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$HBF_4{\cdot}OEt_2$ as a versatile reagent for the Hosomi–Sakurai allylation and Prins cyclization: one-pot synthesis of symmetrical 4-fluorotetrahydropyrans

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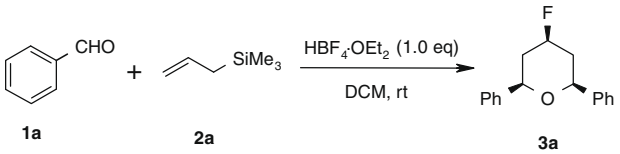
ABSTRACT

The synthesis of symmetrical 2,6-disubstituted 4-fluorotetrahydropyran derivatives has been achieved using $HBF_4{\cdot}OEt_2$ via a tandem allylation and Prins cyclization. This is a highly efficient and diastereoselective approach for the preparation of 4-fluorotetrahydropyrans in a single step. The use of readily available and easy to handle reagent $HBF_4{\cdot}OEt_2$ makes this method simple, convenient and practical.

The synthesis of fluorine-containing molecules has received considerable attention in pharmaceutical industry.[1] The introduction of fluorine onto organic molecule often increases the stability and also alters the lipophilicity and reactivity.[1] Therefore, we have attempted the synthesis of 4-fluoro-substituted tetrahydropyrans as they are structural components in one of our research projects in bioorganic and medicinal chemistry. The tetrahydropyran ring is a core structure in various natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins and acutiphycins and is also a part of the backbone of several important carbohydrates, polyether antibiotics and marine macrolides.[2] Tetrahydropyran derivatives are usually prepared via Prins-cyclization using acid catalysis.[3] Recently, several efforts have been made to introduce various substituents at C-4 position of the pyran ring using various nucleophiles such as halides, hydroxyls, organic nitriles, azide, thiocyanate and thiols.[4–6] Only a few methods have been reported for the synthesis of fluorinated tetrahydropyrans.[7] In most cases, the products are formed as a mixture of 4-fluoropyrans and 4-hydroxypyrans approximately in 1:1 ratio. Subsequently, HF/ionic liquid system has also been reported for the synthesis of fluorinated tetrahydropyran derivatives.[8] However, to the best of our knowledge, there have been no reports on the synthesis of symmetrical 2,6-disubstituted 4-fluorotetrahydropyran derivatives from aldehyde and allyltrimethylsilane using $HBF_4{\cdot}OEt_2$.

In continuation of our research programme on the Prins cyclization in the total synthesis of biologically active natural products,[9] we herein report a one-pot method for the synthesis of symmetrical 2,6-disubstituted 4-fluorotetrahydropyrans from aldehydes and allyltrimethylsilane by means of a tandem allylation and Prins-cyclization using a ethereal solution of tetrafluoroboric acid. Initially, we have attempted the coupling of benzaldehyde (2.2 equiv) with allyltrimethylsilane (1.0 equiv) using $HBF_4{\cdot}OEt_2$ (1.0 equiv) in dichloromethane. The reaction went to completion within 25 min at room temperature and the corresponding 4-fluoro-2,6-diphenyl-tetrahydro-2*H*-pyran **3a** was isolated in 80% yield with all cis-selectivity (Scheme 1).

This result encouraged us to extend this process to various aldehydes. Interestingly, aryl aldehydes such as 4-chloro-, 2-nitro-, 4-nitro-, 4-methyl- and 3-nitrobenzaldehydes underwent smooth coupling with allyltrimethylsilane to give the corresponding 2,6-diaryl-4-fluorotetrahydropyrans in high yields (Table 1, entries b–f). This method is also effective for sterically hindered substrate, for example, 2-naphthaldehyde (Table 1, entry g). Next, we examined the reaction of allyltrimethylsilane with aliphatic aldehydes under similar conditions. For example, the treatment of cyclohex-



Scheme 1. A tandem allylation and Prins cyclization of benzaldehyde.

