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Highly Stereoselective Synthesis of 2,5-Disubstituted 3-Vinylidene Tetetrahydrofurans via Prins-Type Cyclization

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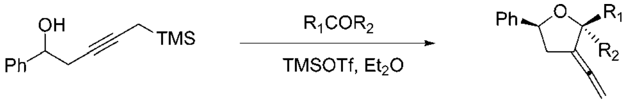
ABSTRACT

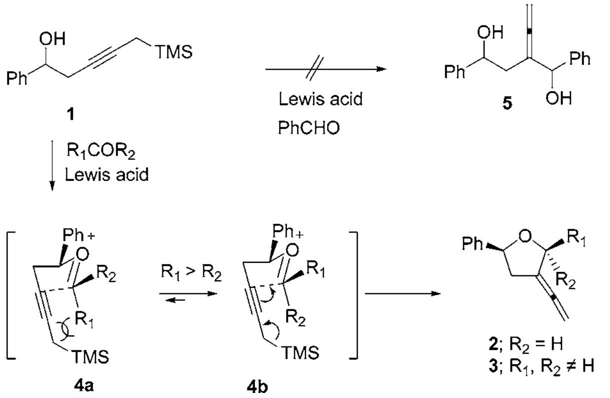


A novel synthetic methodology for 2,5-disubstituted tetrahydrofurans having an allenyl group at the 3-position via Prins-type cyclization was developed. The reaction led to excellent selectivity and moderate to high yields.

The tetrahydrofuran moiety is an important heterocycle constituent in many bioactive natural products. A number of methodologies for preparation of polysubstituted tetrahydrofuran have been explored.[1] Especially, synthetic methods for *cis*-2,5-disubstituted terahydrofuran derivatives have attracted considerable attention.[2] Recently, Prins-type cyclization has been reported to be a powerful method to prepare the various tetrahydropyrans.[3]

In this Letter, we report on a novel methodology for stereoselective synthesis of *cis*-disubstituted tetrahydrofurans bearing an allenyl group at the 3-position via Prins-type cyclization. By condensation of alcohol **1**[4] and aldehyde (or ketone) in the presence of a Lewis acid, an intermediate oxocarbenium ion **4a** and 4b was generated and followed by Prins-type cyclization to generate the tetrahydrofuran **2** (or **3**) (Scheme 1).

Scheme 1



Initially, Prins-type cyclization of substrate **1** with benzaldehyde was tried under various conditions (Table 1). Among Lewis acids, TMSOTf in Et_2O produced the tetrahydrofuran **2a** with high *cis/trans* ratio (40/1) in high yield.

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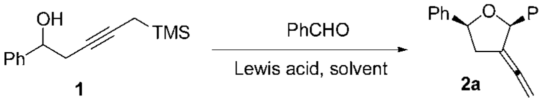
(1) (a) For a review, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. (b) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc*. **2004**, *126*, 1620−1621. (c).Ajamian, A.; Gleason, J. L. *Org. Lett*. **2001**, *3*, 4161−4164. (d) Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetraheron: Asymmetry* **2004**, *15*, 405−412. (e) Duan, S.; Moeller, *Org. Lett*. **2001**, *3*, 2685−2688. (f) Chirskaya, M. V.; Vasil'ev, A. A.; Sergovskaya, N. L.; Shorshnev, S. V.; Sviridov, S. L. *Tetraherdon Lett*. **2004**, *45*, 8811−8813. (g) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc*. **1984**, *106*, 2668−2671. (h) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc*. **1989**, *111*, 2204−2210.

10.1021/ol051058r CCC: $30.25

Table 1. Prins-Type Cyclization of Substrate **1** and Benzaldehyde under Various Conditions[a]



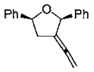
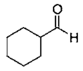
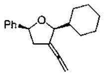
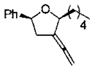
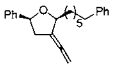
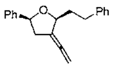
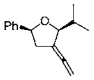
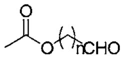
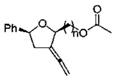
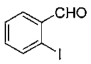
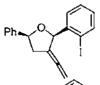
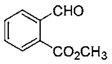
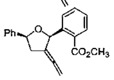
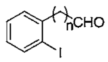
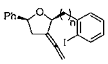
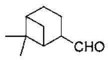
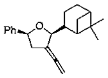
entry	Lewis acid	solvent	time (h)	yield **2a** (%)[b]	*cis/trans*[c]
1	$InCl_3$	CH_2Cl_2	17	22	40:1
2	$BF_3.Et_3O$	CH_2Cl_2	17	69	8:1
3	$SnCl_4$	CH_2Cl_2	17	80	40:1
4	$SnCl_4$	Et_2O	15	80	40:1
5	TMSOTf	CH_2Cl_2	4	33	3:1
6	TMSOTf	Et_2O	4	91	40:1

[a] All reactions were carried out on a 0.35 mmol scale at −78 °C to room temperature in the presence of 1.1 equiv of Lewis acid. [b] Isolated yields. [c] Ratio based on ^1H NMR spectra.

