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Lewis acid-catalyzed one-pot crossed Prins cyclizations using allylchlorosilane as allylating agent

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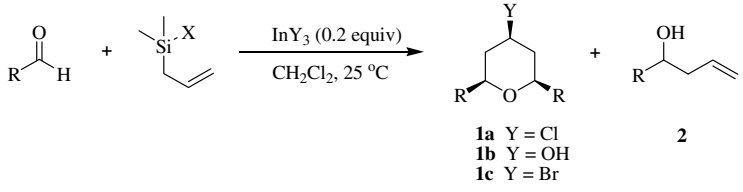
Abstract—A one-pot multi-component Lewis acid-catalyzed Prins cyclization was developed with high yield and selectivity. The crossed 2,4,6-trisubstituted tetrahydropyran products were formed with high stereoselectivity. This catalytic method could also be used with α,β-unsaturated aldehydes affording moderate yields of products.

Tetrahydropyran rings are part of the backbones of many complex natural products.[1] Prins cyclization offers a diverse olefin–aldehyde condensation method for the formation of pyran rings.[2] The use of strong mineral acids (e.g., sulfuric acid) or Lewis acids (e.g., $AlCl_3$) in such reactions has previously been reported. Such harsh conditions often result in unwanted polymerized products, and are also not applicable to aromatic or conjugated aldehydes. The development of various Lewis acid-promoted condensations[3] offers elegant and efficient methods for the synthesis of both *meso* and unsymmetrical 2,4,6-trisubstituted tetrahydropyrans. One very good example was described by Li and co-workers[3c] using $InCl_3$ to achieve high-yielding Prins cyclization products. However, the Lewis acids were used in stoichiometric amounts, and hence did not play a catalytic role in the reaction. Despite many applications of Prins cyclizations, interest in achieving stereoselective crossed Prins cyclizations and to reduce its substrate limitations remains unabated. Our group has developed a simple, one-pot Prins cyclization catalyzed by mild indium-based Lewis acids in allylsilane (Scheme 1).

The product formed is highly dependent on three factors: (i) the type of acid catalyst used; (ii) the type and amount of silicon-based reagent; (iii) the sequence of aldehyde addition. When we introduced an aldehyde and a derivatized silane into a Lewis acid system, we obtained primarily the *meso* products shown in Table 1. The homoallylic alcohol **2** was obtained as the major product when excess allylsilane was employed (Table 1, entry 3).[4] Slow addition of the aldehyde to a solution of allylsilane and Lewis acid is also critical in obtaining the homoallylic alcohol. Addition of a mixture of allylsilane and aldehyde into a dilute solution of the Lewis acid yielded the 2,4,6-trisubstituted tetrahydropyran instantaneously.

When allylsilanol was used with $InCl_3$, the 4-chloro tetrahydropyran was obtained in moderate yield,



1a Y = Cl
1b Y = OH
1c Y = Br

2

Scheme 1.

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Table 1. Direct Prins cyclization with allylchlorosilane or allylsilanol (R = $PhCH_2CH_2$–)

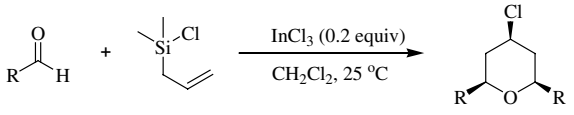
Entry	X	Y	Allylsilane (equiv)[a]	Yield (%)			
				1a	**1b**	**1c**	**2**
1	Cl	Cl	1.2	67	—	—	14
2	Cl	Cl	2.0	10	—	—	76
3	**Cl**	**Cl**	**3.0**	**6**	—	—	**83**
4	OH	Br	1.2	—	23	36	—
5	OH	F	1.2	—	48	—	—
6	**Cl**	**OTf**	**1.2**	**90**	**5**	—	—
7	OH	Cl	1.2	53	3	—	4
8	OH	OTf	1.2	—	68	—	23

[a] Amount of allylsilane with respect to aldehyde.

whereas only the 4-hydroxy product was observed when $In(OTf)_3$ was employed. Unexpectedly, the 4-hydroxy product was also observed using InF_3, possibly due to the high affinity of fluoride to silicon.

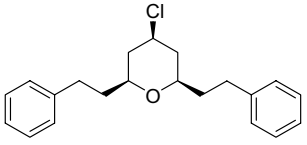
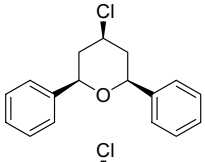
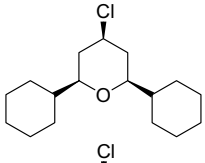
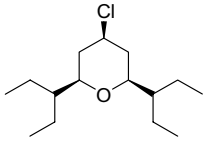
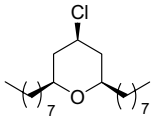
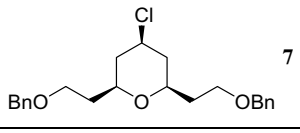
The chloride at the 4-position of the 2,4,6-trisubstituted tetrahydropyran must come from the allylchlorosilane when we used a catalytic amount of $In(OTf)_3$. Hence the use of excess Lewis acid is avoided compared to the recently reported methods. The reaction also produced equivalent yields and selectivity in a 1% water–CH_2Cl_2 mixture, showing excellent tolerance of the catalytic species to the presence of a controlled amount of moisture.[5]

The optimized method[6] (Scheme 2) produced the Prins cyclized products in moderate to high yields for aliphatic aldehydes (Table 2), but no desired product was obtained with conjugated systems such as cinnamaldehyde or *trans*-2-pentenal.



Scheme 2.