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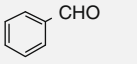
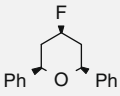
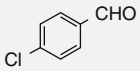
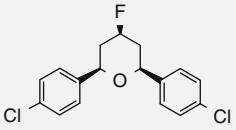
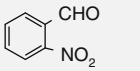
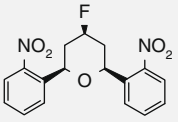
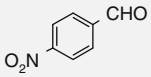
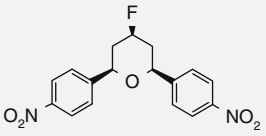
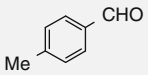
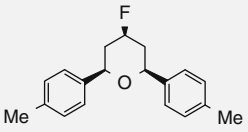
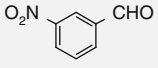
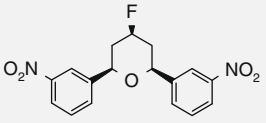
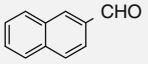
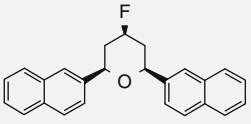
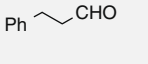
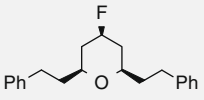
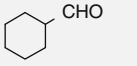
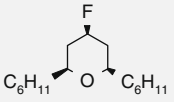
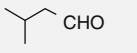
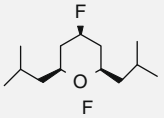
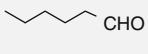
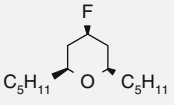
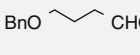
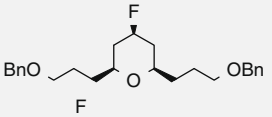
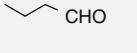
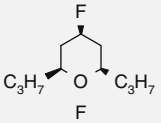
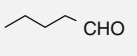
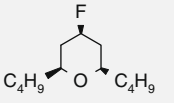
Table 1
One-pot synthesis of symmetrical 4-fluorotetrahydropyrans using $HBF_4{\cdot}OEt_2$

Entry	Aldehyde	Product (**3**)[a]	Yield[b] (%)	Time (min)
a			80	25
b			75	30
c			78	35
d			82	30
e			70	40
f			75	36
g			75	35
h			75	30
i			70	45
j			78	45
k			75	50
l			85	35
m			75	55
n			70	50

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

anecarboxaldehyde with allyltrimethylsilane in the presence of $HBF_4{\cdot}OEt_2$ gave the 2,6-dicyclohexyl-4-fluoro tetrahydro-2*H*-pyran **3i** in 70% yield (Scheme 2).

Other aliphatic aldehydes such as 3-phenylpropanaldehyde, 2-methylbutyraldehyde, *n*-hexanaldehyde, 4-(benzyloxy)butanal, *n*-butyraldehyde and *n*-pentanaldehyde also underwent smooth coupling with allyltrimethylsilane to give the corresponding 2,6-dialkyl-4-fluorotetrahydropyrans in high yields (Table 1, entries h–n). However, no reaction was observed in the absence of $HBF_4.OEt_2$ even after an extended reaction time (15 h). As solvent, dichloromethane gave the best result. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields and with all cis-diastereoselectivity as determined from the NMR spectra of the crude products. Only a single diastereoisomer was obtained from each reaction. The formation of the products may be explained by initial allylation and a subsequent hemi-acetal formation followed by Prins-type cyclization and fluorination (Scheme 3). A rationale for the all cis-selectivity involves the formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favours equatorial attack of the nucleophile.[10]

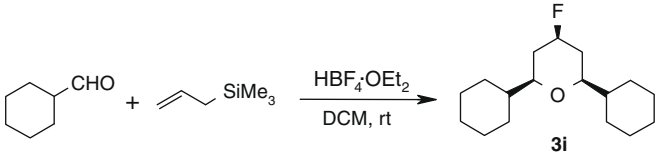
The scope and generality of this process are illustrated with respect to various aldehydes and the results are presented in Table 1.[11] As shown in Table 1, this method works well with both electron-donating and electron withdrawing aldehydes.

Next, we attempted the coupling of 1 equiv of benzaldehyde with 1.2 equiv of 3-buten-1-ol in the presence of 1 equiv of $HBF_4{\cdot}OEt_2$. Interestingly, the reaction was complete in 20 min and the corresponding 2-phenyl-4-fluoro-tetrahydropyran in 76% yield with cis-selectivity (Scheme 4).

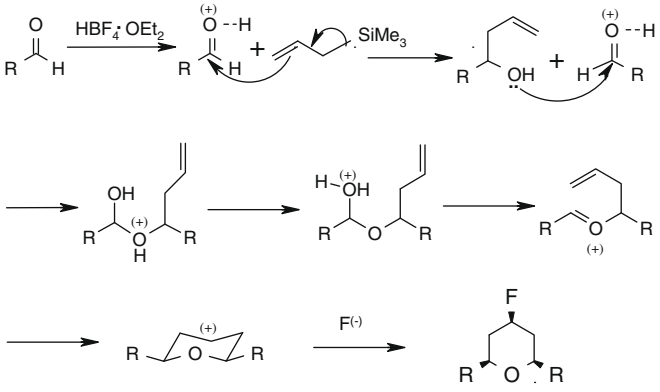
In this way, we have extended our method to prepare unsymmetrical 4-fuorotetrahydropyran derivatives (Table 2).

