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Introduction

The production of chemicals for medicinal chemistry relies heavily on hydrocarbons from petrochemical sources to provide small molecule synthons. Considering the inevitable exhaustion of fossil fuels and the increased restriction of their use due to concerns relating to climate change, the key to future chemical processes will be the exploitation of renewable resources from plant biomass.¹ An important sustainable feedstock is sugar beet, with a production cycle from seeds-toseeds of only two years. Cultivated predominantly in temperate regions for the production of sucrose, the processing of the beet also generates large quantities of pulp, which is considered as a low-value waste product and is usually used as

Functionalised tetrahydrofuran fragments from carbohydrates or sugar beet pulp biomass†

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Carbohydrate biomass represents a potentially valuable sustainable source of raw materials for chemical synthesis, but for many applications, selective deoxygenation/dehydration of the sugars present is necessary to access compounds with useful chemical and physical properties. Selective dehydration of pentose sugars to give tetrahydrofurans can be achieved by treatment of the corresponding *N*,*N*-dimethyl-hydrazones under acidic or basic conditions, with the two approaches showing complementary stereo-selectivity. The dehydration process is readily scalable and the THF hydrazones derived from arabinose, ribose, xylose and rhamnose were converted into a range of useful fragments containing primary alcohol, ketone, carboxylic acid or amine functional groups. These compounds have potentially useful physio-chemical properties making them suitable for incorporation into fragment/lead generation libraries for medicinal chemistry. It was also shown that L-arabinose hydrazone could be obtained selectively from a crude sample of hydrolysed sugar beet pulp.

animal feed.^{2,3} This material is highly enriched in carbohydrates, with the pulp being composed of polymeric glucose (cellulose) and pectin (a co-polymer of hexoses and pentoses). The latter fraction contains a high proportion of L-arabinose as well as other sugars, which could potentially be exploited as valuable chemical feedstocks, but processing is required to release the monomeric sugars, and strategies for this have been reported.^{4,5}

A variety of transformations are now available to produce small molecule building blocks from sugar monomers.^{4,5} However, with the exception of some partial reduction methods,^{6–8} carbohydrate biomass treatment often results in the loss of functional groups and chiral information, and it remains very challenging to selectively remove one or more hydroxyl groups from a polyol, without resorting to extensive protecting group manipulations.^{9,10} For this reason, the range of more complex targets retaining stereochemical information from biomass sugars prepared *via* succinct methods avoiding extensive protection–deprotection steps has remained limited.

Recently, some approaches have been developed which take advantage of the intrinsic functionalities and chirality of carbohydrates to develop novel methodology to access small 3D-building-blocks.^{11,12} Indeed, we have recently developed a selective method for the dehydration of pentose sugars to afford hydroxy-functionalised THFs without the need for protecting groups (Scheme 1).¹² In this paper, we describe the



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[†] Electronic supplementary information (ESI) available: Procedures for the preparation of all compounds, together with characterisation data and X-ray crystallographic data. CCDC 1877937 and 1877938. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9gc00448c

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Scheme 1 Dehydration of pentose sugars for the synthesis of chiral building-blocks.

optimisation of this chemistry on a multigram scale, the development of a novel base-mediated cyclic dehydration of sugar hydrazones to access other stereoisomers, and the extension of this methodology to a range of pentoses. We also demonstrate the application of these dehydration reactions to the construction of a small library of chiral THF fragments as useful building blocks for medicinal chemistry,^{13,14} *via* routes that offer selectivity, scalability, and sustainability. In addition, the direct synthesis of one of our key starting materials directly from sugar beet pulp is described, to demonstrate the feasibility of 'up-grading' waste from biomass into complex chiral building blocks.

Results and discussion

Synthesis of chiral THFs from pentose sugars

The conversion of L-arabinose into 1a-3a was conducted following the procedure described in our preliminary communication for the acid catalysed dehydration of pentoses.¹² Hydrazone 1a was obtained quantitatively under acidic conditions and subsequently cyclised using catalytic TFA (Scheme 2). In our previous studies, this reaction had yielded the THF in only moderate yield (67%), but the fate of the remaining material was unclear. However, when the cyclisation was performed on a larger scale (5–20 g), formation of two side-products 4 and 5 in 22% and 5% yields respectively was observed. The formation of methyl ether 4 could be rationalised by the reaction of the vinyldiazenium intermediate 2awith methanol. The formation of ketone 5 most likely results from the aerobic oxidation of 1a at the C-2 position.

