



Sc(OTf)₃-catalyzed one-pot ene-Prins cyclization: a novel synthesis of octahydro-2*H*-chromen-4-ols

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ABSTRACT

(*R*)-Citronellal undergoes initial ene reaction followed by Prins cyclization with aldehydes in the presence of 5 mol % of scandium triflate at ambient temperature to furnish octahydro-2*H*-chromen-4-ols in good yields and with high *cis*-selectivity. The use of scandium triflate makes this procedure simple, more convenient, and practical.

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The rapid construction of natural product-like molecules from readily available precursors with the control of stereochemistry in a single-step operation is a versatile technique in synthetic chemistry.¹ In this context, ‘Tandem’ reactions, in which multiple reactions are combined into single operation in a convergent way, have been reported extensively.² The advantages of Tandem reactions are the formation of several bonds by a single catalyst in a one-pot operation. High degree of selectivity, efficiency, and atom economy can be achieved without the change of reaction conditions or any further addition of reagents. The Prins cyclization is one of the best examples of such a process and has received much attention in recent years.³ Generally, Lewis acids and Bronsted acids are known to catalyze the coupling of homoallylic alcohols with aldehydes to produce a wide range of tetrahydropyran derivatives under mild conditions.^{4,5} This approach has been successfully employed to the synthesis of complex natural products.^{6,7}

The Lewis acid-catalyzed intramolecular carbonyl-ene reaction is one of the most attractive methods for ring closure, leading to the formation of two contiguous stereocenters with a high degree of stereoselectivity.⁸ (*R*)-Citronellal is known to undergo intramolecular carbonyl-ene reaction to produce a mixture of diastereomeric products. The diastereoselectivity generally depends on the reaction conditions including the nature of the Lewis acid⁹ used. In particular, the *trans* diastereomer isopulegol is favored with a diastereomeric ratio of up to 94:6.¹⁰

In continuation of our interest on the Prins-cyclization,^{5,7} we herein report a simple and direct ene-Prins reaction for the synthesis of pyran derivatives from (*R*)-citronellal and aldehydes using a catalytic amount of scandium triflate under mild conditions. Initially, we attempted the coupling of (*R*)-citronellal with benzaldehyde in the presence of 5 mol % of scandium triflate in dichloromethane. The reaction was carried out at -78°C to room temperature and the corresponding product was obtained as diastereomeric mixtures **3a** and **4a** in a ratio of 9:1 with 88% overall yield. The isomers were separated by column chromatography (Scheme 1).

The structure and stereochemistry of the product were established by making a comparison of the spectral data with authentic sample.¹¹ This result provided incentive for further study of reactions with various aromatic aldehydes such as 1-naphthaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, *p*-nitrobenzaldehyde, and *o*-nitrobenzaldehyde. In all cases, the respective chromanes were obtained in good yields (Table 1, entries b–h). Furthermore, the reaction of (*R*)-citronellal with hydrocinnamaldehyde gave **3i** and **4i** as separable isomers in a ratio of 8:2 (Table 1, entry i). Next, we studied the reactivity of aliphatic aldehydes such as propanaldehyde, cyclohexanecarboxaldehyde, and isovelaraldehyde which gave the corresponding chromanes in good yields (Table 1, entries j–l). Interestingly, acid sensitive *trans*-cinnamaldehyde also participated effectively in this reaction (Scheme 2, Table 1, entry m).

In the absence of catalyst, no reaction was observed under similar conditions. As solvent, dichloromethane was found to give the best results. All the products were characterized by NMR, IR, and mass spectrometry. Mechanistically, the reaction proceeds via

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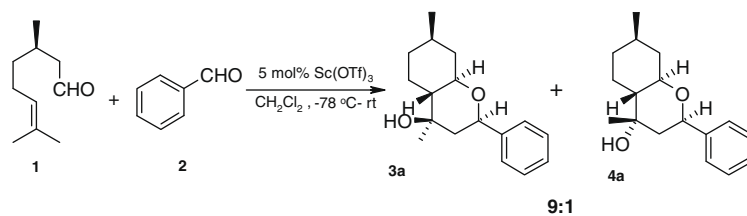
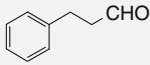
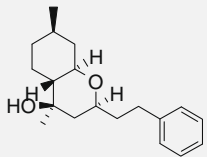
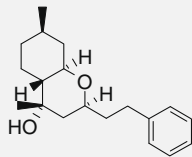

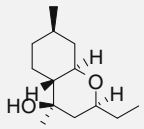
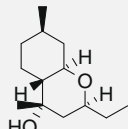
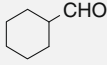
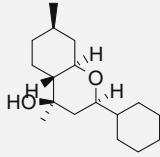
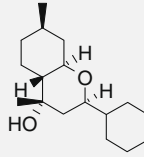
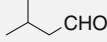
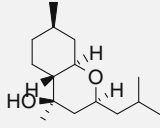
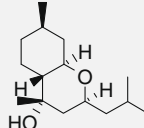
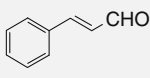
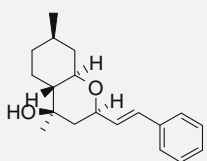
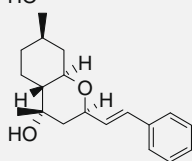


