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Prins Cyclizations in Silyl Additives with Suppression of Epimerization: Versatile Tool in the Synthesis of the Tetrahydropyran Backbone of Natural Products

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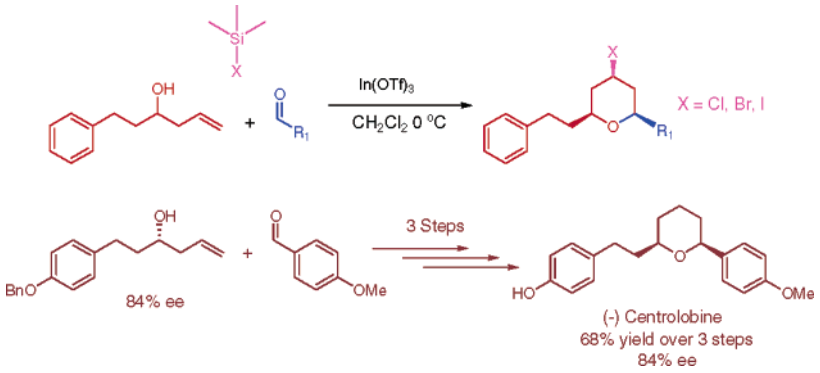
ABSTRACT



A catalytic Prins cyclization reaction has been developed. The involvement of trimethylsilyl halides offers a versatile route to the formation of *cis*-4-halo-2,6-disubstituted tetrahydropyran rings. The problem of epimerization in Prins cyclization has also been addressed in the total synthesis of (–)-centrolobine using this methodology.

The tetrahydropyran (THP) ring is featured widely in many natural products such as phorboxole A, pysmberin, and (−)-centrolobine. Among the many methods available, Prins cyclization[1] offers one of the most versatile methods for the construction of the THP ring. However, most of the reported methods encompassed limitations such as substrate limitation, nonconvergent nature due to the need to form an oxonium intermediate using indirect methods, the need to use a stoichiometric amount of Lewis acid, the trapping of the carbocation with only one halide, epimerization of the starting homoallylic alcohols due to the transfer[2] between the homoallylic alcohol and the aldehyde, etc. Therefore, there is still an urgent need to develop a new Prins reaction that can overcome some, if not all, of these limitations. In this paper, we report a new strategy to the synthesis of 4-halo THP rings using catalytic indium complex and trimethylsilyl

(1) (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913−915. (b) Wei, Z. Y.; Li, S. J. Wang, D.; Chan T. H. *Tetrahedron Lett.* **1987**, *28*, 3441−3444. (c) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (d) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163−3166. (e) Wei, Z. Y.; Li, S. J. Wang, D.; Chan T. H. *J. Org. Chem.* **1989**, *54*, 5768−5774. (f) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron* Lett. **1987**, *28*, 973−976. 1(g) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128−4130. (h) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271−7274. (i) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387−8390. (j) Ramesh, J.; Vitale, J.; Rychnovsky, S D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905. (k) Colobert, F.; Des Mazery, R.; Solladie, G.; Carreno, M. C.; Urbano, A. *J. Org. Chem.* **2003**, *68*, 7779−7787. (l) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426−3427. (m) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662−15663.

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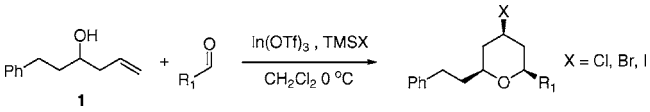
halides as additives with suppression of epimerization. The efficiency and practicality of this method is demonstrated by the highly convergent enantioselective synthesis of (−)-centrolobine. We envisage that a catalytic amount of Lewis acid such as an indium[3] complex will catalyze the formation of the oxonium ion for the Prins cyclization. The carbocation can then be trapped with halide using trimethylsilyl halide[1j] as additive. Therefore, 1-phenylhex-5-en-3-ol, **1**, was subjected to various aldehydes in the presence of a catalytic amount of $In(OTf)_3$ (Scheme 1). The results are summarized in Table 1.

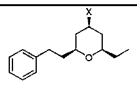
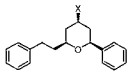
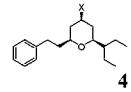
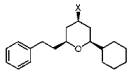
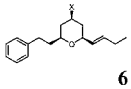
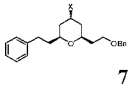
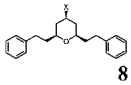
Scheme 1. Prins Cyclizations with Trimethylsilyl Halides



In all cases, the Prins cyclization with various aldehydes proceeded to form crossed 4-halo-2,6-trisubstituted THP products with moderate to excellent yields. Especially noteworthy is the excellent stereoselectivity observed where only the all-cis configuration products were obtained. Furthermore, the reaction also worked well for α,β-unsaturated aldehydes and was insensitive to the steric and electronic influences of the substrates. Note that the trimethylsilyl halide additives serve as sources of halides and have been shown to work well to afford the corresponding halide containing THP compounds.

