong Hu, Teck-Peng Loh *

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

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ABSTRACT

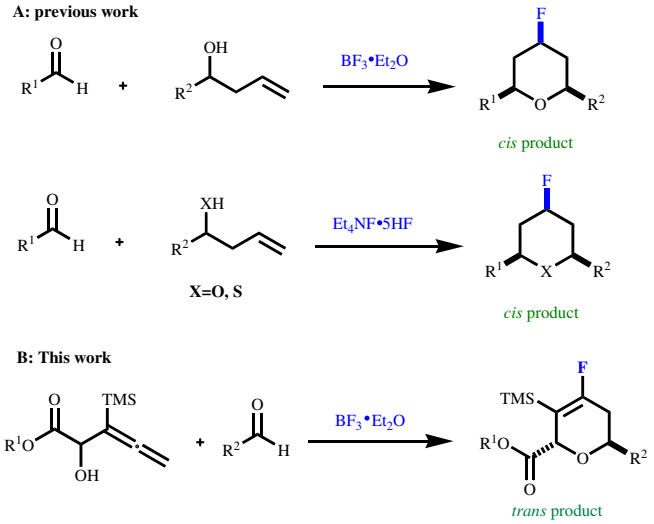
A highly efficient method for the synthesis of fluorinated 2,6-*trans* dihydropyrans via $BF_3{\cdot}Et_2O$-promoted Prins cyclization of allenic alcohols and aldehydes is developed. Various 2,6-*trans* fluorodihydropyrans are obtained in moderate to good yields with excellent diastereoselectivities.

Organofluorine compounds play important roles in medicinal, agrochemical, and materials sciences. This is because the introduction of fluorine atoms into organic molecules significantly alters their biological activity, metabolism, solubility, hydrophobicity, and bulk properties.[1]

It is well known that 2,6-substituted tetrahydropyrans are common features of many natural products and biologically active compounds, and many strategies for their synthesis have been reported.[2] Among them, the Prins cyclization involving the reaction of a homoallylic alcohol with an aldehyde is one of the most attractive methods.[3] Moreover, several groups have described access to the *trans* pyran skeleton by direct Prins-type cyclization, with control of the trans stereochemistry by using α-hydroxy esters or via 1,3-diaxial interactions.[4]

However, few methods for the synthesis of fluorinated pyranyl motifs have been explored.[5] Among these methods, $BF_3{\cdot}Et_2O$ and $Et_4NF{\cdot}5HF$ have been demonstrated to be both good catalysts and fluorine sources to achieve Prins cyclization of homoallylic alcohols into fluorinated pyranyl motifs (Scheme 1A).[5a,b] In particular, all reports involving Prins cyclization almost exclusively led to the fluorinated 2,6-*cis* pyranyl motifs. In comparison, the diastereocontrolled formation of fluorinated 2,6-*trans* pyranyl motifs is still elusive. Therefore, development of a more efficient and highly diastereoselective synthesis of fluorinated 2,6-*trans* pyranyls is still highly desirable for the exploration of new pharmaceuticals.

In this Letter, we report the development of an efficient method for the synthesis of fluorinated 2,6-*trans* dihydropyrans using allenic alcohols as substrates (Scheme 1B). The reactions proceeded smoothly in the presence of $BF_3{\cdot}Et_2O$ to afford the fluorinated 2,6-*trans* dihydropyrans in moderate to good yields with excellent diastereoselectivities.



Scheme 1. Synthesis of fluorinated pyranyl motifs.

* Corresponding author. Tel.: +65 6316 8899; fax: +65 6791 1961.
E-mail address: teckpeng@ntu.edu.sg (T.-P. Loh).

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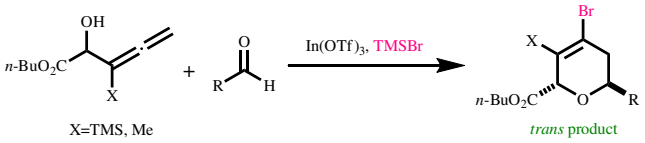


Scheme 2. Synthesis of 2,6-*trans* pyranyl motifs using allenic alcohols.

