

Scandium triflate catalyzed *in situ* Prins-type cyclization: formations of 4-tetrahydropyranols and ethers

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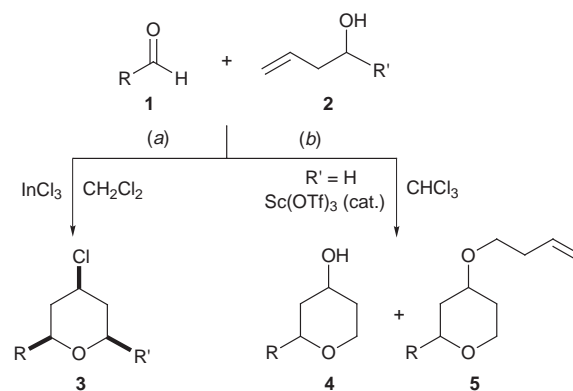
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The reaction of aldehydes with homoallyl alcohols catalyzed by scandium triflate generates tetrahydropyran-4-ol and ethers in good yields.

The acid-catalyzed olefin–aldehyde condensation, known as the Prins reaction, is one of the fundamental reactions for carbon–carbon bond formation.¹ However, the synthetic application of this important reaction has been under-explored due to the classical conditions of strong acids (*e.g.* sulfuric acid) and high reaction temperatures, which often generate a mixture of a range of products. The importance of the tetrahydropyran ring is exemplified by the ring's function as the backbone of various carbohydrates and natural products.² Its importance calls for the continuing search for methods of synthesizing tetrahydropyran derivatives.³ Recently, during our investigation of indium-mediated reactions under solventless conditions,⁴ we observed the formation of tetrahydropyran-4-ols and 4-bromotetrahydropyran derivatives. In order to explain the formation of the tetrahydropyran derivatives, we postulated that the product was generated through a tandem carbonyl allylation–hemiacetal

formation–Prins reaction. We speculated that the reaction of a homoallyl alcohol with an aldehyde should generate the



Scheme 1

Table 1 Tetrahydropyran derivatives *via* $\text{Sc}(\text{OTf})_3$ catalyzed Prins-type cyclization

Entry	RCHO	Product (% yield)		Overall yield (%)	Entry	RCHO	Product (% yield)		Overall yield (%)
		4	5				4	5	
1	1a	4a (14)	5a (63)	77	8	1h	4h (17)	5h (49)	66
2	1b	4b (19)	5b (50)	69	9	1i	4i (14)	5i (72)	86
3	1c	4c (12)	5c (57)	69	10	1j	4j (20)	5j (58)	78
4	1d	4d (16)	5d (69)	85	11	1k	4k (13)	5k (62)	75
5	1e	4e (13)	5e (71)	84	12	1l	4l (18)	5l (64)	82
6	1f	4f (11)	5f (65)	76	13	1m	4m (10)	5m (56)	66
7	1g	4g (15)	5g (68)	83	14	1n	4n (9)	5n (70)	79

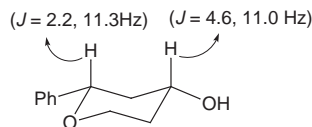


Fig. 1 Coupling constants in **4a**.

corresponding tetrahydropyran derivatives. Subsequently, by controlling the reaction conditions, we have developed an efficient synthesis of 4-chlorotetrahydropyrans **3** mediated by indium trichloride [Scheme 1, route (a)].⁵ We also conceived that if we replaced the chloride ion with a non-nucleophilic anion, then the tetrahydropyranol **4** or its ether **5** would become the major products [route (b)]. However, to do so we would need a Lewis acid to facilitate the Prins reaction. It appears that the scandium triflate chemistry developed by Kobayashi and others would be the best choice for this reaction.⁶ Here, we report that the reaction of aldehydes with homoallyl alcohols catalyzed by scandium triflate generates the corresponding desired products readily (Scheme 1).⁷