There might be two possible competitive reactions in this reaction. One is to generate the desired product **2** via Prins-type cyclization. The other one is to produce the diol **5** by carbon−carbon bond formation between alcohol **1** and benzaldehyde by removal of TMS.[5] The reaction proceeded to give only the product **2** or **3**, and no diol **5** was observed.

Prins-type cyclization was carried out in the presence of TMSOTf in Et_2O at −78 °C to room temperature. Table 2 illustrates the results of the Prins-type cyclization of substrate **1** and various aldehydes. All products showed only a *cis*-relationship between the 2- and 5-positions except for entry 1.[6] The observed excellent stereoselectivity can be explained by the fact that the quasiequatorial position (**4b**) is the more favorable orientation compared to the quasiaxial position (**4a**) as a result of the steric interaction between R_1 and the TMS-methylene group in the transition state (when $R_1 > R_2$ in size, Scheme 1).

Table 2. Prins-Type Cyclization of Substrate **1** and Various Aldehydes[a]

entry	aldehyde	product	No	yield[b]	cis/trans[c]
1	Ph-CHO		**2a**	91	40:1
2			**2b**	86	cis only
3	$CH_3(CH_2)_4CHO$		**2c**	71	cis only
4	$Ph(CH_2)_5CHO$		**2d**	63	cis only
5	$Ph(CH_2)_2CHO$		**2e**	73	cis only
6	$(CH_3)_2CHCHO$		**2f**	83	cis only
7			**2g** **2h** **2i**	82 (n=3) 86 (n=4) 98 (n=5)	cis only cis only cis only
8			**2j**	93	cis only
9			**2k**	58	cis only
10			**2l** **2m** **2n**	82 (n=1) 78 (n=2) 77 (n=3)	cis only cis only cis only
11			**2o**	85	cis only

[a] All reactions were carried out on a 0.35−0.55 mmol scale. [b] Isolated yields. [c] Ratio based on ^1H NMR spectra.

In most cases, various aldehydes provided the corresponding product in moderate to good yields with excellent selectivity. Entries 4 and 9 showed somewhat lower yield. Substituted benzaldehyde (entry 8) and phenyl alkanals (entry 10) also provided the corresponding product in high yields. When we examined the THP-protected substrate **5** without an aldehyde under the same reaction condition, the product **6** having a butyl alcohol group at the 2-position was obtained in 48% yield (Scheme 2).

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(2) (a) Moinuddin, S. G. A.; Hishiyama, S.; Cho, M.-H.; Davin, L. B.; Lewis, N. G. *Org. Biomol. Chem.* **2003**, *1*, 2307−2313. (b) Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895−1897. (c) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415−1419. (d) Walkup, R. D.; Mosher, M. D. *Tetrahedron* **1993**, *49*, 9285−9294.; (e) Lee, E.; Jeong, E. J, Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131−10132. (f) Cohen, F.; MacMillan, D. W. C.; Overman, L. E.; Romero, A. *Org. Lett.* **2001**, *3*, 1225−1228. (g) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861−7864. (h) Ericsson, C.; Engman, L. *Org. Lett.* **2001**, *3*, 3459−3462. (i) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3667−3675. (j) Shi, H. S.; Liu, H.; Bloch, R.; Mandville, G. *Tetrahedron* **2001**, *57*, 9335−9341. (k) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

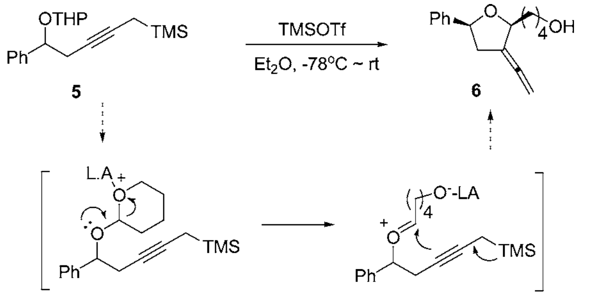
(3) (a) Cho, Y. S.; Karupaiyan, K.; Kang, H. J.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H. *Chem. Commun.* **2003**, 2346−2347. (b) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025−2028. (c) Kang, H. J.; Kim, S. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Choi, K. I.; Han, S.-Y.; Cho. Y. S. *Synlett* **2004**, *14*, 2545−2548. (d) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (e) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219. (d) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652−8653. (d) Yang, J.; Viswanathan, G. S.; Li, C-J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (e) Viswanathan, G. S.; Yang, J.; Li, C-J. *Org. Lett.* **1999**, *1*, 993−995. (f) Li, C-J.; Zhang, W-C. *Tetrahedron* **2000**, *56*, 2403−2411. (g) Yang, X- F.; Mague, J. T.; Li, C-J. *J. Org. Chem.* **2001**, *66*, 739−747. (h) Li, J.; Li, C-J. *Tetrahedron Lett.* **2001**, *42*, 793−796. (i) Frater, G.; Muller, U.; Kraft, P. *Helv. Chim. Acta* **2004**, *87*, 2750−2763. (j) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251−6254. (k) Marko, I. E.; Bayston, D. J. *Tetraheron Lett.* **1993**, *34*, 6595−6598. (l) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. J. *J. Org. Chem.* **1992**, *57*, 2211−2213.