Recently, we described a highly diastereocontrolled synthesis of 2,6-*trans* pyranyl motifs using allenic alcohols (Scheme 2).[6] Encouraged by this work, we embarked on the synthesis of fluorinated 2,6-*trans* pyranyl motifs via the Prins cyclization by using different Lewis acids (LA) as catalysts and various fluorine sources. After several trials, fluorinated 2,6-*trans* pyranyl motifs were obtained successfully in good yields and with excellent diastereoselectivities mediated by $BF_3{\cdot}Et_2O$ using allenic alcohols and aldehydes as substrates (Table 1, entry 4). It can be seen from Table 1 that Lewis acids such as InF_3, and $In(OTf)_3$, and fluorine sources such as InF_3, NaF, and $Et_3N{\cdot}3HF$ were inactive in this system. Further experiments showed that $BF_3{\cdot}Et_2O$ was the most efficient choice where $BF_3{\cdot}Et_2O$ acts as an efficient Lewis acid and serves as the source of fluorine.

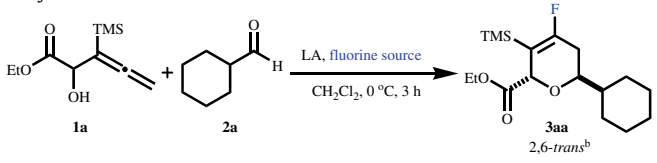
With optimal conditions in hand, we next investigated the reactions of trimethylsilyl allenic alcohols bearing different ester groups with cyclohexanecarboxaldehyde in the presence of $BF_3{\cdot}Et_2O$ (3.0 equiv). The results are summarized in Table 2. In all cases, the expected fluorinated 2,6-*trans* dihydropyrans were obtained in good yields and excellent diastereoselectivities (Table 2, entries 1–4). The highest diastereoselectivity was obtained when a trimethylsilanyl allenic alcohol with an isopropyl ester (**1c**) was used as the substrate (Table 2, entry 3). However, the desired product was not obtained when the trimethylsilyl allenic alcohol contained a carboxylic acid group (Table 2, entry 5).

Next, we explored the scope of the reactions using trimethylsilyl allenic alcohol **1c** and different aldehydes as substrates under the typical conditions. The results are summarized in Table 3. To our delight, the Prins cyclization proceeded smoothly to afford the desired products in excellent diastereoselectivities (up to 94:6 dr). In addition, both aliphatic and aromatic aldehydes bearing *p*-chloro, *p*-trifluoromethyl, and *p*-NO_2 groups gave the desired fluorinated dihydropyrans in moderate to good yields (Table 3, entries 1–11).

We also used a trimethylsilyl allenic alcohol bearing a $PhCH_2CH_2$ group, but no cis or trans fluorinated product was generated as was indicated by ^{19}F NMR spectroscopy (Scheme 3). Only intractable products were observed by TLC analysis. Hence, the allenic alcohol possessing an ester moiety plays a very important role in this reaction.

The relative stereochemistries of the major products were confirmed by NOESY experiments which showed that the 2,6-substituted functional groups in the products were in trans-configuration. The relative stereochemistry of the cyclization product **3ce** (Table 3, entry 5) was further confirmed by a single crystal X-ray analysis (CCDC: 722707) (Fig. 1).

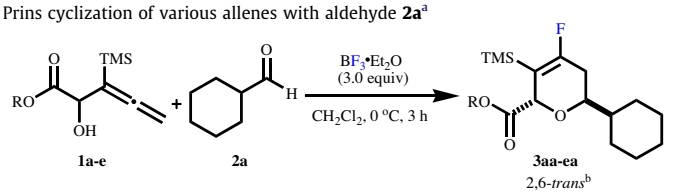
Table 1
Lewis acid catalyzed fluorination by Prins cyclization of allenic alcohol **1a** with aldehyde **2a**[a]



Entry	LA	Fluorine source	Yield[c] (%)	dr (trans/cis)[d]
1	InF_3	InF_3	0	—
2	$In(OTf)_3$	NaF	0	—
3	$In(OTf)_3$	$Et_3N{\cdot}3HF$	0	—
4	$BF_3{\cdot}Et_2O$	$BF_3{\cdot}Et_2O$	84	91:9

[a] Reactions were performed with **1a** (0.3 mmol, dissolved in 1 mL of CH_2Cl_2), aldehyde (0.36 mmol), LA (0.03 mmol) and fluorine source (0.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C.
[b] Stereochemistry was assigned by NOESY experiments.
[c] Isolated yield based on allenic alcohol.
[d] The trans/cis ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.

