The synthesis of a range of fluorinated heterocycles is described via a Lewis acid-mediated Prins-type cyclisation.

Although naturally occurring fluorinated organic molecules are rare, the introduction of fluorne into natural products is currently the focus of much synthetic interest due to the profound effect that the fluorne atom may have on the properties of the compound. Strategically positioned fluorne atom(s) may greatly influence the biological properties of a compound. For example, deoxyfluoro-sugars have been used to probe the mechanism of action of various enzymes. Methods for the preparation of fluorinated sugars and related heterocycles are currently the focus for considerable synthetic effort. For example, Linclau et al. have recently reported the enantioselective synthesis of tetratetrafluoroethylene-containing monosaccharides and Percy et al. have developed routes to a range of difluorinated sugar mimetics. The search for a rapid and efficient method for the synthesis of simple monofluorinated compounds, however, is still ongoing.

The Prins cyclisation is a well-established method for the preparation of a range of heterocycles, most notably tetrahydro-pyran and more recently dihydropyran. A range of Lewis acids have been reported in recent years to promote the Prins reaction and indeed have been used to incorporate fluorne into the 4-position of tetrahydropyrans. We have gained considerable experience of using indium trichloride as a Lewis acid for Prins cyclisation reactions and embarked on a project to apply this methodology to the synthesis of fluorinated heterocycles.

Indium trichloride promotes the Prins cyclisation of various simple and complex homoallylic alcohols and homopropargylic alcohols to the corresponding pyran. We reasoned that by incorporating fluorne into the homoallylic alcohol, it may be possible to build fluorinated pyrans using the Prins cyclisation.

The method of Hedhli and Baklouti appeared ideal for the preparation of the desired fluorinated homoallylic alcohols. Reaction of triethylamine trihydrogen fluoride with various alcohols to the corresponding pyran.

Table 1 Synthesis of simple 2-alkyl-4-chloro-5-fluorotetrahydropyrans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>% Yield</th>
<th>Control % yield (no fluorne)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenylacetaldheyde</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Hexanal</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexancarboxaldehyde</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>2-Ethylbutyraldehyde</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Diphenylacetaldheyde</td>
<td>57</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>Benzaldehyde</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>4-Nitrobenzaldehyde</td>
<td>54</td>
<td>66</td>
</tr>
</tbody>
</table>

Table entries 8–10 show that the reaction is not limited to using aldehydes as a substrate, and that epoxides and acetals may also be employed without compromising the focus of much synthetic interest due to the profound effect that the fluorne atom may have on the properties of the compound.
the yield significantly (there is literature precedent for epoxides generally being lower yielding in Prins reactions compared to aldehydes). Both epoxides and acetals gave single diastereomeric tetrahydropyran products.

The reaction is believed to proceed by the accepted Prins cyclisation mechanism, with the formation of a carbocation adjacent to the fluorine atom. It does not appear that the presence of the highly electronegative fluorine atom has any bearing on the outcome of the reaction, since yields are consistent (within experimental error) with those obtained in the absence of fluorine, as indicated by the control results in Table 1. Interestingly, however, was the requirement to perform the reaction in dichloromethane at reflux temperature in order to obtain the fluorinated tetrahydropyrans, yet it would proceed rapidly at room temperature in the absence of fluorine.

The relative configuration of the substituents was obtained by nOe studies, which clearly showed that the product in each case was the all cis configuration, with the fluorine adopting an axial orientation at the C-5 position (see Fig. 1).11 Similar diastereoselectivity was observed for each of the fluorinated products obtained.

Table 2  Effect of employing different Lewis acids in the Prins reaction of simple aldehydes with 2-fluoro-3-buten-1-ol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Lewis acid/conditions</th>
<th>X in product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenylacetaldehyde</td>
<td>TMSOTf/ −78 °C, DCM</td>
<td>OTf</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>Hexanal</td>
<td>TMSOTf/ −78 °C, DCM</td>
<td>OTf</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexanecarboxaldehyde</td>
<td>TMSOTf/ −78 °C, DCM</td>
<td>OTf</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>Hexanal</td>
<td>InBr/DCM, rt to reflux</td>
<td>Br : Cl12 (1.2 : 1)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Hexanal</td>
<td>InBr/CH2Br2, rt to reflux</td>
<td>Br</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>Cyclohexanecarboxaldehyde</td>
<td>InBr/CH2Br2, rt to reflux</td>
<td>Br</td>
<td>66</td>
</tr>
</tbody>
</table>

* All are purified yields and all products gave satisfactory spectroscopic data. 12 Two compounds inseparable by column chromatography, ratio obtained from GC-MS.
yields. A range of anions may be incorporated during the
cyclisation process, some of which may be subsequently
eliminated to give fluorinated dihydropyrans. We are currently exploring this
methodology for the preparation of more complex tetrahydropyrans in enantiopure form and their subsequent elaboration to fluorinated sugar analogues.

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UK (ORS award to SM) for funding.

Notes and references

† Representative procedure for the formation of 2-substituted-4-trifluoromethanesulfonyl-5-fluorotetrahydropyrans: a solution of the aldehyde (2 eq., in range 5–10 mmol) in dry dichloromethane (15 ml) was cooled to −78 °C and treated with trimethylsilyl trifluoromethanesulfonate (2.5 eq.) and stirred for 30 min at this temperature. 2-Fluorobut-3-en-1-ol (1 eq.) was
then warmed to room temperature over 16 h before adding water (20 ml). The two layers were separated and the aqueous layer extracted
with dichloromethane. The combined dichloromethane layers were dried (MgSO4) and concentrated in vacuo to give the crude product, which was purified by flash column chromatography. The method to prepare

2-substituted-4-halo-5-fluorotetrahydropyrans involved identical molar
ratio equivalents of reagents being added in the same order, but with the
addition occurring at room temperature (rather than −78 °C) and the
reaction subsequently being heated to reflux temperature for 5–15 h, as
indicated by consumption of the starting material.

‡ Representative procedure for the triflate elimination from substituted 4-trifluoromethanesulfonyl-5-fluorotetrahydropyrans: to a solution of the
4-trflate-substituted tetrahydropyran (range 1–3 mmol, 1 eq.) in dry THF (5 ml) under a nitrogen atmosphere was added the base either at 0 °C (NaH) or at room temperature (KOtBu and LHMDS, equivalents in Table 3). The reaction was stirred at room temperature for variable periods of time, until no further change was observed by t.l.c. (indicative times for each base given in Table 3). The reaction was quenched with water (10 ml) and stirred for a further 20 mins. The aqueous solution was extracted with
diethyl ether (36 ml), the organic phases combined, dried (MgSO4),
filtered and concentrated in vacuo to give the crude product, which was
purified by flash column chromatography (typically 10% ethyl acetate in
petroleum ether (40–60 fraction)).

1 For an excellent recent review of the emerging role of fluorine in synthetic, medicinal, pharmaceutical and biological systems, see the Special Issue: Fluorine in the Life Sciences, ChemBioChem, 2004, 4, 557–726.
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