Next, we applied this methodology to the enantioselective synthesis of (−)-centrolobine,[4] **17**, isolated from the heartwood of *Centrolobium robustum*.[5] The retrosynthetic analysis is outlined in Scheme 2.

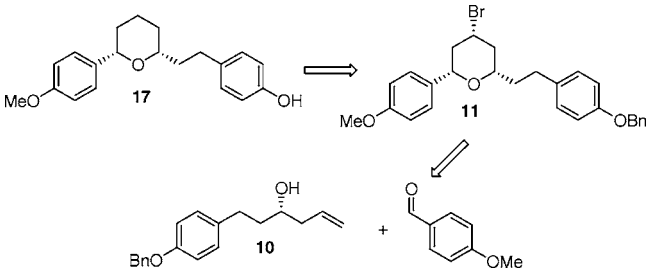
Table 1. Catalytic Prins Cyclizations with Trimethylsilyl Halides[a]

entry	R^1	product	yield (%) a (X = Cl)	b (X = Br)	c (X = I)
1	$-CH_2CH_3$	 **2**	71	76	82
2	-Ph	 **3**	74	82	82
3	$-CH(CH_3CH_2)_2$	 **4**	76	81	91
4	-Cy	 **5**	67	86	89
5	$-CH{=}CHCH_2CH_3$	 **6**	77	82	83
6	$-(CH_2)_2OBn$	 **7**	61	66	64
7	$-CH_2CH_2Ph$	 **8**	94	83	86

[a] Note: 5% yield of the *meso*-product **8** was obtained in each of the entries 1−6. *Meso*-products containing fragments of R^1 were not observed.

We proposed two key steps to obtain the chiral THP backbone. The first step was the asymmetric allylation of 3-(4-benzyloxy)phenyl)propanal, **15**, using (*R*)-BINOL indium complex and allyltributyltin as allylating agent,[6] recently reported by our group. The second key step of the reaction would be the formation of 4-bromo-THP ring via catalytic Prins cyclization, the main focus in this paper.

Scheme 2. Retrosynthetic Analysis of (−)-Centrolobine



The asymmetric allylation of **15** proceeded well to give **10** in moderate yield and 84% ee. We subsequently encountered the problem of epimerization in the catalytic Prins cyclization reaction. The use of 20 mol % of $In(OTf)_3$ in

(2) (a) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Hughes, R. A.; Simpson, T. J.; Smith, R. W.; Willis, C. L.; Harding, J. R.; King, C. D. *Chem. Commun.* **2001**, 835−836. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580. (c) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407−3410. (d) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6609−6610. (e) Nokami, J.; Anthony, L.; Sumida, S.-I. *Chem. Eur. J.* **2000**, *6*, 2909−2913. (f) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168−9169. (g) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450−2451. (h) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921−2922. (i) Loh, T.-P.; Lee, C.-L. K.; Tan, K.-T. *Org. Lett.* **2002**, *4*, 2985−2987. (j) Hussain, I.; Komasaka, T.; Ohga, M.; Nokami, J. *Synlett* **2002**, *4*, 640−642.

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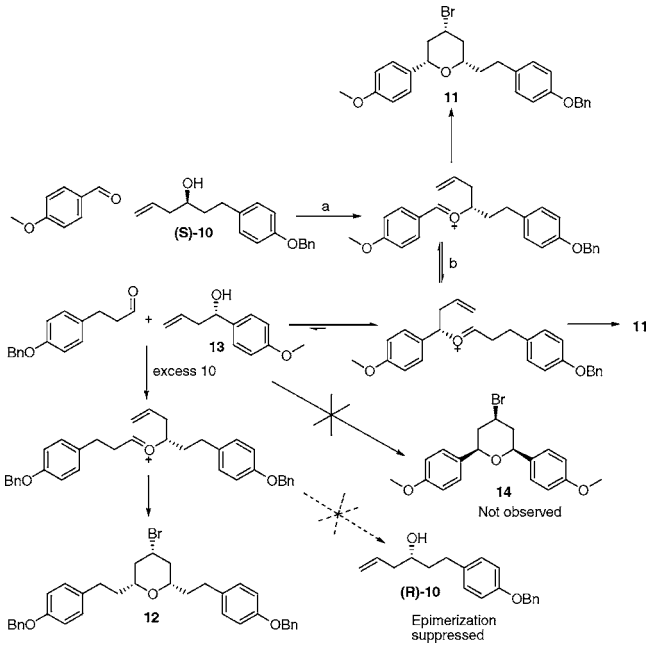
(4) For other synthees of (−)-centrolobine: (a) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919−3922. (b) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883−3885. (c) Colober, F.; Mazery, R. D.; Solladie, G.; Carreno, M. *Otg. Lett.* **2002**, *4*, 1723−1725. (d) Jennings, Michael P.; Clemens, Ryan T. *Tetrahedron Lett.* **2005**, *46*, 2021−2024. (e) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609−1610. (f) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadere, B. *Tetrahedron Lett.* **2004**, *45*, 6603−6605. (g) Clarke, Paul A.; Martin, William H. C. *Tetrahedron Lett.* **2004**, *45*, 9061−9063.