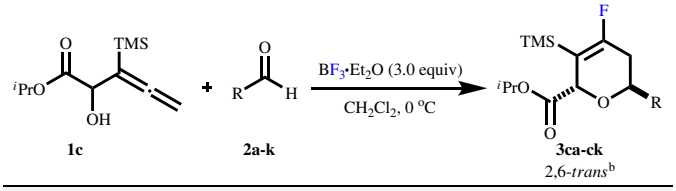
Table 2
Prins cyclization of various allenes with aldehyde **2a**[a]

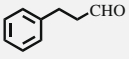
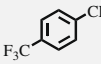


Entry	R	Product	Yield[c] (%)	dr (trans/cis)[d]
1	Ethyl	**3aa**	84	91:9
2	Methyl	**3ba**	83	89:11
3	Isopropyl	**3ca**	85	93:7
4	*n*-Butyl	**3da**	85	91:9
5	H	**3ea**	0	—

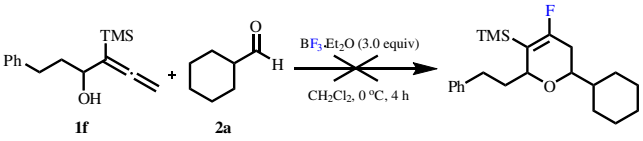
[a] Reactions were performed with allenic alcohol (0.3 mmol, dissolved in 1 mL of CH_2Cl_2), aldehyde (0.36 mmol), $BF_3{\cdot}Et_2O$ (0.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C.
[b] Stereochemistry was assigned by NOESY experiments.
[c] Isolated yield based on allenic alcohol.
[d] The trans/cis ratios were determined by ^{19}F NMR spectroscopy of the crude

Table 3
Prins cyclization of trimethylsilyl allenic alcohol **1c** with various aldehydes[a]



Entry	Aldehyde	Time (h)	Product	Yield[c] (%)	dr (trans/cis)[d]
1		3	**3ca**	85	93:7
2	$n\text{-}C_8H_{17}CHO$	3	**3cb**	82	92:8
3		3	**3cc**	80	94:6
4		3	**3cd**	78	93:7
5		3	**3ce**	77	93:7
6	$n\text{-}C_4H_9CHO$	3	**3cf**	83	92:8
7		3	**3cg**	78	89:11
8		6	**3ch**	51	93:7
9		6	**3ci**	53	94:6
10		6	**3cj**	68	94:6
11		10	**3ck**	43	91:9

[a] For detailed reaction conditions, see Table 1, footnote a.
[b] Stereochemistry was assigned by NOESY experiments.
[c] Isolated yield based on allenic alcohol.
[d] The trans/cis ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.



Scheme 3. Prins cyclization of **1f** bearing a $PhCH_2CH_2$ group.

