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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1641–1644

Suppression of epimerization due to selectivity leakage: an application towards the total synthesis of (−)-centrolobine

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Received 26 October 2005; revised 12 December 2005; accepted 21 December 2005
Available online 23 January 2006

Abstract—An $InCl_3$-mediated Prins cyclization of homoallylic alcohols with aldehydes has been established. The enantioselectivities of the trisubstituted tetrahydropyrans are almost retained through the suppression of epimerization. The synthetic value of this protocol is demonstrated by the total synthesis of (−)-centrolobine.

For the past decade, indium(III) complexes have emerged as useful reagents for C–C bond formation reactions and synthetic transformations.[1] Prins cyclization has emerged as a powerful method for the synthesis of substituted tetrahydropyrans (THPs),[2] which are common in many biologically active natural products.[3] Among the many methods of preparation,[4] significant effort has been devoted towards the $InCl_3$-mediated Prins cyclization, which generates 4-chloro-THPs in high yields and stereoselectivities.[5,6] However, there are limited reports regarding enantioselective Prins syntheses,[7] which play a critical role in the synthesis of optically active THPs. We report herein an enantioselective $InCl_3$-mediated Prins cyclization, affording the corresponding 2,6-disubstituted-4-chloro-THPs with high stereo- and enantioselectivities.

In our preliminary investigation, the optically active homoallylic alcohol **1a**[8] was added to a stirred solution of 2-methylbenzaldehyde **2a** and $InCl_3$ in dichloromethane (Table 1, entry 1) and allowed to stir for 4 h. The desired product **3a** was obtained in 76% yield, with preservation of enantioselectivity (88% ee) even at room temperature. In addition, complete preservation of enantioselectivity was observed for entries 2–4 in Table 1 as shown.

It is worth noting that the Prins cyclization reaction proceeded smoothly without protection of a phenolic group (Table 1, entry 3). However, we observed a leakage in enantioselectivity for entries 5 and 6. Recently, our group has demonstrated that low selectivity was observed due to racemization of the enantioselective homoallylic alcohol **1** mediated by the reverse reaction with aldehyde **2′** generated during the course of the reaction.[10] Thus, the presence of **1′** will lead to the opposite enantiomer of **3**, which gradually undermines the enantioselectivity of the THP product (Scheme 1).

Instead of carrying out the reaction at room temperature, the Prins cyclization reactions of **1a** with aldehydes **2e** and **2f**, respectively, were carried out at 0 °C. In both cases, enantioselectivities were retained, furnishing the THPs in yields of 55% and 56%. This is consistent with our earlier paper on the suppression of epimerization by performing the reaction at a lower temperature.[8,10]

In an attempt to extend the scope of this methodology, cyclic homoallylic alcohol **1b**[8] was employed, as the presence of a sterically hindered group allows the alcohol to be more susceptible to epimerization. The results are shown in Table 2.

Notably, the Prins cyclization reaction proceeded well for entries 1 and 2, without selectivity leakage even at room temperature. We believe that the reactive aldehydes **2b** and **2g** play a role in the prevention of epimerization. Leakage of enantioselectivity was observed with the Prins cyclization reaction for entries 3–6.

Keywords: Prins cyclization; Tetrahydropyrans; Epimerization; Centrolobine.
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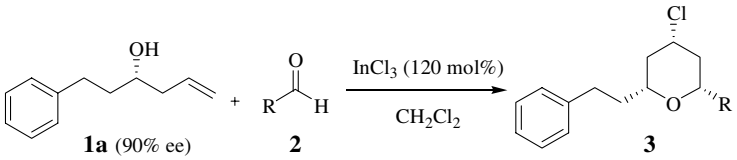
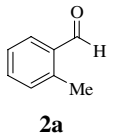
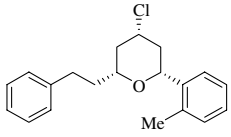
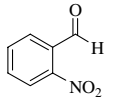
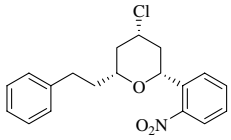
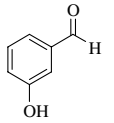
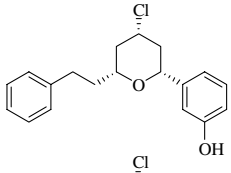
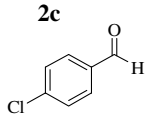
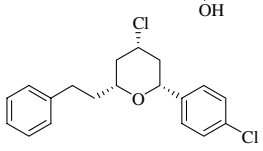
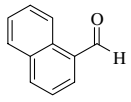
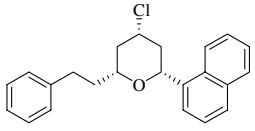
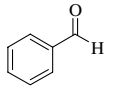
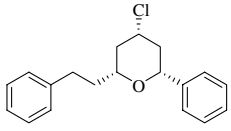
doi:10.1016/j.tetlet.2005.12.108