These issues were readily solved by running the cyclisation in a less nucleophilic solvent (isopropanol) and under an argon atmosphere (see ESI[†]). Under these conditions, **3a** was obtained in 81% yield routinely on a 20 g scale. When these reaction conditions were applied to other pentose sugars, the



Scheme 2 Selective dehydration of L-arabinose and side-products formed.

yields were generally superior to the previously reported procedure, with no significant difference in the diastereoselectivity observed (Scheme 3). THFs *anti-3a* and *anti-3b* derived from L-arabinose and D-ribose could be recrystallised from THF/Petrol to give the pure *anti-*isomer in each case.

Investigations also established that the cyclisation of the sugar hydrazones could be achieved to give THFs under basic conditions, by activating the sugar-hydrazone **1a** with dimethylcarbonate (DMC).¹⁵ The reaction occured at room temperature and afforded the chiral THF *syn-3a* from arabinose in excellent yield, with good diastereoselectivity. Importantly, this provides a complementary approach to the acid-catalysed cyclisation in terms of the THF isomer produced. These conditions were also applied successfully to other pentoses, with the major THF isomer in each case having *syn-*stereochemistry at the THF carbons C-1 and C-2 (Table 1).

Full conversions were obtained after 4 hours and no change in the diastereomeric ratio was noted during the course of the



Scheme 3 Optimised synthesis of chiral THFs *anti-3a-anti-3d*. *Yield obtained under previous conditions.¹²

Table 1 Synthesis of chiral THFs syn-3a to syn-3e under basic conditions



Yields were determined by ¹H NMR using *tert*-but anol as internal standard (1 eq.).

cyclisation reaction. The presence of dimethylcarbonate and a stoichiometric amount of base were essential for the reaction to proceed in high yield. When a purified sample of the THF *anti-3a* was submitted to the DMC/K₂CO₃ reaction conditions, no epimerisation was observed after 24 hours suggesting that there was no interconversion of the two isomers and that the two products *anti-3a* and *syn-3a* were likely formed *via* two different reaction pathways under the basic conditions. This is in stark contrast to the acidic cyclisation conditions under which the two products can rapidly interconvert, leading to production of a thermodynamic mixture of products.

Taking this into account, along with the observed diastereomeric ratios of the products obtained from L-arabinose, D-ribose, D-xylose and D-lyxose it is evident that epimerisation of the C-2 stereocentre must take place prior to irreversible cyclisation, with the observed products resulting from the relative rates of cyclisation of the two diastereomers. Thus, arabinose hydrazone **1a** must first be converted into cyclic carbonate **6a** (Scheme 4), which can only cyclise relatively slowly to give *anti*-**3a** but can undergo epimerisation to **7a** which cyclises more rapidly to give *syn*-**3a**. Epimerisation may take place *via* ring opening of the cyclic carbonate to generate zwitterion **8a**. In the case of D-ribose hydrazone **1b**, the initially formed carbonate **6b** (the enantiomer of **7a**) cyclises relatively rapidly so less epimerisation to **7b** (and subsequent cyclisation to *anti*-**3b**) takes place leading to a slightly higher diastereo-



Scheme 4 Proposed mechanism for the basic cyclisation of L-arabinose hydrazone 1a and D-ribose hydrazone 1b.

selectivity in this reaction in comparison to the formation of *syn-3a*. A similar rationale can be used to explain the observed diastereoselectivities resulting from cyclisation of D-xylose hydrazone **1c** and D-lyxose hydrazone **1f**. The selective formation of the cyclic carbonate at C-2/C-3 could perhaps be explained by involvement of the hydrazone group as a general base that activates the C-2 alcohol towards reaction with dimethyl carbonate (Scheme 5a). Furthermore, general base



Scheme 5 Base mediated (a) cyclic carbonate 6a formation, (b) cyclisation of 7a.

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assistance could also be invoked in the cyclisation reaction (Scheme 5b), as in each case the cyclisation reaction which proceeds fastest involves reaction of an intermediate in which the hydrazone and nucleophilic primary alcohol are arranged on the same face of the 5-membered carbonate ring. Cyclisation with inversion at C-2 then leads to the THF ring in which the C-3 alcohol and the hydrazone are on the same face of the newly formed ring.