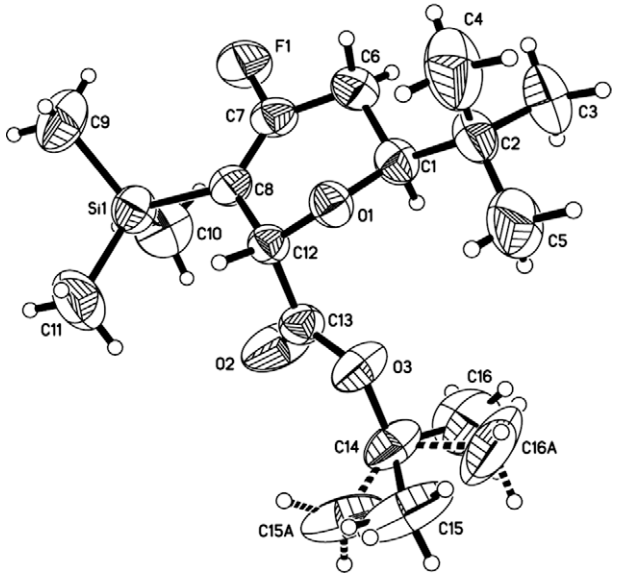
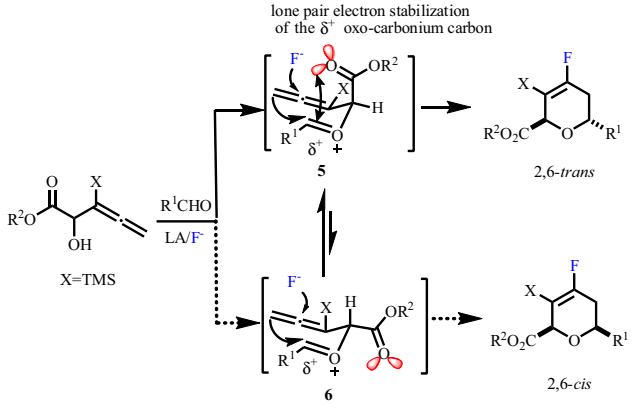


Figure 1. ORTEPdiagram of **3ce**.



Scheme 4. Proposed Prins cyclization pathway.

We propose that the Prins cyclization of the allenic alcohol can take place through a distorted chair transition state (Scheme 4). In this reaction, $BF_3{\cdot}Et_2O$ acts both as a Lewis acid catalyst and provides fluoride.

Here the lone pairs of the ester group adjacent to the allenic alcohol moiety are important as they stabilize the δ^+ on the oxo-carbonium carbon,[4,6,7] therefore, forcing the carbonyl group to adopt an axial orientation, which offers stereoelectronic induction to form the desired intermediate **5** and suppresses generation of the undesirable intermediate **6** (Scheme 4). As a consequence, intermediate **5** gives the desired fluorinated 2,6-*trans* dihydropyran, selectively.

In summary, we have demonstrated an efficient $BF_3{\cdot}Et_2O$-promoted Prins cyclization for the synthesis of fluorinated 2,6-*trans* dihydropyrans in moderate to good yields with excellent diastereoselectivities by using allenic alcohols and various aldehydes as substrates. This Letter provides a new method for the synthesis of biologically active fluorinated 2,6-*trans* pyranyl motifs. Further application of this method to the synthesis of other fluorinated compounds is currently in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.068.

References and notes

1. For an important early review on the subject, see: (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197; (b) Special Issue on 'Fluorine in the Life Sciences', *ChemBioChem* **2004**, *5*, 557–726.; (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
2. (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773; (b) Pospísil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516–3517; (c) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862–9863; (d) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425–2430.
3. (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577–580; (b) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun.* **1999**, 291–292; (c) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387–8390; (d) Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun.* **2004**, 2456–2457; (e) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491–4494; (f) Liu, F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063–2066.
4. (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426–3427; (b) Roush, W. R.; Dilley, G. T. *Synlett* **2001**, 955–959; (c) Markó, I. E.; Dobbs, A.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1977**, *38*, 2899–2902.
5. (a) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876–3878; (b) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471–2483; (c) Dobbs, A. P.; Pivevi, L.; Penny, M. J.; Martinovic, S.; Lley, J.; Stephenson, P. T. *Chem. Commun.* **2006**, 3134–3136; (d) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D. T.; Simpson, J. R.; Smith, W.; Willis, C. L. *Chem. Commun.* **2001**, 835–836; (e) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686.
6. Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741–1743.
7. For the role of the lone pair of ester groups in the stabilization of oxo-carbeniums in asymmetric synthesis, see: (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692–10697. and references therein; (b) Loh, T. P.; Wang, R. B.; Sim, K. Y. *Tetrahedron Lett.* **1996**, *37*, 2989–2992; (c) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322–5323; (d) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528; (e) Mulzer, J.; Meyer, F.; Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503–3506.