(4) (a) Han, Y.; Huang, Y. Z. *Tetrahedron Lett.* **1994**, *35*, 9433−9434. (b) Loh, T. P.; Lin, M. J.; Tan, K. L. *Tetrahedron Lett.* **2003**, *44*, 507−509. (c) Henk, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 1407−1410.

(5) For a review, see: Rhebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385−1489.

(6) The *cis* relationship identification was determined by NOE experiments.

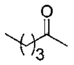
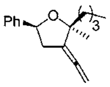
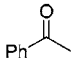
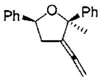
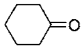
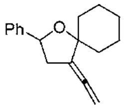
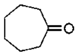
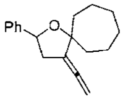
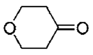
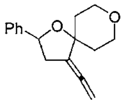
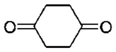
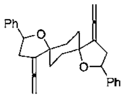
Scheme 2



We next extended this method to various ketones. Under the same reaction condition, Prins-type cyclization for ketones also proceeded smoothly to generate the tetrahydrofurans **3** in moderate to high yields. The results are summarized in Table 3. In entry 1, 2-hexanone gave the product **3a** with *cis*/*trans* ratio = 1.5/1 in 90% yield. When a phenyl group was introduced in place of butyl in entry 1 (entry 2), the ratio (*cis*/*trans* = 7/1) was increased.

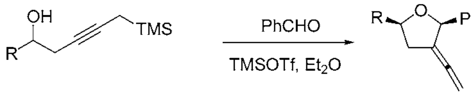
1,4-Cyclohexanedione gave the dispiro product **3f** in 48% yield. Its configuration was determined by X-ray analysis.

Table 3. Prins-Type Cyclization of Substrate **1** and Various Ketones[a]

entry	ketone	product	No	yield[b]	cis/trans[d]
1			**3a**	90	1.5:1
2			**3b**	55	7:1
3			**3c**	95	-
4			**3d**	62	-
5			**3e**	71	-
6[c]			**3f**	48	-

[a] All reactions were carried out on a 0.35−0.55 mmol scale. [b] Isolated yields. [c] Substrate 1 (2.0 equiv) was used. [d] Ratio based on ^{1}H NMR spectra.

Scheme 3



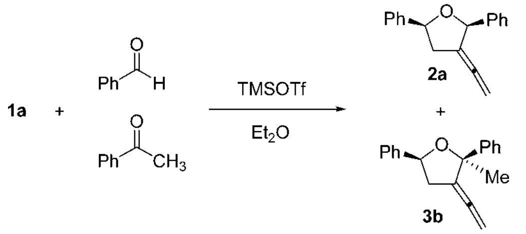
7: R = isopropyl (65%)
8: R = n-octyl (70%)

Cycloketones (entries 3 and 4) gave the corresponding tetrahydrofuran (**3c** and **3d**) having spiro moiety at the 2-position.[7] Especially, the product **3c** was obtained in 95% yield.[8] In the case of entry 5, 1,8-dioxa-spiro[4.5]decane derivatives **3e** was efficiently obtained in 71% yield.

As shown in Scheme 3, when alkyl groups were introduced in place of the pheny group of substrate **1**, *cis*-only products **7** and **8** were obtained under the same reaction condition in 65% and 75% yields, repectively.

To check the chemoselectivity of Prins-type cyclization, we carried out the reaction between benzaldehyde and acetophenone with substrate **1** under the same reaction condition (Scheme 4). A very high chemoselective ratio (**2**a/**3b** = 54/1) was shown.

Scheme 4



(**2a**/**3b** = 54/1)

In conclusion, we have developed a novel synthetic methodology for 2,5-disubstituted tetrahydrofurans having an allenyl group at the 3-position via Prins-type cyclization. The reaction led to excellent selectivity and moderate to high yields with various aldehydes and ketones.

Acknowledgment. This work was supported by Korea Institute of Science and Technology (2E18800).

Supporting Information Available: Experimental detail and spectroscopic and analytical data for products **2** and **3**, NOE data for **2a**, and X-ray structure of **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051058R

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[7] Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828−1835.

[8] Bauer, V. J.; Ong, H. H.; Kosley, R. W., Jr. *J. Heterocycl. Chem.* **1982**, *19*, 1069−1072.