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A Novel Stereoselective Cyclization to Functionalized Dihydropyrans

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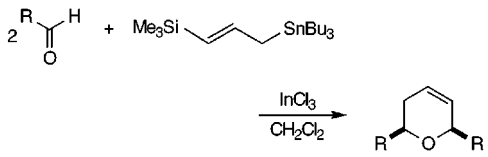
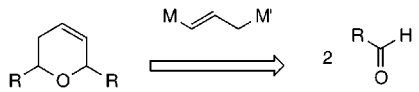
ABSTRACT



An indium trichloride-mediated highly diastereoselective tandem carbonyl allylation–Prins cyclization–chlorination of aldehydes with allylstannane-generated 4-halotetrahydropyrans in high yields. The reaction of 3-trimethylsilylallyltributylstannane with aldehydes led to the formation of 2,6-dialkyl-3,4-dihydropyrans with a *cis* diastereoselectivity.

Tetrahydropyran is the structural core of most carbohydrates and their polymers. These materials are the most abundant biological molecules on earth and play several crucial roles in living organisms. They are found in the cell walls and the protective coatings of many organisms and also fuel various metabolic processes. In addition to being the structural core of carbohydrates, many biologically important natural products and potential pharmaceutical agents bear tetrahydropyran structures. Thus, many efforts have been made toward the synthesis of tetrahydropyran type compounds.[1] Examples are via hetero-Diels−Alder reactions,[2] oxiranyl anions,[3] carbonyl ylides,[4] Claisen rearrangements,[5] ring opening of epoxides,[6] iodocyclizations,[7] olefin metathesis,[8] and others. Among the various methods for tetrahydropyran syntheses, the hetero-Diels−Alder and the olefin-metathesis approaches provide dihydropyrans in which the unsaturation provides a handle and versatility for attaching additional functionalities. Recently, the potential of using the Prins cyclization[9] for synthesizing tetrahydropyran derivatives has been recognized.[10] By using cross-cyclizations between aldehydes and homoallyl alcohols, tetrahydropyrans were obtained. We wish to report here a new cyclization that generates functionalized dihydropyrans stereoselectively (Scheme 1).

Scheme 1



Because of their effectiveness in controlling reactivity and selectivity as well as the mildness of the reaction conditions, allylstannanes have been widely used in synthesis (such as allylation of aldehydes).[11] To start our research, we examined the formation of tetrahydropyrans via a tandem allylation−cyclization of aldehydes **1** with allylstannane **2** (Scheme 2). The milder conditions associated with the tin reaction were envisioned as advantageous for the formation of dihydropyrans.

When a mixture of 2 equiv of benzaldehyde and 1 equiv of allyltributylstannane was stirred with indium chloride in methylene chloride at room temperature, the disappearance

(1) For a review, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(2) For a review, see; Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19. Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.
(3) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849.
(4) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.
(5) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
(6) For an example, see: Nicolaou, K. C.; Prasad, C. V. C.; Somers, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
(7) For a review, see: Bartlett. P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984, Vol. 3, Part B, Chapter 6.
(8) For examples of cycloether formations, see: Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192. Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321 and references therein. For a review, see: Grubbs, R. H.; Chang, *S. Tetrahedron* **1998**, *54*, 4413.