(5) (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964**, 287. (b) Galeffi, C.; Giulio Casinovi, C.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1965**, *95*, 95−100.

(6) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, *10*, 1318−1320.

the THP ring formation yielded the desired product **11** with an 8% reduction in ee (Scheme 3). This is in contrast to

Scheme 3. Mechanistic Interpretation of Catalytic Prins Cyclization without Racemization[a]



[a] Note: (a) the alcohol is treated to various conditions to achieve suppression of epimerization in the presence of TMSBr and *p*-anisaldehyde; (b) allyl transfer pathway.

previously established results[1,2h] where severe epimerization was observed in similar reactions. We envisaged that the rate of Prins cyclization might be much faster than the rate of epimerization in a catalytic system. A reduction in temperature, catalyst loading, and Lewis acidity of the reaction may be factors that can retard the allyl transfer process, which in turn would influence epimerization. This prompted us to carry out a series of experiments to further investigate methods to suppress the epimerization (Figure 1, Table 2).

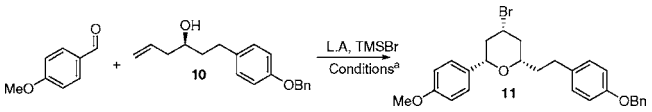


Figure 1. Synthetic studies toward (−)-centrolobine. [a]Conditions are specified in Table 2.

It was found that reduction in both temperature and catalyst loading failed to suppress epimerization. However, with a weaker Lewis acid like $InBr_3$, we achieved comparable yield and retention of enantiomeric purity after the reaction. It can be concluded that Lewis acidity must have played an important role in reducing the rate of epimerization (Scheme 3).

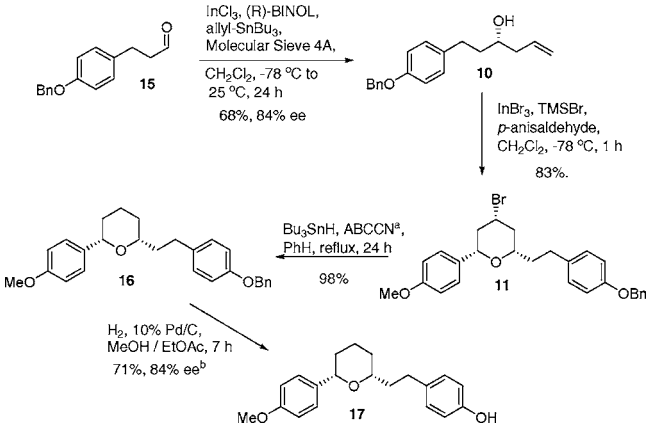
Table 2. Optimization of Reaction Conditions for Chiral 4-Bromo-THP Ring Intermediate **11**

entry	LA[a] (equiv)	TMSBr[b] (equiv)	*T* (°C)	time (h)	yield (%)	ee[c] (%)
8	$In(OTf)_3$ (0.2)	1.2	0	2	88	76
9	$In(OTf)_3$ (0.05)	1.2	−78	1	87	78
10	$In(OTf)_3$ (0.05)	2.5	0	1	72	76
11	$InBr_3$ (0.1)	1.2	−78	1	83	84

[a] Amount of Lewis acid in the reaction with respect to *p*-anisaldehyde. [b] Amount of TMSBr in the reaction with respect to *p*-anisaldehyde. [c] The reactions were carried out with the alcohol (1-(4-(benzyloxy)phenyl)hex-5-en-3-ol) with 84% ee.

In all of the experiments, we obtained approximately 5% of **12** in the purified products. No formation of **10** and **14** was observed. It was obvious that the allyl transfer process has taken place with absolute chirality transfer to *p*-anisaldehyde, forming **13**. Since the rate of allyl transfer has been completely retarded, asymmetric Prins cyclization became the dorminant process, accomplished with complete retention of ee. This study thus provides a valuable insight into the characteristics of the oxonium species in Lewis acid mediated reactions. Most importantly, however, the surmounting of this second key step in our efforts toward the synthesis of (−)-centrolobine allowed us to realize our synthetic strategy. We thus proceeded to synthesize (−)-centrolobine (Scheme 4) in accordance with our retrosynthetic plan.

Scheme 4. Synthesis of (−)-Centrolobine[a]



[a] Key: (a) ABCCN denotes 1,1′,-azobis(cyclohexane) carbonitrile; (b) overall yield (over four steps) is 46%.

In conclusion, we have reported a versatile catalytic Prins cyclization to synthesize 4-halo-THP rings using trimethylsilyl halides as additives. The problems of substrate limitations and epimerization in conventional Prins cyclization have been overcome, as demonstrated in the total enantiomeric synthesis of (−)-centrolobine. All in all, the use of

our strategy demonstrated both efficiency as well as effectiveness in natural product synthesis. Further works on the total synthesis of other natural products with the THP backbone are currently in progress.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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