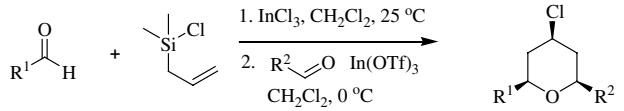
Table 2. *meso*-4-Halo-tetrahydropyrans prepared via one-pot indium-silyl Prins cyclization

Entry	R	Time (h)	Product	Yield
1	$PhCH_2CH_2$–[9]	2	 **1a**	90
2	Ph–	4	 **3**	45
3	Cy–	2	 **4**	65
4	$(C_2H_5)_2CH$–	1	 **5**	94
5	$CH_3(CH_2)_7$–	1	 **6**	65
6	$BnO(CH_2)_2$–	4	 **7**	45

By increasing the amount of allylchlorosilane, the homoallylic alcohol was formed predominantly. Addition of more aldehyde promoted in situ Prins cyclization. Hence we developed a one-pot crossed Prins cyclization (Scheme 3)[7] with high yields and selectivity (Table 3).

As we expected, the use of mild Lewis acid conditions and the step-wise formation of homoallylic alcohol enabled the coupling of an α,β-unsaturated aldehyde to form **12**, a structure, which has potentially high synthetic value (Table 3, entry 5).

Furthermore, the X-ray crystal structure of 4-chloro-2,6-dicyclohexyltetrahydro-2*H*-pyran **4** revealed that only the *syn* product was observed in both the *meso* and the crossed 2,4,6-trisubstituted tetrahydropyran product (Fig. 1).[8] This is consistent with the results established by Li and co-workers.[3c]



Scheme 3.

Table 3. Crossed Prins cyclization (R^1 = $PhCH_2CH_2$)

Entry	R^2	Product	Yield (%)
1	$-CH_2CH_3$	**8**	83
2	–Ph	**9**	85
3	$-CH(CH_3CH_2)_2$	**10**	89
4	–Cy	**11**	68
5	$-CH{=}CHCH_2CH_3$	**12**	70
6	$-(CH_2)_2OBn$	**13**	65

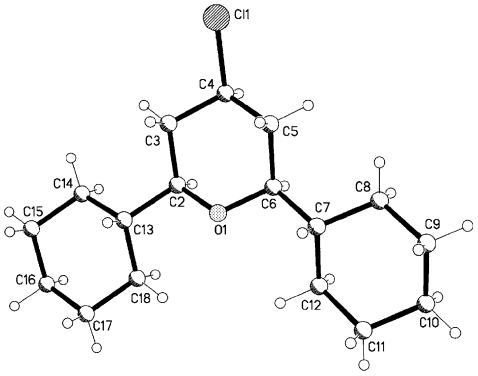


Figure 1. Crystal structure of 4-chloro-2,6-dicyclohexyltetrahydro-2*H*-pyran, showing the all-*cis* configuration at the 2, 4, and 6 positions.

In summary, we have successfully demonstrated that a catalytic amount of an indium Lewis acid can catalyze a one-pot crossed Prins cyclization with high yield and stereoselectivity. Further investigations on the mechanism and applications are in progress.

Acknowledgements

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References and notes

1. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinham, 1996.
2. (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672; (b) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505–555.
3. (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; (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.
4. For mechanistic studies on allylsilane and allyllation reactions, see: (a) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963–4965; (b) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153–4156; (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793; (d) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295–1298; (e) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673–1675.
5. For more information, see: Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New-York, 1997.
6. General procedure for the synthesis of *meso*-4-halo-tetrahydropyrans: $In(OTf)_3$ (0.225 g, 0.4 mmol) was stirred in CH_2Cl_2 (18 mL) to form a suspension. A mixture of

allylchlorodimethylsilane (0.323 g, 2.4 mmol) and aldehyde (2 mmol) in CH_2Cl_2 (2 mL) was added to the suspension at room temperature. The mixture was stirred for at least 1 h, then quenched with saturated $NaHCO_3$ solution. After stirring for 15 min, the mixture was extracted with ether (3×20 mL). The combined organic phase was successively washed with water (2×15 mL), saturated brine (2×10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

7. General procedure for the synthesis of crossed 4-chlorotetrahydropyrans: allylchlorodimethylsilane (0.336 g, 2.5 mmol) and $InCl_3$ (0.044 g, 0.2 mmol) were stirred in CH_2Cl_2 (4 mL) to form a suspension. A solution of hydrocinnamaldehyde (1 mmol) in CH_2Cl_2 (1 mL) was added to the suspension at room temperature. The mixture was stirred for at least 1 h, and then cooled to 0 °C. The mixture was diluted with CH_2Cl_2 (4 mL), and then a solution of aldehyde in CH_2Cl_2 (1 mL) was added over a period of 5 min. The mixture was allowed to stir at 0 °C for at least 0.5 h, then quenched with saturated $NaHCO_3$ solution. After stirring for 15 min, the mixture was extracted with ether (3×20 mL). The combined organic phase was successively washed with water (2×15 mL), saturated brine (2×10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.
8. CCDC 246493 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
9. Characterization of product **1a**: white solid after purification on silica gel (ether–hexane = 1:99): IR (neat, NaCl) 3025, 2914, 2838, 1494, 1319, 1082 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.19 (m, 10H), δ 3.96 (tt, $J = 4.53$, 11.85 Hz, 1H) 3.26 (m, 2H), 2.86 (m, 2H), 2.76 (m, 2H), 2.11 (dd, $J = 4.18$, 12.2 Hz, 2H), 1.92 (m, 2H), 1.78 (m, 2H), 1.57 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.8, 128.5, 128.4, 125.9, 75.4, 55.8, 42.6, 37.4, 31.7.