Chiral functionalised THFs as 3D fragments for medicinal chemistry

The next objective of this study was to synthesise carefully chosen targets for applications in medicinal chemistry, which contained suitable functional groups for derivatisation in order to prepare potential fragments and/or intermediates for incorporation into lead-like molecules. Three families of compounds were selected: (i) THF-triols 9, (ii) THF-carboxylic acids 10 and (iii) THF-amines 11 (Fig. 1). It was envisioned that these three compound classes would be ideal for generating libraries for fragment-based lead discovery as they are of low molecular weight ($M_{\rm w} < 150 \text{ g mol}^{-1}$), are highly soluble in water, and contain a functional group ready for further elaboration (primary alcohol, carboxylic acid, primary amine). In addition, the targets could be used as strategic reagents¹⁶ for the final derivatisation of core molecules so as to dramatically lower $\log D$ by incorporation of the compact polyol moiety. Finally, by using different pentose sugars, we aimed to prepare a range of different stereoisomers, each with a diastereomeric ratio >90:10, suitable for use in these applications.¹⁷

The THF-hydrazone **3** is a versatile platform for accessing several functionalities (*e.g.* aldehyde, alcohol, nitrile, protected-amine, alkene).¹² As previously reported the hydrazone can be rapidly hydrolysed to give the aldehyde hydrate **12** using an acidic resin (Amberlyst 15). The reaction was easily scaled-up (>10 g) and extended to the other pentoses (Scheme 6). The reaction could safely be conducted on the mixture of diastereomers obtained after cyclisation, as epimerisation takes place under the acidic hydrolysis conditions. Remarkably, in the case of L-rhamnose the hydrate was obtained with a higher diastereoselectivity than the corresponding hydrazone.

The epimerisation at C-2 during the hydrolysis of hydrazone **3a** to hydrate **12a** offers an opportunity to maximise the value of the material (Scheme 7). Thus, recrystallisation of 6.8 g of **3a** obtained directly from the acidic cyclisation (dr 78:22)



Fig. 1 Selected targets and their calculated properties



Scheme 6 Synthesis of THF-hydrates 12.



Scheme 7 Hydrolysis and increase in diastereoselectivity of 3a to 12a.

yielded 2.4 g of *anti-3a* as a single isomer. A second crop of high purity *anti-3a* was also obtained (1.4 g, dr 95:5), leaving the remaining mother liquor as an equimolar mixture of diastereomers. Submitting this material to the hydrolysis conditions led to an increase in the diastereomeric ratio (dr 80:20) in the product hydrate **12a**, allowing efficient recycling of the mother liquor from the recrystallisation of *anti-3a* (Scheme 7).

The reduction of the hydrate using sodium borohydride provided the alcohol **9a** in excellent yield and without significant change in the diastereomeric ratio (Scheme 8). Alcohols **9a** and **9b**, respectively derived from L-arabinose and D-ribose could be recrystallised to afford the pure *anti* isomers in high yield. The relative stereochemistry was confirmed through an X-ray structure of ribose derivative **9b** (Fig. 2).

For the alcohols **9c** and **9d** obtained from the *D*-xylose and *L*-rhamnose hydrates **12c** and **12d** respectively, the diastereoselectivity was lower than required, and separation of the two isomers was necessary. In order to discriminate between the two species, formation of a benzylidene acetal on the 1,3-diol was performed as selectivity for the *syn*-diol should be expected.¹⁸ Indeed, the reaction of the *D*-xylose-triol **9c** with benzaldehyde in the presence of catalytic *p*-toluenesulfonic acid and a dehydrating agent resulted in the selective for-



Scheme 8 Synthesis of THF-triols 9.



Fig. 2 X-ray crystal structure of triol 9b. The thermal ellipsoids are shown at the 50% probability level, while hydrogen atoms are drawn as fixed spheres with a radius of 0.15 Å.

mation of the acetal **13** along with unreacted *anti-9c* (Scheme 9a). The stereoselectivity of this acetal protection was confirmed by single crystal X-ray crystallography of the analogous compound **13-Br.**¶ The triol *anti-9c* and acetal **13** were easily separated by column chromatography. Finally, hydrolysis of **13** using Amberlyst 15 as a catalyst quantitatively afforded *syn-9c*. Acetal **13** was also oxidised with a catalytic amount of TEMPO using PhI(OAc)₂ as co-oxidant to afford the ketone **14** in high yield. This reaction sequence was also applied to L-rhamnose triol **9d** allowing the separation of *anti-***9d** and *syn-***9d** *via* efficient formation of the acetal **15** (Scheme 9b). Ketone **16** was similarly obtained by oxidation of secondary alcohol **15**.