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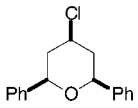
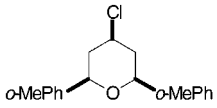
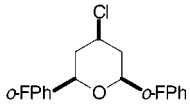
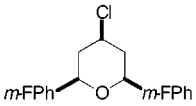
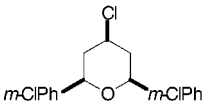
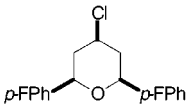
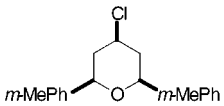
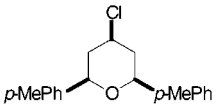
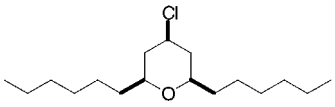
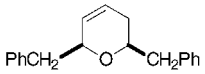
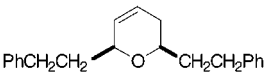
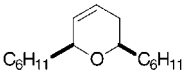
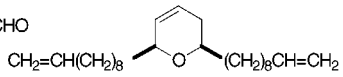
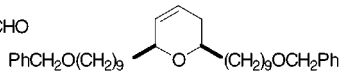
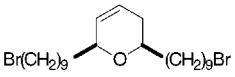
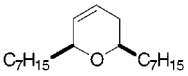
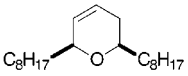
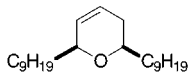
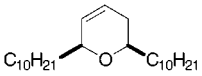
Table 1. Tetrahydropyran Derivatives via Indium Trichloride-Mediated Tandem Allylation−Cyclization Reaction[a]

Entry	RCHO (**1**)	Product (**3**)	Yield (%)*
1	PhCHO		72
2	*o*-MePhCHO		60
3	*o*-FPhCHO		90
4	*m*-FPhCHO		75
5	*m*-ClPhCHO		70
6	*p*-FPhCHO		80
7	*m*-MePhCHO		60
8	*p*-MePhCHO		25
9	$C_6H_{13}CHO$		69

[a] All reactions were carried out in methylene chloride at room temperature. An asterisk indicates that the yields are isolated yields after flash column chromatography.

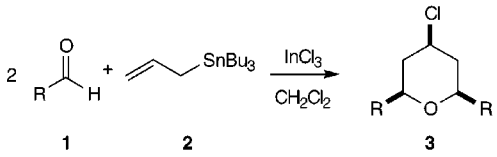
Table 2. Dihydropyran Derivatives via Indium Trichloride-Mediated Tandem Allylation−Cyclization Reaction[a]

Entry	RCHO	Product (**5**)	Diastereoselectivity Yield (%)*
1	$PhCH_2CHO$		(8:1) 68
2	$PhCH_2CH_2CHO$		(7.5:1) 57
3	$C_6H_{11}CHO$		(6:1) 69
4	$CH_2=CH(CH_2)_8CHO$		(7:1) 50
5	$PhCH_2O(CH_2)_9CHO$		50[a]
6	$Br(CH_2)_9CHO$		(>20:1) 51
7	$C_7H_{15}CHO$		(5:1) 55
8	$C_8H_{17}CHO$		(8.5:1) 59
9	$C_9H_{19}CHO$		(5:1) 61
10	$C_{10}H_{21}CHO$		(>10:1) 65

[a] All reactions were carried out in methylene chloride under an atmosphere of air and at room temperature. Asterisk indicates that the yields are isolated yields after flash column chromatography. Diastereoselectivities were determined by GC-MS and ^{1}H NMR. a: no diastereomer was detected by NMR or GC-MS.

of the starting materials was observed by TLC within 5 h. To ensure that the reaction was complete, the stirring was continued overnight. After the reaction mixture was concentrated in vacuo, the ^{1}H NMR spectrum of the crude reaction mixture showed a clean conversion of benzaldehyde to the cyclization product **3**. Subsequently, column chromatography of the crude product on silica gel provided 4-chloro-2,6-diphenyltetrahydropyran in 72% yield. Due to partial overlap of the product with a tin derivative, some product was lost during the isolation. By comparing the spectroscopic data with our earlier studies as well as literature reported values, the product was identified as the stereoisomer in which the two phenyl groups and the chlorine are all equatorial. The diastereoselectivity for the reaction was estimated to be greater than 10:1 as the formation of the other diastereomer (cis-trans-cis) was vaguely observable in the ^{1}H NMR of the crude material and was not isolated. When allylsilane was used for the cyclization, under the same reaction conditions, a low (ca. 20%) conversion was observed. Other compounds including both aromatic and

Scheme 2

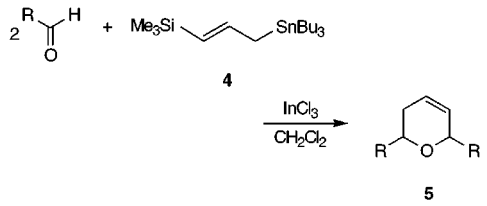


1 2 3

aliphatic aldehydes were similarly converted into 4-chlorotetrahydropyran derivatives (Table 1).