When a mixture of benzaldehyde and but-3-en-1-ol was stirred with $\text{Sc}(\text{OTf})_3$ in CHCl_3 under a refluxing temperature overnight, 63% of a tetrahydropyran ether **5a** was isolated together with 14% of the corresponding tetrahydropyranol **4a**.[†] Measurement of the coupling constants of the benzylic hydrogen ($J = 2.2$ and 11.3 Hz) as well as the hydrogen on the

carbon bearing the hydroxy group ($J = 4.6$ and 11.0 Hz) of the tetrahydropyranol **4a** indicated a structure where the hydroxy and the phenyl groups are in a *cis* relationship and are equatorial (Fig. 1). The formation of other stereoisomers is negligible as shown by the ^1H NMR measurement of the crude reaction mixture. A variety of other aromatic aldehydes reacted similarly generating the corresponding products (Table 1) in good isolated (overall) yields. Aliphatic aldehydes were less effective for the reactions. Other solvents that we have tested (such as CH_2Cl_2 , hexane, toluene, THF and Et_2O) were not as effective as CHCl_3 for the reaction. The catalytic cycle of this Prins-type reaction is postulated in Scheme 2. A similar mechanism has been used to explain a cross-allylation of aldehydes by Nokami and co-workers very recently.⁸ In conclusion, we have developed an effective $\text{Sc}(\text{OTf})_3$ -catalyzed Prins-type reaction to form tetrahydropyrans and related ether derivatives. The conditions for the catalyzed reaction are much milder than the classical Prins reaction using strong acids. Presently, we are evaluating a range of synthetic potentials of this catalyzed reaction.

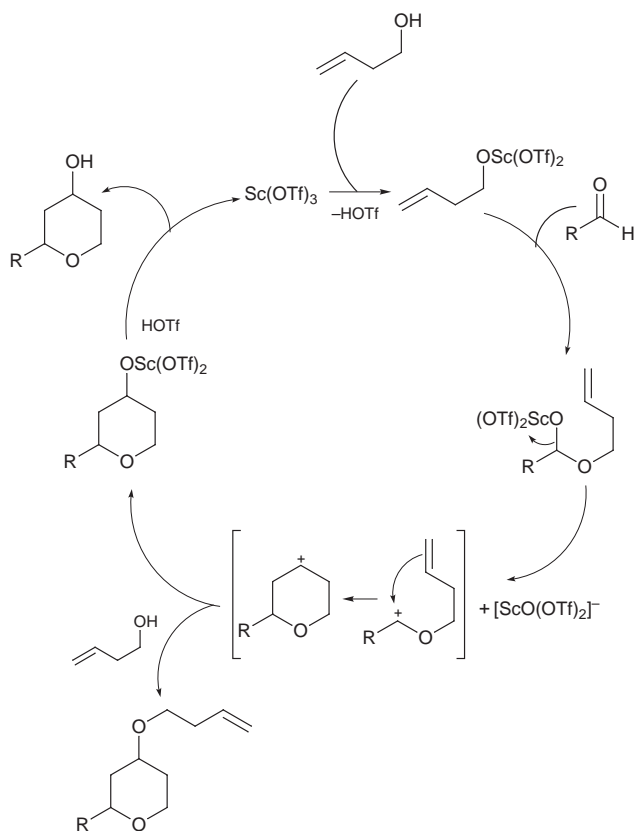
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Notes and references

[†] Typical experimental procedure: A mixture of **1** (2 mmol), but-3-en-1-ol **2** (4 mmol) and scandium triflate (5 mol%) was mixed in CHCl_3 (5 ml). The reaction mixture was refluxed under nitrogen overnight. After concentrated *in vacuo*, the crude reaction mixture was subjected to column chromatography on silica gel eluting with hexane– EtOAc (gradient eluent: 27:1 to 3:1) to yield products **4** and **5**.

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Scheme 2 Proposed mechanism for the $\text{Sc}(\text{OTf})_3$ catalyzed tetrahydropyran formations.