Oxidation of triol **9a** into the carboxylic acid-THF **10a** required a more conventional synthetic approach, using a protecting group to allow selective oxidation of the primary alcohol moiety. Protection of the *syn* 1,2-diol was performed with 2,2-dimethoxypropane in the presence of Amberlyst 15 (Scheme 10a). The acetal-protected triol **17a** was obtained in high yield and was subsequently oxidised following a procedure previously described for the oxidation of nucleosides.¹⁹



Scheme 9 Separation of the *anti* and *syn* isomers of (a) D-xylose triol 9c and (b) L-rhamnose triol 9d; yields in parentheses are based on the quantity of the relevant diastereoisomer present in the starting mixture; X-ray crystal structure of compound 13-Br with the thermal ellipsoids shown at the 50% probability level, and hydrogen atoms drawn as fixed spheres with a radius of 0.15 Å.



 $^{\|\,\}rm Tables$ of selected crystallographic data for 9b and 13-Br can be found in the ESI.† CCDC 1877937 and 1877938 contain the supplementary crystallographic data for compounds 9b and 13-Br respectively.

 $[\]label{eq:seecond} \ensuremath{\P{The selectivity of the acetal protection was confirmed by obtaining an X-ray crystal structure of $13-Br, \|$ an analogue of 13 prepared from 4-bromobenzalde-hyde (see ESI† for full details).}$

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The reaction proceeded at room temperature with a catalytic amount of TEMPO as primary oxidant, using PhI(OAc)₂ as the stoichiometric oxidant. The unprotected carboxylic acid **10a** was then released under acidic conditions in moderate yield over two steps and with high isomeric purity. The carboxylic acid was also accessible directly from the THF-hydrate **12a** thus reducing the number of steps and the stoichiometry of oxidant required (Scheme 10b). Protection of the hydrate-THF **12b** resulted in a significant loss of diastereomeric purity. However, after oxidation followed by deprotection, the carboxylic acid **10a** was isolated in moderate yield with a high diastereomeric ratio in favour of the *anti* isomer. This rise in diastereomeric ratio during the oxidation could be explained by a higher reactivity of the *anti*-THF hydrate with the hindered oxidant TEMPO in comparison to the *syn*-THF hydrate.

Finally, we sought an effective method for accessing the THF-amine 11 by direct hydrogenation of the THF-hydrazones 3. Although the literature is quite rich in precedent for the hydrogenation of hydrazones to hydrazines, the reduction of a hydrazone directly to an amine is rare at low hydrogen pressure.²⁰ In our previous work, we presented a procedure to prepare the THF-amine under 1 bar of hydrogen with Bocanhydride as an additive and Pd(OH)₂/C as catalyst (Scheme 11).¹² Reactions were initially conducted in CPME,²¹ but in subsequent studies better reproducibility was achieved in a mixture of isopropanol/water (2:1). The Boc-protected amine 20 was isolated in moderate yield on a small scale from the hydrogenation of ribose-derived hydrazone 3b, and standard deprotection using hydrochloric acid in methanol afforded the hydrochloride salt 11a·HCl (Scheme 11). The scalability of the hydrogenation proved to be problematic, however, with a dramatic loss of yield and increased reaction time as the scale was increased to gram quantities of material. The drop in the conversion can probably be explained by a poor gas-liquid-solid contact in the reaction mixture. Therefore, subsequent reductions were attempted at higher pressures of hydrogen (up to 5 bar) but did not lead to the desired amine, and instead partial reduction to the hydrazine 19 was observed (Scheme 11).

Hydrogenation can present serious safety issues in large scale batch reactions with high pressure, flammable solvents and pyrophoric catalysts. We therefore moved to a flow-chemistry set-up which offers several advantages in comparison with more traditional hydrogenation procedures, including the possibility to work at high pressure and temperature with an encapsulated catalyst to reduce the leaching of toxic metal into the reaction mixture (Scheme 12).²²⁻²⁴ As a starting point, iPrOH: $H_2O(2:1)$ was used as solvent and $Pd(OH)_2/C$ as catalyst to remain close to the initial set of reaction conditions. However even at high pressure (100 bar), the transformation did not proceed to the amine at room temperature with mostly the hydrazine 21a being formed. Moreover, when the hydrazine 21a obtained was re-submitted to a second hydrogenation-cycle, no amine product was observed. The use of Bocanhydride as additive did not solve the issue, and as Pd(OH)₂/ C did not seem an efficient catalyst under these conditions we



