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Stereoelectronic versus Steric Tuning in the Prins Cyclization Reaction: Synthesis of 2,6-*trans* Pyranyl Motifs

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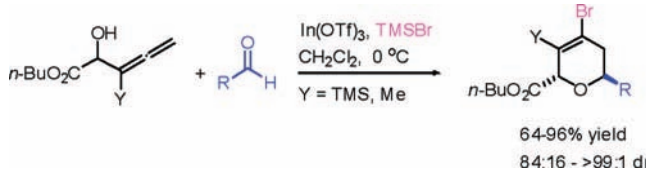
ABSTRACT



The use of carboalkoxyl allenic alcohol for the efficient synthesis of pyranyl motifs via Prins cyclization is described. This method provides easy access to 2,6-*trans* dihydropyrans in good yield and high diastereoselectivity.

Functionalized pyran rings have featured prominently in a wide variety of natural products[1] and therefore have been a popular target for organic chemists.[2] Among the many popular methods available,[3] the Prins cyclization reaction involving a homoallylic alcohol and an aldehyde is one of the most efficient methods.[4] Many groups, including ours, have contributed to this approach, which allows easy and practical access to 2,6-*cis* tetrahydropyrans.[5] Despite significant advancement in this area, Prins cyclization leading to the highly selective 2,6-*trans* pyranyl motifs is still not available.[6] Recently, we demonstrated that α-alkoxy tethered homoallylic alcohol can undergo Prins cyclization with various aldehydes to afford the 2,6-*trans* tetrahydropyrans, albeit with low selectivity (*cis*/*trans* = 50/50).[7] We believe that the carbonyl group stabilizes the δ^+ of the oxocarbenium,[8] therefore forcing the carbonyl group to adopt the axial orientation. As a consequence, it leads to the formation of the 2,6-*trans* tetrahydropyran selectively. The low selectivity observed in those reactions is probably due to the competing 1,3-diaxial interaction versus the lone pair

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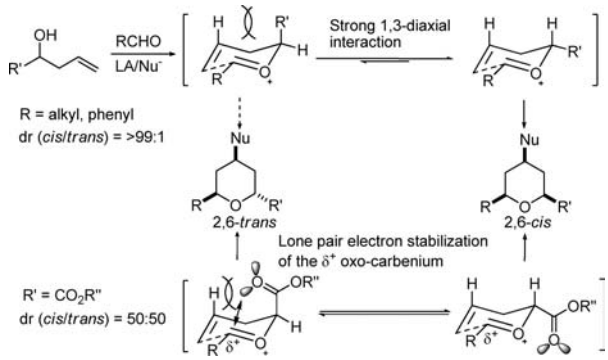
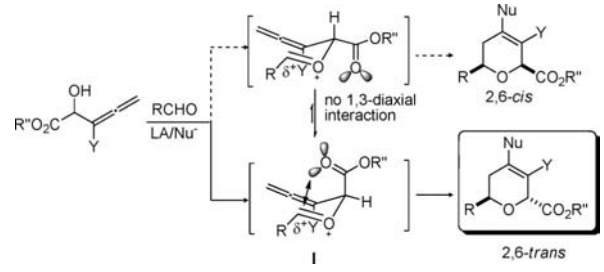
stabilization of the oxo-carbenium by the alkoxy group (Scheme 1). We envisage that removal of the 1,3-diaxial

Scheme 1. Interplay between 1,3-Diaxial Interaction and Stereoelectronic Effect



interaction by using allenic alcohols instead of the homoallylic alcohols may lead to higher 2,6-*trans* selectivity (Scheme 2). In this Letter, we describe a highly efficient

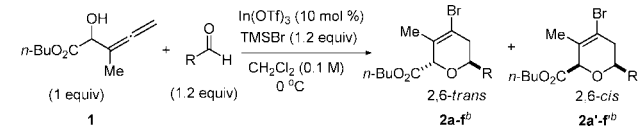
Scheme 2. Proposed Cyclization Pathway Using Allenic Alcohol through a Distorted Chair Transition State



Prins cyclization method for synthesizing 2,6-*trans* dihydropyrans using allenic alcohols and aldehydes promoted by an indium salt catalyst.

