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LETTERS

Highly Effective Synthesis of 4-Halo-Tetrahydropyrans *Via* A Highly Diastereoselective *in situ* Prins-Type Cyclization Reaction

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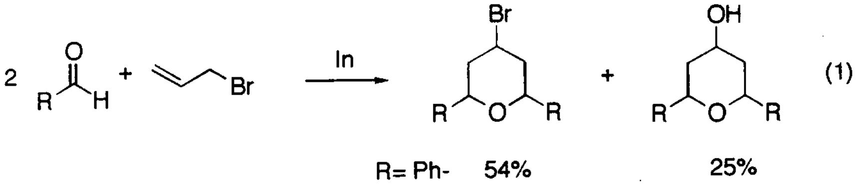
Abstract: *The reaction of aldehyde with homoallyl alcohols mediated by indium trichloride generated 4-chlorotetrahydropyrans in high yields and with high stereoselectivity. The same type of compounds can be generated through a single step, multi-component coupling between aldehyde and allyl bromide mediated by indium* © 1999 Elsevier Science Ltd. All rights reserved.

The acid-catalyzed olefin-aldehyde condensation, known as the Prins reaction, is a fundamental reaction for carbon-carbon bond formation.[1] However, the synthetic application of this important reaction has been underexplored due to the classical conditions of strong acids (e.g., sulfuric acid) and high reaction temperatures, which often generated a range of products. The pyran ring is part of the backbone of various important carbohydrates and natural products.[2] Recently, during our investigation of indium-mediated reactions under neat conditions (Eq. 1),[3] we sometimes observed an instant polymerization of the reaction mixture. Although they initially eluded our attention, a subsequent analysis of the mixture revealed the presence of small amount of tetrahydropyran derivatives.[4]



To explain the formation of the tetrahydropyran derivatives, we postulated that the product was generated through a tandem carbonyl allylation-hemiacetal formation-Prins reaction (Scheme 1). In order to test the viability of the proposed reaction pathway, we conceived that the reaction of a homoallyl alcohol with an aldehyde should generate the corresponding tetrahydropyran derivatives in the presence of an indium halide. In addition, the reaction could be pushed to a single 4-halo derivative rather than a mixture of alcohol and

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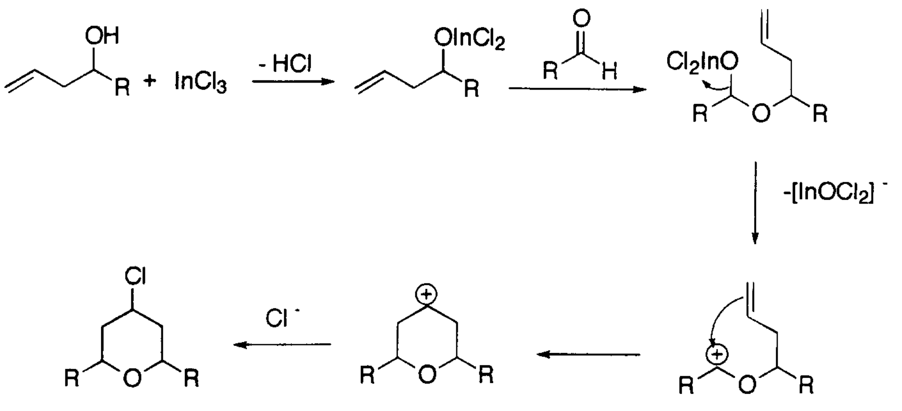
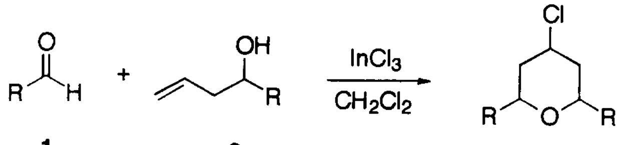
halide. We report here that an intramolecular Prins-type cyclization mediated by indium trichloride generates tetrahydropyran derivatives in high yields with high diastereoselectivity (Eq. 2).[5]



Scheme 1. Proposed Mechanism for the Indium Trichloride Mediated Tetrahydropyran Formations



1 **2** **3**

(2)