Scheme 11 Synthesis of Boc-protected amine 20 and scalability issues.

moved to RANEY® Nickel which has been reported previously as a good catalyst for the hydrogenation of hydrazones.²⁵ At room temperature and 100 bar of hydrogen, only reduction of hydrazone **3a** to the hydrazine **21a** was noticeable. However, at 80 °C, **3a** was fully converted to the amine **11a**. Importantly no additives were required for this transformation, and the amine was isolated in high yield directly after evaporation of the solvent (Scheme 12). Moreover, no erosion of the diastereoselectivity was observed compared to the initial hydrazone **3a**. This method was then applied to the synthesis of amines **11b**-**11d** in 68–94% yield. This direct hydrogenation of the hydrazone provides an alternative route for accessing the amines **11** to our recently reported biocatalytic approach involving reaction of hydrates **12** with transaminase enzymes.²⁶

Synthesis of sugar hydrazones from sugar beet pulp

Sugar beet pulp contains significant quantities of L-arabinose, so we were interested in its potential application as a feedstock for the synthesis of these chiral THF building blocks. It was therefore important to establish that hydrazone **1a** could be prepared from waste pulp material. To determine this, a solubilised sample of sugar beet pulp after steam explosion and acidic hydrolysis treatment was generated (Scheme **13**).²⁷⁻²⁹ Analysis of the solution prepared in this way indicated it con-



Scheme 12 Synthesis of amines 11 by reduction of the THF-hydrazones 3 using flow chemistry.



Scheme 13 Synthesis of L-arabinose hydrazone 1a from a solubilised sample of sugar beet pulp.



Fig. 3 Chiral THFs prepared in this work. All compounds shown above were obtained in >95:5 dr (except 11c/11d).

tained sodium sulfate (80 g L^{-1}) and arabinose (12 g L^{-1}), together with galacturonic acid (5 g L^{-1}), galactose (3 g L^{-1}), rhamnose (1 g L^{-1}) and glucose (1 g L^{-1}) monomers. Initially, a model synthetic mixture containing these components was treated with N,N-dimethylhydrazine (2 eq. wrt arabinose). Surprisingly, analysis of the crude product by NMR spectroscopy revealed the selective formation of the hydrazone 1a derived from L-arabinose under these conditions in quantitative yield, with only traces of the rhamnose hydrazone present. This selectivity could be explained by (i) the low solubility of galacturonic acid in methanol and (ii) the much slower reaction of hexose sugars with hydrazine compared to the pentoses. Indeed, formation of the hydrazone from galactose was previously observed to require harsher conditions for an extended period of time (3 days) to reach only moderate conversion.¹² Reaction of the heterogeneous mixture derived from sugar beet pulp under similar conditions also led to selective formation of hydrazone 1a. The concentration (>1 M) was found to be a crucial parameter for achieving high conversion in this transformation, so concentration of the crude solution was necessary prior to reaction. After purification, the arabinose hydrazone 1a was isolated in high purity in 30% yield. The discrepancy in yield between the two experiments suggests that partial decomposition of the sugars is taking place during concentration of the crude starting material, and/or that impurities present in the pulp lead to loss of material during the work-up and purification of hydrazone 1a.