Initial efforts were focused on the reactions of α-methyl allenic alcohol bearing an *n*-butyl ester group[9] with a wide range of aldehydes in the presence of $In(OTf)_3$ (0.1 equiv) and TMSBr (1.2 equiv) in CH_2Cl_2 (0.1 M) at 0 °C.[10] The results are summarized in Table 1. In all cases, the expected

Table 1. Cyclization of α-Methyl Allenic Alcohol **1** with Aldehydes[a]



entry	R	time (h)	products (yield, %)[c]	dr (*trans*: *cis*)
1	c-C_6H_{11}	2	**2a** (84), **2a′** (12)	87:13[d]
2	$(CH_3CH_2)_2CH$	2	**2b** (75), **2b′** (6)	93:7[d]
3	$(CH_3)_3C$	1.5	**2c/c′** (84)	92:8[e]
4	$(CH_3)_2CHCH_2$	1.5	**2d** (73), **2d′** (8)	90:10[d]
5	$PhCH_2CH_2$	2	**2e** (70), **2e′** (13)	84:16[d]
6	Ph	3	**2f**[f] (75), **2f′** (8)	89:11[d]

[a] Reactions were performed with **1** (0.3 mmol, dissolved in 1 mL of CH_2Cl_2, syringe pump addition), aldehyde (0.36 mmol), TMSBr (0.36 mmol), and $In(OTf)_3$ (0.03 mmol) in CH_2Cl_2 (2 mL) at 0 °C. [b] Stereochemistry assigned by NOESY experiments. [c] Isolated yield based on allenic alcohol. [d] Determined by isolated yields of respective isomers. [e] Determined by ^1H NMR. [f] X-ray crystal structure of **2f** is shown in Figure 1.

2,6-*trans* dihydropyrans products were obtained in good yields and good selectivities (Table 1, entries 1−6). The findings also showed that the use of aliphatic or aromatic aldehydes had no apparent effect on the diastereoselectivity.

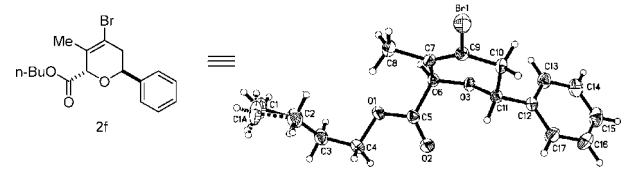


Figure 1. Single crystal X-ray structure of **2f**.

It is worth noting that the major isomers of tetra-substituted dihydropyrans were found to have the 2,6-*trans* relative stereochemistries as assigned by NOESY experiments. The relative stereochemistry of one of the cyclization products (**2f**) was further confirmed by a single crystal X-ray structure as depicted in Figure 1.

With these intriguing results, we further explored the reactions using a bulky silicon-substituted allenic alcohol (Table 2, substrate **3**) under the same conditions as stated above. To our delight, the Prins cyclization proceeded smoothly to afford the desired products with excellent diastereoselectivities (up to >99:1). In addition, both aliphatic

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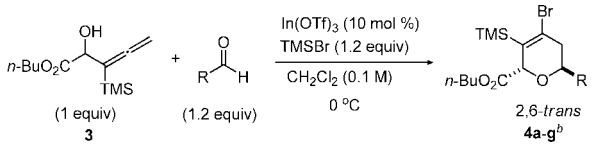
(10) Allenic alcohols and aldehydes could generate aldol-type adducts through 1,3-transposition of oxygen, and thus the reactions were performed at lower temperature with dropwise addition of a decreased concentration of allenic alcohols using syringe pump over a period of 1 h. For reactions of allenic alcohols and aldehydes promoted by Lewis acid, see: (a) Trost, B. M.; Jonasson, C.; Wuchrer, M. *J. Am. Chem. Soc.* **2001**, *123*, 12736–12737. (b) Yu, C. M.; Kim, Y. M.; Kim, J. M. *Synlett* **2003**, 1518–1520.

