Rapid syntheses of difluorinated dihydropyran
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A very short reaction sequence opens with metal-mediated addition of commercial bromodifluoropropene to aldehydes; allylation under phase transfer catalysed conditions sets the stage for a ring closing metathesis (RCM) in the presence of commercial Grubbs’ catalyst to afford potentially useful difluorinated dihydropyran.

Difluorinated carbohydrate analogues are normally prepared by DAST ([diethylamino)sulfur trifluoride] difluorination of highly protected precursors in which a ketonic carbonyl group has been isolated, chemistry which is highly vulnerable to stereoelectronic effects as demonstrated many times by Castillón and coworkers. Even when such difficulties have been overcome, the hazardous nature of the DAST reagent precludes scale-up, while safer versions of the reagent sacrifice reactivity in the cause of thermal stability. Building block chemistry then appears most attractive and the Reformatsky reaction of ethyl bromodifluoroacetate with aldehydes and other electrophiles is a well-worked and productive theme. Our own approaches from trifluoroethanol but we were struck by the simplicity of the RCM technology allowing a very short reaction sequence opens with metal-mediated addition of commercial bromodifluoropropene to aldehydes; allylation under phase transfer catalysed conditions sets the stage for a ring closing metathesis (RCM) in the presence of commercial Grubbs’ catalyst to afford potentially useful difluorinated dihydropyran.

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Initially, we were interested in the reproducibility of the allylindium chemistry described by Momose and coworkers in which bromodifluoropropene adds very smoothly to aldehydes. With the homoallyl alcohols in hand, we would perform an allylation and then expose the allyl homoallyl ether to an RCM catalyst. Both alkenes are made less electron rich by electron-withdrawing substituents at the allyl position and we were concerned that the overall cycle would be slow and that metallofluorine bond destroying the catalyst.

In the event, our fears were groundless. The allylindium chemistry was highly reproducible and homoallyl alcohols were synthesised in moderate to high (57–80%) yield (Scheme 2).

The reactions worked best when the suspensions were shaken or sonicated, and purification was facile. We also explored the replacement of the indium metal with 325-mesh zinc under the conditions described by Wilson and Guazzaroni (saturated NH4Cl, THF). The zinc-mediated reaction was much more effective in the case of benzaldehyde, affording the homoallyl alcohol in 84% yield, but less effective (37%) when the more interesting and electrophilic benzylxoyacetalddehyde was present, despite our observation of an extremely clean 19 F NMR spectrum from the crude material. Pinacol coupling of the aldehyde may be responsible for the low yield though we did not isolate any products of this type.

Allylation was trouble-free as was the RCM reaction at room temperature in dichloromethane, though reaction times of 24 h were required to consume the starting material entirely.

The methallyl ether prepared by an analogous sequence failed to cyclise at all under these conditions suggesting that the additional steric hindrance imposed by a methyl group is enough to prevent coordination and stop the cycle. Dihydropyran formed in a particularly high isolated and purified yield is of the type identified in the analysis, while is potentially interesting for the synthesis of higher sugars and related species; we are continuing to explore the scope of the reaction more fully. This short study clearly shows how potentially important oxygen heterocycles can be assembled in an extremely concise manner using off-the-shelf reagents.

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Notes and references

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Preparation of 2d: 1-bromo-1,1-difluoropropene (0.76 ml, 7.5 mmol) and benzaldehyde (0.70 ml, 5.0 mmol) were added to a sonicated suspension of indium powder (0.86 mg) in DMF (20 ml). The mixture was sonicated at room temperature for 5 h then quenched with 1 M HCl (10 ml). Extractive work up afforded a yellow oil which was purified by column chromatography (30% diethyl ether–light petroleum (bp 40–60 °C)) to afford 2d as a pale yellow oil (0.91 g, 80%) (Rf = 0.23). 1H NMR (CDCl3, 300 MHz) δ 7.40 (m, 1H), 5.95 – 5.86 (m, 1H), 4.37, 4.18 (m, 2H), 3.98 (m, 1H), 5.86 (m, 1H), 4.67 (d, 1H, first half of an AB quartet, JH-H 7.0 Hz), 2.76 (d, 1H, JH-H 5.2 Hz); 13C NMR (CDCl3, 75 MHz) δ 137.8, 135.7 (t, 3F, JF-C 25.5 Hz), 128.4, 127.9, 127.7, 120.9 (t, 2JF-C 9.5 Hz), 119.1 (t, 1JF-C 273.7 Hz), 73.6, 72.2 (t, 2JF-C 33.6 Hz), 68.6; 19F NMR (CDCl3, 282 MHz) δ –107.3 (dt, 1F, second half of an AB quartet, JF-F 251.8, JF-H 10.5 Hz, –111.3 (dt, 1F, second half of an AB quartet, JF-F 251.8, JF-H 11.1 Hz); m/z (ES) 251 (M + Na, 100); HRMS calc. for C13H14O2F2Na 251.0890, found 251.0872.

For other difluoromethylation methods or building blocks, see: 5 M. Carda, E. Castillo, S. Rodriguez, S. Uriel and J. A. Marco, Synlett, 1999, 1639.
7 Preparation of 2d: 1-bromo-1,1-difluoropropene (0.76 ml, 7.5 mmol) and benzaldehyde (0.70 ml, 5.0 mmol) were added to a sonicated suspension of indium powder (0.86 mg) in DMF (20 ml). The mixture was sonicated at room temperature for 5 h then quenched with 1 M HCl (10 ml). Extractive work up afforded a yellow oil which was purified by column chromatography (30% diethyl ether–light petroleum (bp 40–60 °C)) to afford 2d as a pale yellow oil (0.91 g, 80%) (Rf = 0.23). 1H NMR (CDCl3, 300 MHz) δ 7.40 – 7.27 (m, 5H), 6.30 – 6.24 (m, 1H), 5.95 – 5.86 (m, 1H), 4.67 (d, 1H, first half of an AB quartet, JH-H 12.1 Hz), 4.59 (d, 1H, second half of an AB quartet, JH-H 12.1 Hz), 4.37, 4.18 (m, 2H), 3.98 – 3.90 (m, 1H), 3.71 (dd, 1H, first half of an AB quartet, JH-H 9.9, JH-H 3.3 Hz), 3.59 (dd, 1H, second half of an AB quartet, JH-H 9.9, JH-H 7.0 Hz), 2.76 (d, 1H, JH-H 5.2 Hz); 13C NMR (CDCl3, 75 MHz) δ 137.3, 135.7 (t, 3F, JF-C 274.0 Hz), 128.4, 127.9, 121.4 (t, 2JF-C 28.0 Hz), 113.9 (dd, 1JF-C 243.0, 235.7 Hz), 77.0 (d, 2JF-C 30.5 Hz), 73.8, 67.1 (d, 2JF-C 5.7 Hz), 65.2; 19F NMR (CDCl3, 282 MHz) δ –105.6 (ddt, 1F, first half of an AB quartet, JF-F 274.0, JF-H 17.8, 8.9, JH-H = 8.9 Hz), –107.7 (br d, 2F, JF-F 274.0, JF-H 4.4 Hz); m/z (ES) 263 (M + Na, 100); HRMS calc. for C13H14O2F2Na 263.0860, found 263.0853.

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