Conclusions

In conclusion, we have optimised procedures for the selective dehydration of pentose sugars on multigram scales, including: (i) improvement and scale-up (20 g) of the acid-catalysed cyclisation for L-arabinose and other pentoses; (ii) development of a novel cyclisation procedure under basic conditions which preferentially provides THFs with syn stereochemistry at C-2/ C-3. These two complementary procedures offer access to a range of chiral-THFs with varied stereochemistries. The THFhydrazones were subsequently transformed into THF-triols 9, bicyclic ketones 14/16, THF-carboxylic acids 10 and THFamines 11 to build a library of functionalised THFs (Fig. 3) for potential application in medicinal chemistry. Finally, we were able to prepare arabinose hydrazone 1a selectively from a pretreated sample of sugar beet pulp, thus demonstrating the feasibility of preparing many of these chiral THF building blocks from an abundant renewable feedstock.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 Y. Xu, M. A. Hanna and L. Isom, *Open Agric. J.*, 2008, 2, 54–61.
- 2 C. V. Boucque, B. G. Cottyn, J. V. Aerts and F. X. Buysse, *Anim. Feed Sci. Technol.*, 1976, 1, 643–653.
- 3 E. Evans and U. Messerschmidt, J. Anim. Sci. Biotechnol., 2017, 8, 25–35.
- 4 M. Dusselier, M. Mascal and B. F. Sels, in *Top. Curr. Chem.*, Springer-Verlag, Berlin Heidelberg, 2014, vol. 353, pp. 1–31.
- 5 F. W. Lichtenthaler and S. Peters, C. R. Chim., 2004, 7, 65–90.
- 6 L. L. Adduci, T. A. Bender, J. A. Dabrowski and M. R. Gagné, *Nat. Chem.*, 2015, 7, 576–581.
- 7 Y. Seo and M. R. Gagné, ACS Catal., 2018, 8, 6993-6999.
- 8 J. M. Lowe, Y. Seo and M. R. Gagné, ACS Catal., 2018, 8, 8192–8198.
- 9 T. Saloranta and R. Leino, Synlett, 2015, 26, 421-425.
- 10 I. S. Young and P. S. Baran, Nat. Chem., 2009, 1, 193-205.
- 11 T. A. Bender, J. A. Dabrowski and M. R. Gagné, *Nat. Rev. Chem.*, 2018, **2**, 35.
- 12 R. W. Foster, C. J. Tame, D. K. Bučar, H. C. Hailes and T. D. Sheppard, *Chem. – Eur. J.*, 2015, 21, 15947–15950.
- 13 G. Romeo, U. Chiacchio, A. Corsaro and P. Merino, *Chem. Rev.*, 2010, **110**, 3337–3370.
- 14 L. P. Jordheim, D. Durantel, F. Zoulim and C. Dumontet, *Nat. Rev. Drug Discovery*, 2013, **12**, 447–464.

- 15 K. M. Tomczyk, P. A. Gunka, P. G. Parzuchowski, J. Zachara and G. Rokicki, *Green Chem.*, 2012, **14**, 1749–1758.
- 16 F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry and N. P. Tomkinson, *Drug Discovery Today*, 2015, 20, 11–17.
- 17 G. M. Keserű, D. A. Erlanson, G. G. Ferenczy, M. M. Hann, C. W. Murray and S. D. Pickett, *J. Med. Chem.*, 2016, 59, 8189–8206.
- 18 H. Y. Zhang, H. W. Yu, L. T. Ma, J. M. Min and L. H. Zhang, *Tetrahedron: Asymmetry*, 1998, 9, 141–149.
- 19 J. B. Epp and T. S. Widlanski, J. Org. Chem., 1999, 64, 293– 295.
- 20 G. Bégis, D. E. Cladingboel, L. Jerome, W. B. Motherwell and T. D. Sheppard, *Eur. J. Org. Chem.*, 2009, 1532–1548.
- 21 P. M. Murray, F. Bellany, L. Benhamou, D.-K. Bučar,
 A. B. Tabor and T. D. Sheppard, *Org. Biomol. Chem.*, 2016,
 14, 2373–2384.
- 22 R. Porta, M. Benaglia and A. Puglisi, Org. Process Res. Dev., 2016, 20, 2–25.
- 23 P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey and C. P. Gordon, *Org. Biomol. Chem.*, 2015, **13**, 7119–7130.
- 24 G. Jas and A. Kirschning, *Chem. Eur. J.*, 2003, **9**, 5708–5723.
- 25 *The Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries and C. J. Elsevier, WILEY-VCH Verlag, Weinheim, 2008.
- 26 F. Subrizi, L. Benhamou, J. Ward, T. Sheppard and H. C. Hailes, *Angew. Chem., Int. Ed.*, 2019, 58, 3854–3858.
- 27 C. Hamley-Bennett, G. J. Lye and D. J. Leak, *Bioresour. Technol.*, 2016, 209, 259–264.
- 28 D. P. Ward, P. Hewitson, M. Cárdenas-Fernández, C. Hamley-Bennett, A. Díaz-Rodríguez, N. Douillet, J. P. Adams, D. J. Leak, S. Ignatova and G. J. Lye, *J. Chromatogr. A*, 2017, **1497**, 56–63.
- 29 M. Cárdenas-Fernández, M. Bawn, C. Hamley-Bennett, P. K. V. Bharat, F. Subrizi, N. Suhaili, D. P. Ward, S. Bourdin, P. A. Dalby, H. C. Hailes, P. Hewitson, S. Ignatova, C. Kontoravdi, D. J. Leak, N. Shah, T. D. Sheppard, J. M. Ward and G. J. Lye, *Faraday Discuss.*, 2017, 202, 415–431.