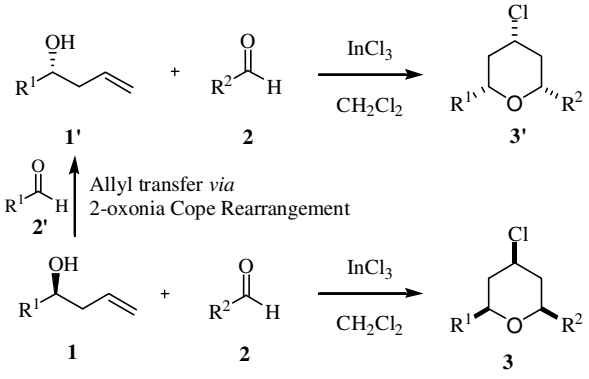
Table 1. Prins cyclization of **1a** with various aldehydes[9]



Entry	Aldehyde	Product		Temp (°C)	Yield (%)	ee (%)[a]
1	 **2a**		**3a**	25	76	88
2	 **2b**		**3b**	25	68	90
3	 **2c**		**3c**	25	59	88
4	 **2d**		**3d**	25	67	88
5	 **2e**		**3e**	25 0	65 55	80 90
6	 **2f**		**3f**	25 0	69 56	82 90

[a] HPLC analysis employing Daicel chiral columns.

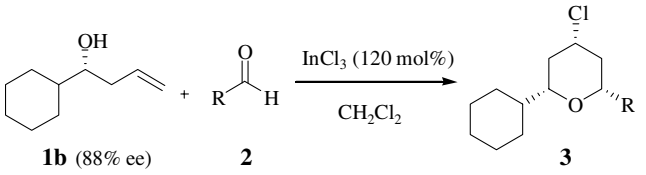
Given the success in retaining the enantioselectivities as mentioned in Table 1, the Prins cyclization reactions for these entries were carried out at 0 °C (Table 2, entries 3 and 4) and −10 °C (Table 2, entries 5 and 6), respectively, in order to suppress the epimerization completely. These observations suggested that the Prins cyclization could be faster than the undesirable 2-oxonia Cope rearrangement, allowing preservation of enantioselectivity. In all cases, enantioselectivities were retained, furnishing the products in moderate to good yields.



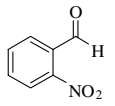
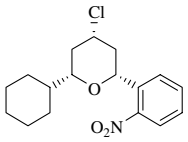
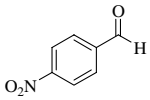
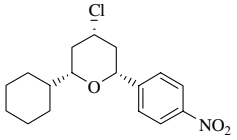
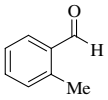
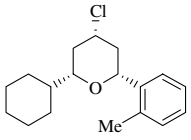
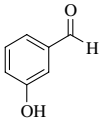
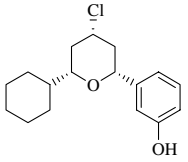
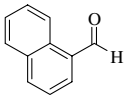
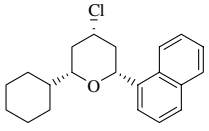
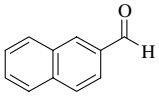
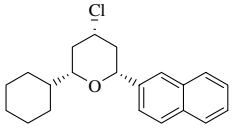
Scheme 1. $InCl_3$-mediated Prins cyclization.