Table 2. Prins Cyclization of Allenic Alcohol with Aldehydes[a]



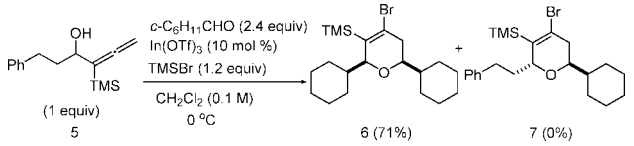
entry	product	R	time (h)	yield (%)[c]	dr *trans*/*cis*[d]
1	**4a**	*o*-C_6H_{11}	1	90	96:1
2	**4b**	$(CH_3CH_2)_2CH$	1.5	84	96:4
3	**4c**	$(CH_3)_3C$	1	86	94:6
4	**4d**	$CH_3(CH_2)_6CH_2$	1.5	82	>99:1
5	**4e**	$(CH_3)_2CHCH_2$	1.5	80	>99:1
6	**4f**	$PhCH_2CH_2$	2	83	93:7
7	**4g**	Ph	2.5	68	>99:1
8	**4h**	*m*-NO_2-C_6H_4	3	64	>99:1

[a] For the conditions, see Table 1, footnote a. [b] Stereochemistry assigned by NOESY experiments. [c] Isolated yield based on allenic alcohol. [d] *trans*/*cis* ratios were determined by ^{1}H NMR.

and aromatic aldehydes gave the desired dihydropyrans in good yields (Table 2, entries 1−7).

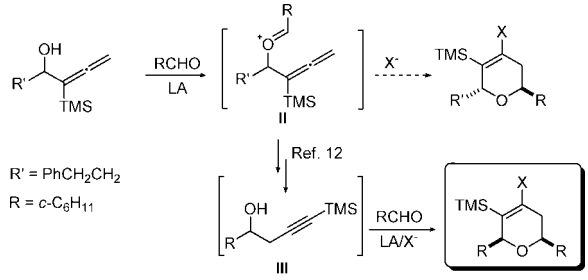
Of mechanistic interest, we carried out the reaction of alkyl-substituted allenic alcohol **5** with cyclohexanecarboxaldehyde (Scheme 3). In this case, 2,6-*cis*-dicyclohexyl

Scheme 3



dihydropyran **6** was obtained.[11] No crossover product **7** was detected. A plausible mechanism was proposed to account for this phenomenon (as shown in Scheme 4). During this

Scheme 4. Proposed Mechanism of Cyclization of Alkyl-Substituted Allenic Alcohol with Aldehyde



process, homopropargylic transfer reaction occurred before the Prins cyclization reaction. This is consistent with the result we observed previously.[12] Subsequently, Prins-type cyclization of homopropargylic alcohol **III** with another equivalent of cyclohexanecarboxaldehyde[13] took place, leading to unexpected product **6**. However, the ester-substituted allenic alcohols (substrates **1** and **3**) underwent Prins cyclization without any detection of the homopropargylic transfer product.

The carboalkoxyl group adjacent to the allenic alcohol moiety performed two functions: (1) stereoelectronic induction to form the desired intermediate **I** (Scheme 2) with 2,6-*trans* configuration through stabilization of the δ^+ oxocarbenium and (2) efficient suppression of the unwanted oxonia-Cope rearrangement due to the electron-withdrawing property of the ester functional group, as suggested by Roush.[14] As a consequence, the reactive intermediate **I** favored the direct Prins cyclization prior to oxonia-Cope rearrangement.

In conclusion, we have developed a general method that allows easy access to 2,6-*trans* pyranyl motifs. Prins cyclization using carboalkoxyl allenic alcohols is the key to the success of this method. The ester group provides an anomeric effect[8c−e] as well as lone pair stabilization of the δ^+ of the oxo-carbenium intermediate. It also suppresses the propargyl transfer process. The use of the allenic alcohols instead of the homoallylic alcohols removes the 1,3-steric repulsion of the ester group with hydrogen through a distorted six-membered ring transition state, thus promoting the ester group to adopt the axial orientation preferentially. We believe that this method of tuning the stereoelectronic versus steric effect to direct the reaction pathway will become a prevailing strategy in organic synthesis. The ester functional group in the product has the advantage of being convertible to other functional groups such as alcohols, alkenes, etc. Application of this Prins cyclization method toward the synthesis of natural products is now in progress.

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Supporting Information Available: Additional experimental procedures and characterization data for the reactions products including one CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Stereochemistry of **6** was determined by NOESY.

(12) The allenic alcohol can undergo propargylic transfer in the presence of aldehyde and Lewis acid via oxo-carbenium[3,3]-sigmatropic rearrangement. Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun.* **2004**, 2456–2457.

(13) For Prins cyclization of homopropargylic alcohols with aldehydes, see: (a) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 1633–1636. (b) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979–1982. (c) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617–3619.

(14) Roush, W. R.; Dilley, G. T. *Synlett* **2001**, 955–959.