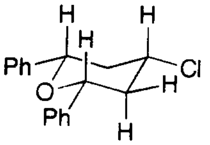
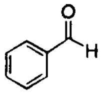
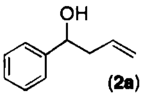
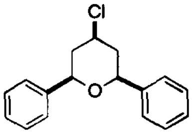
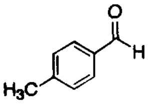
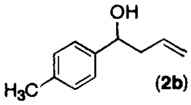
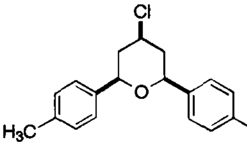
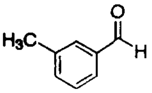
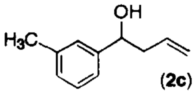
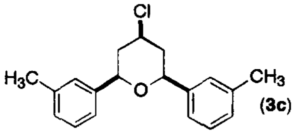
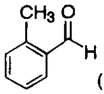
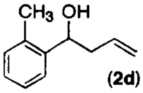
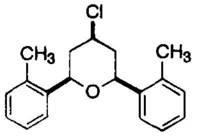
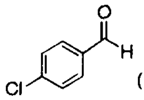
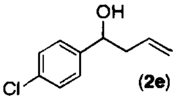
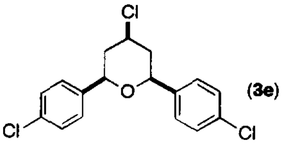
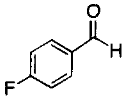
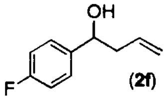
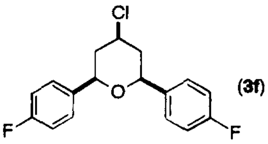
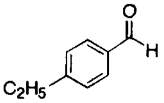
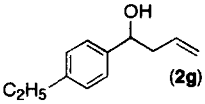
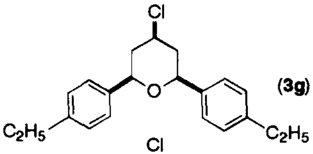
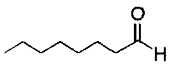
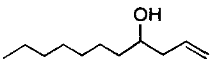
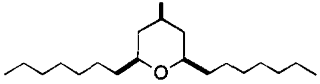


Figure 1.

When a mixture of benzaldehyde and 1-phenyl-3-buten-1-ol was stirred with indium chloride in methylene chloride at room temperature, the diasppearence of the starting materials was observed by TLC over 2 h. The reaction mixture was concentrated in vacuo and the ^1H NMR spectrum of the crude reaction mixture showed a quantitative conversion of the homoallyl alcohol to the cyclization product. Subsequently, column chromatography of the crude product on silica gel provided 4-chloro-2,6-diphenyltetrahydropyran in 81% yield. By comparing the spectroscopic data with literature reported values, the product was identified as the stereoisomer in which the two phenyl groups and the chlorine are equatorial (Fig. 1).[5] The predominant formation of this particular stereoisomer is most likely due to thermodynamic effect. Other compounds including both aromatic and aliphatic substrates were similarly converted into 4-chlorotetrahydropyran derivatives with both a high yield and high stereoselectivity. This is in contrast to the reported method of titanium tetrachloride and aluminum trichloride, with which low yield or no reaction was observed when both the aldehyde and the alcohol are aromatic.[5] The present method also avoids the use of inert gas to prevent the hydrolysis of the highly hydroscopic titanium and aluminum halides. Other solvents such as chloroform, hexane, toluene, tetrahydrofuran, and ether were less effective for the reaction. The reaction also proceeds in

Table 1. Tetrahydropyranols *via* Indium Trichloride Mediated Prins-Type Cyclization

Entry	RCHO (1)	RCH(OH)CH$_2$CH=CH$_2$ (2)	Product (3)	Isolated Yield(%)
1	 (1a)	 (2a)	 (3a)	81%
2	 (1b)	 (2b)	 (3b)	79%
3	 (1c)	 (2c)	 (3c)	76%
4	 (1d)	 (2d)	 (3d)	88%
5	 (1e)	 (2e)	 (3e)	70%
6	 (1f)	 (2f)	 (3f)	78%
7	 (1g)	 (2g)	 (3g)	73%
8	 (1h)	 (2h)	 (3h)	73%

the presence of a small amount of water,[6] but this slightly decreases the reaction rate and the yield of the product. In conclusion, we have developed highly effective, stereoselective method for the preparation of 4-chloro-tetrahydropyran derivatives. Presently, we are evaluating the synthetic potential of the indium-mediated as well as the indium trichloride catalyzed syntheses.

A typical experiment follows:

To a mixture of benzaldehyde (53 mg, 0.50 mmol) and 1-phenyl-3-buten-1-ol (82 mg, 0.55 mmol) in 3 mL of methylene chloride, which was pre-dried with 4Å molecular sieve overnight, was added indium chloride (133 mg, 0.60 mmol) in one portion. The reaction flask was capped with a rubber septum and the mixture was stirred at room temperature for 4h. The reaction mixture was concentrated in vacuo to give crude product which was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10 :1) (yield 110 mg, 81%).

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4. Identification and isolation of these compounds were initially carried out by G. S. Viswanathan in the author list.
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