The promising results of the tetrahydropyran study led us to investigate the formation of dihydropyrans as illustrated in Scheme 3. When aromatic aldehydes were stirred with

Scheme 3



tin−silicon reagent **4**,[12] together with indium chloride in methylene chloride at room temperature, disappearance of the starting materials was observed overnight. However, no distinctive product was obtained with these aldehydes. On the other hand, when an aliphatic aldehyde was used, the reaction led to the smooth formation of the desired dihydropyran product **5**. The ^{1}H NMR of the crude material revealed predominantly a single diastereomer (see Table 2 for diastereoselectivities) together with unidentified polymeric materials in each case. The stereochemistry of the main product was assigned by comparing the ^{1}H NMR data with our tetrahydropyran derivatives as well as by NOE experiments. Consequently, various aliphatic aldehydes were similarly reacted with the tin−silicon reagent to generate the corresponding dihydropyrans (Table 2). It should be pointed out that although the reaction of aromatic aldehydes did not lead to the cyclization product, aliphatic aldehydes bearing aromatic substituents did not affect the cyclization (entries, 1, 2, and 5). A halogen (entry 6), a benzyl ether (entry 5), and an olefin (entry 4) all survive the reaction conditions.

In conclusion, an indium trichloride-mediated tandem carbonyl allylation−Prins cyclization−chlorination of aldehydes with allylstannane generated 4-halotetrahydropyrans diastereoselectively. The reaction of 3-trimethylsilylallyltributylstannane with aldehydes mediated by indium chloride led to a diastereoselective formation of 2,6-dialkyl-3,4-dihydropyrans. Presently, the synthetic potential of this new dihydropyran formation is under investigation.

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(9) For reviews, see: Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505. Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. Snider, B. B. In *Comprehensive Organic Synthesis*; Trost. B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 527−561.

(10) For examples, see: Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441. Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913. Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768. Chan, T. H.; Arya, P. *Tetrahedron Lett.* **1989**, *30*, 4065. Metzger, J. O.; Biermann, U. *Bull. Soc. Chim. Belg.* **1994**, *103*, 393. Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *37*, 141. Markó, I. E.; Chellé, F. *Tetrahedron Lett.* **1997**, *38*, 2895. Markó, I. E.; Dobbs, A. P.; Bayston, D. J. *Tetrahedron lett.* **1997**, *38*, 2899. Markó, I. E. In *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Springer: Germany, 1998. Semeyn, C.; Blaauw, R. H. Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Commun. (Cambridge)* **1999**, 291. Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. Samoshin, V. V.; Gremyachinskiy, D. E.; Gross, P. H. *Mendeleev Commun.* **1999**, 53. Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett.* **1999**, *40*, 1153.

(11) For some examples, see: Fleming, I. In *Comprehensive Organic Synthesis*; Trost. B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 563−593. Maruyama, K.; Naruta, Y. *Chem. Lett.* **1978**, 431. Gambaro, A.; Peruzzo, V.; Plazzohna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45. Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1979**, 917. Keck, G. E.; Gressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345. Gung, B. W.; Smith, D. T.; Wolf, M. A. *Tetrahedron Lett.* **1991**, *32*, 13. Evans, D. A.; Dart, M. J.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619. Wang, D. K.; Dai, L. X.; Hou, X. L. *Tetrahedron Lett.* **1995**, *36*, 8649. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920. Nakamura, H.; Iwama, H.; Yamamoto, Y. *Chem. Commun.* **1996**, 1459. Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714. Thomas, E. J. *Chem. Commun.* **1997**, 411. For a review on allylation of carbonyl compounds, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(12) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083.