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

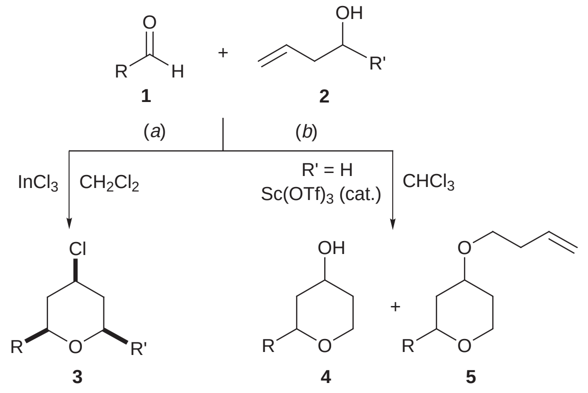
Wen-Chun Zhang, Ganapathy S. Viswanathan and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118, USA.
E-mail: cjli@mailhost.tcs.tulane.edu

Received (in Corvallis, OR, USA) 11th November, 1998, Accepted 16th December 1998

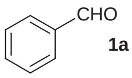
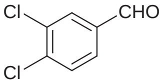
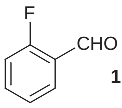
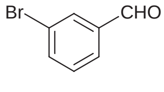
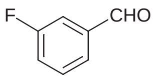
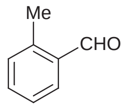
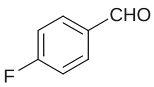
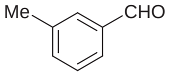
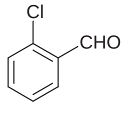
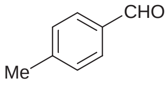
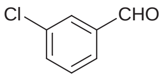
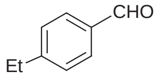
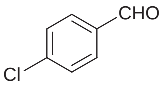
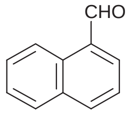
The reaction of aldehydes with homoallyl alcohols catalyzed by scandium triflate generates tetrahydropyran-4-ol and ethers in good yields.

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* $Sc(OTf)_3$ catalyzed Prins-type cyclization

		Product (% yield)		Overall yield (%)			Product (% yield)		Overall yield (%)
Entry	RCHO	4	5		Entry	RCHO	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

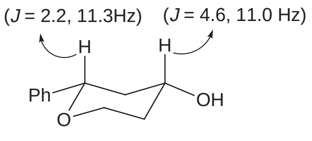
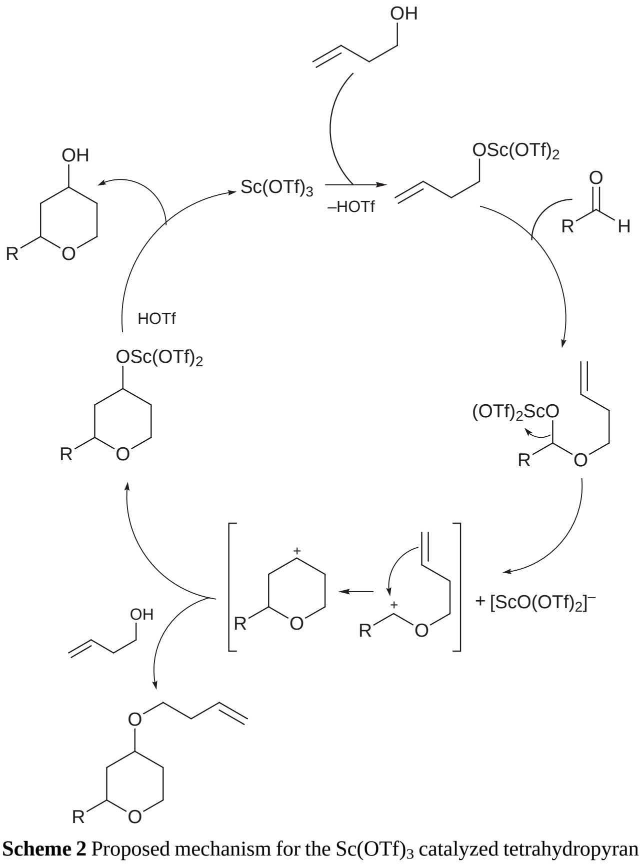


Fig. 1 Coupling constants in **4a**.

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 $Sc(OTf)_3$ 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 $Sc(OTf)_3$-catalyzed Prins-type reaction to form tetrahydropyranols 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.



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

We are grateful to US NSF-EPA, LEQSF and the NSF Early CAREER Award program for partial support of this research.

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**.

1 For reviews, see: E. Arundale and L. A. Mikeska, *Chem. Rev.*, 1952, **51**, 505; D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661.
2 K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, 1996.
3 The best known method in this regard is probably the hetero-Diels–Alder reaction with Danishefsky's diene; for examples, see: S. J. Danishefsky, W. H. Pearson and D. F. Harvey, *J. Am. Chem. Soc.*, 1984, **106**, 2456; S. J. Danishefsky and C. J. Maring, *J. Am. Chem. Soc.*, 1989, **111**, 2193.
4 X. H. Yi, J. X. Haberman and C. J. Li, *Synth. Commun.*, 1998, **28**, 2999.
5 J.Yang, G. S. Viswanathan and C. J. Li, *Tetrahedron Lett.*, in the press. Such compounds were also accessible through $TiCl_4$ and $AlCl_3$ catalyzed allylsilane reactions of aldehydes and cross−coupling between homoallyl alcohols and aldehydes, however, when both substituents are aromatic, the reaction provided no or a low yield of the product, see: Z. Y. Wei, J. S. Li, D.Wang and T. H. Chan, *Tetrahedron Lett.*, 1987, **28**, 3441; F. Perron and K. F. Albizati, *J. Org. Chem.*, 1987, **52**, 4130; Z. Y. Wei, D. Wang, J. S. Li and T. H. Chan, *J. Org. Chem.*, 1989, **54**, 5768; L. Coppi, A. Ricci and M. Taddei, *J. Org. Chem.*, 1988, **53**, 913. Very recently, Rychnovsky and co-workers reported an interesting $SnBr_4$-mediated segment-coupling Prins cyclization, see: S. D. Rychnovsky, Y. Hu and B. Ellsworth, *Tetrahedron Lett.*, 1998, **39**, 7271.
6 For a leading reference, see: S. Kobayashi and I. Hachiya, *J. Org. Chem.*, 1994, **59**, 3590; For a related review, see: S. Kobayashi, *Synlett*, 1994, 689.
7 All products have been fully characterized and produced satisfactory ^1H and ^{13}C NMR, IR and elemental analysis results. For a $Yb(OTf)_3$ catalyzed allylation of aldehydes with allylsilane to generate homoallyl alcohols, see: Y. Yang, M. Wang and D. Wang, *Chem. Commun.*, 1997, 1651.
8 J. Nokami, K. Yoshizane, H. Matsuura and S. Sumida, *J. Am. Chem. Soc.*, 1998, **120**, 6609.

Communication 8/08960D