Table 1
Sc(OTf)₃-catalyzed one-pot ene-Prins cyclization with *R*-citronellal and various aldehydes

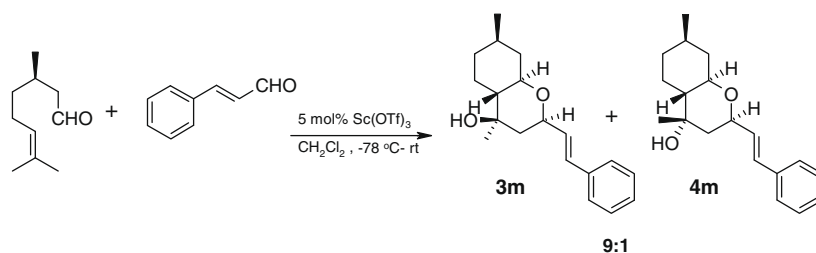
Entry	Aldehyde	Alcohol ^a (3)	Alcohol ^a (4)	Time (h)	Yield ^b (%) (3:4)
a				10.0	88(9:1)
b				10.5	86(9:1)
c				10.5	83(9:1)
d				11.0	82(9:1)
e				10.0	84(9:1)
f				12.0	78(9:1)
g				13.0	76(9:1)
h				14.0	70(9:1)

Table 1 (continued)

Entry	Aldehyde	Alcohol ^a (3)	Alcohol ^a (4)	Time (h)	Yield ^b (%) (3:4)
i				10.5	90(8:2)
j				10.0	90(8:2)
k				11.0	88(8:2)
l				10.0	86(8:2)
m				12.0	85(9:1)

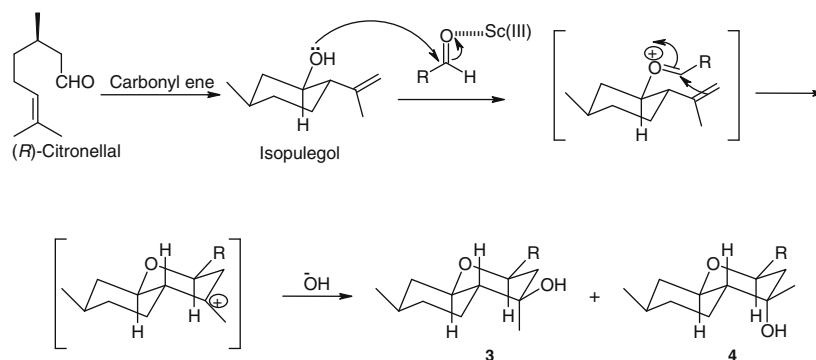
^a All products were characterized by ¹H NMR, IR, and mass spectroscopy.

^b Yield refers to pure products after chromatography.

Scheme 2. Preparation of **3m** and **4m**.

ene-reaction of citronellal. The resulting homoallylic alcohol subsequently may undergo the Prins cyclization with aldehyde affording the desired product (Scheme 3). The scope and generality of

this process are illustrated in Table 1.¹² The efficiency of various acid catalysts such as ZnBr₂, FeCl₃, and AlCl₃ has been tested for this transformation and the results are presented in Table 2.



Scheme 3. A plausible reaction mechanism.

Table 2A comparative study of various Lewis acids for the preparation of **3a**

S. No.	Lewis acid (equiv)	Reaction time (h)	Yield ^a (%)
a	Sc(OTf) ₃ (0.05)	10.0	88
b	ZnBr ₂ (1.0)	14.0	48
c	FeCl ₃ (0.1)	11.0	12
d	AlCl ₃ (0.1)	12.0	20

^a Isolated yield after chromatography.

Of these, Sc(OTf)₃ was found to be the catalyst in terms of yields.

In summary, we have demonstrated a tandem ene-Prins cyclization using Sc(OTf)₃ as a catalyst. The coupling of (*R*)-citronellal with aldehydes provides a simple and convenient route for the synthesis of chromane derivatives. Further studies to the reactions are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.03.100](https://doi.org/10.1016/j.tetlet.2010.03.100).

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- General procedure:** To a solution of *R*-citronellal (5.0 mmol), in dichloromethane (10 mL) was added scandium triflate (0.25 mmol) at -78 °C. After completion of the ene reaction (1.5 h) as indicated by TLC, aldehyde (5.0 mmol) in dichloromethane (6 mL) was added to the reaction mixture at the same temperature. Then temperature was slowly brought to rt. The reaction mixture was stirred at room temperature for a specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 1.0–9.0) gave the pure products.