In all cases, 4-fluorotetrahydropyrans were obtained exclusively without the formation of hydroxypyrans under present reaction conditions.

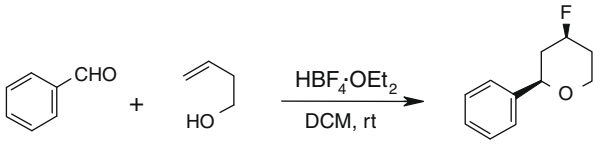
In summary, we have developed a direct one-pot method for the preparation of 4-fluorotetrahydropyrans by means of a tandem allylation and Prins-cyclization using $HBF_4{\cdot}OEt_2$. This method offers significant advantages including mild conditions, operational



Scheme 2. Preparation of 2,6-dicyclohexyl-4-fluoro-tetrahydropyran **3i**.

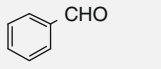
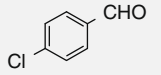
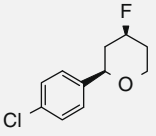
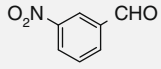
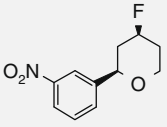
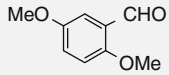
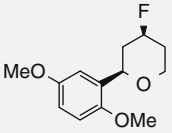
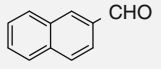
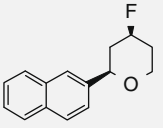
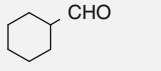
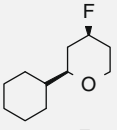
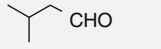
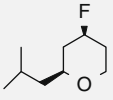


Scheme 3. A plausible reaction mechanism.



Scheme 4. Preparation of 2-phenyl-4-fluoro-tetrahydropyran.

Table 2
Preparation of unsymmetrical 4-fluorotetrahydropyrans using $HBF_4{\cdot}OEt_2$

Entry	Aldehyde	Product (**4**)[a]	Yield[b] (%)	Time (min)
a			76	20
b			78	25
c			75	35
d			72	30
e			65	35
f			68	40
g			74	45

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

simplicity of the reagent, no formation of by-products and short reaction times. This method provides an easy access to 4-fluoro-tetrahydropyrans with diverse chemical structures for biological evaluation.

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References and notes

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11. *General procedure*: A mixture of aldehyde (2.2 mmol), allyltrimethylsilane (1 mmol) and $HBF_4{\cdot}OEt_2$ complex (1 mmol) in dichloromethane (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5:9.5) gave the pure 4-fluorotetrahydropyran. The products thus obtained were characterized by IR, NMR and mass spectroscopy. Spectral data for selected compounds: Compound **3a**: *4-fluoro-2,6-diphenyl-tetrahydro-2H-pyran* (Table 1): Light yellow solid, mp 68–70 °C; IR (KBr): ν 3030, 2922, 2851, 1494, 1451, 1059, 754, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.21 (m, 10H), 5.02–4.85 (m, 1H), 4.52 (d, J = 11.7 Hz, 2H), 2.45–2.39 (m, 2H), 1.83–1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.2, 128.3, 127.5, 125.7, 90.5, 88.2, 40.3. ESI-MS: m/z: 279 $(M+Na)^+$. HRMS (ESI) [M+Na] calcd for $C_{17}H_{17}OFNa$: 279.1161, found: 279.1164. Compound **3g**: *4-fluoro-2,6-di(naphthalen-2-yl)-tetrahydro-2H-pyran* (Table 1): Colourless solid, mp 164–168 °C; IR (KBr): ν 2922, 2852, 1463, 1367, 1067, 818, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.80–7.76 (m, 14H), 5.18–4.91 (m, 1H), 4.76 (d, J = 11.5 Hz, 2H), 2.60–2.51 (m, 2H), 2.00–1.87 (m, 2H); ESI-MS: m/z: 357 $(M+H)^+$, 374 $(M+NH_4)^+$, 379 $(M+Na)^+$. HRMS (ESI) [M+Na] calcd for $C_{25}H_{21}OFNa$: 379.1474, found: 379.1479. Compound **3l**: *2,6-bis(3-(benzyloxy)propyl)-4-fluoro-tetrahydro-2H-pyran* (Table 1): White solid, mp 58–60 °C; IR (KBr): ν 2922, 2852, 1453, 1364, 1096, 999,736, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.18 (m, 10H), 4.69–4.40 (m, 5H), 3.49–3.37 (m, 4H), 3.23–3.13 (m, 2H), 1.83–1.52 (m, 12H); ESI-MS: m/z: 401 $(M+H)^+$, 423 $(M+Na)^+$. HRMS (ESI) [M+Na] calcd for $C_{25}H_{33}O_3FNa$: 423.2311, found: 423.2317.