We highlight the synthetic value of this protocol with the total synthesis of the natural product, (−)-centrolobine (Scheme 2). Centrolobine A is an antibiotic isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* found in rain forests. The total synthesis of this natural product has been independently completed by several research groups.[11] The crucial steps in this total synthesis include enantioselective allyl transfer[8] and a Prins cyclization, which highlight

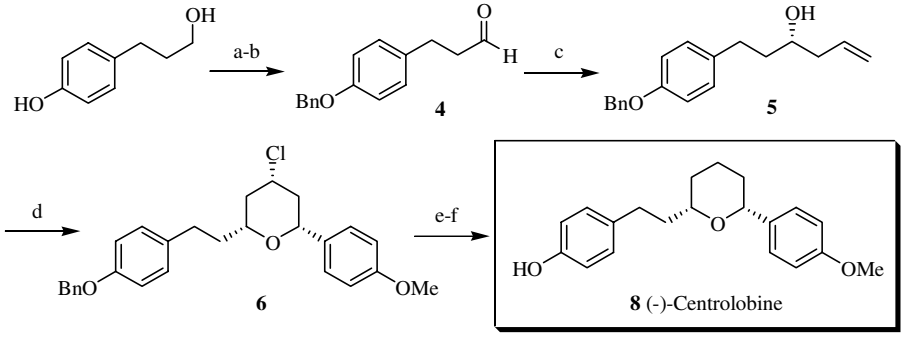
Table 2. Prins cyclization of **1b** with various aldehydes[9]



1b (88% ee) **2** **3**

Entry	Aldehyde	Product		Temp (°C)	Yield (%)	ee (%)[a]
1	 **2b**		**3g**	25	71	88
2	 **2g**		**3h**	25	69	88
3	 **2a**		**3i**	0	59	88
4	 **2c**		**3j**	0	60	88
5	 **2e**		**3k**	0 −10	63 52	80 88
6	 **2h**		**3l**	0 −10	66 53	80 88

Note: Reactions with aliphatic aldehydes were carried out, but chiral HPLC separation of enantiomers were unsuccessful.
[a] Determined by HPLC analysis employing Daicel chiral columns.



Scheme 2. Enantioselective total synthesis of (−)-centrolobine. Reagents and conditions: (a) BnBr, Ag_2O, CH_2Cl_2, 0 °C, 80%; (b) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 76%; (c) camphor-derived homoallylic alcohol,[12] CSA, CH_2Cl_2, 15 °C, 68%, 90% ee; (d) $InCl_3$, *p*-anisaldehyde, 0 °C, 70%, 90% ee; (e) 1,1′-azobis(cyclohexanecarbonitrile), Bu_3SnH, C_6H_6, reflux, 94%; (f) H_2, 10% Pd/C, 86%, 90% ee.

the utility of the two methodologies developed in our group. In both cases, the desired products were furnished with high selectivities. Furthermore, the selectivity was preserved throughout the subsequent transformations, affording the natural product in six steps with an overall yield of 24%.

In conclusion, we have developed the first example of $InCl_3$-mediated Prins cyclization with the preservation of enantioselectivity. Through suppression of epimerization by performing the reaction at a lower temperature, the method has been applied for the enantioselective total synthesis of (−)-centrolobine, with an overall yield of 24%. Application of this method to the synthesis of other natural products is still in progress.

Acknowledgements

We are grateful to Nanyang Technological University and National University of Singapore for their generous financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.108.

References and notes

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5. For examples of $InCl_3$-mediated Prins cyclizations, see: (a) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627–1630; (b) Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993–995; (c) Yang, X. F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739–747.
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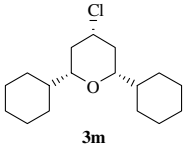
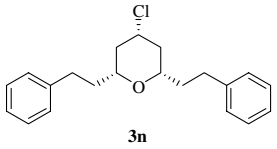
8. Homoallylic alcohols **1a** and **1b** were synthesized employing our allyl transfer method. See: Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 5819–5822.
9. <10% of *meso* Prins products (**3m** and **3n**) were isolated for all entries in Tables 1 and 2.



3m



3n

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12. The camphor derived homoallylic alcohol was prepared by a typical Grignard reaction between (+)-camphor and allyl bromide.