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Uncharted Pathways for CrCl₃ Catalyzed Glucose Conversion in Aqueous Solution

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Abstract

Innovative processes for converting carbohydrates to materials and fuels form the basis for profitable bio-based economies of the future. For such innovation, approaches that provide detailed structural information would be desirable to detect uncharted chemistries of carbohydrate conversion. Among the most important value-added products accessible though conversion of biomass is 5-hydroxymethylfurfural (HMF), whose market values strongly depends on the quality of the product. Here, we use high-field *in situ* NMR spectroscopy to shed light on obscure competing reactions of CrCl₃-catalyzed carbohydrate conversion to HMF in water. High-field NMR spectroscopy has enormous prowess in distinguishing isomeric and dehydrated products formed from glucose. Previously unidentified compounds were identified with this approach and include anhydrosugars and a variety of branched and linear mono- and disaccharides. Other identified compounds leverage the understanding of the active catalyst species. In addition to providing mechanistic insight, the approaches and findings described herein help to measure and manage carbon balances and product quality in HMF production.

Keywords

2D NMR, cascade reactions, catalysis, chromium trichloride, HMF, sugars

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1 Introduction

A change towards sustainable production of materials and fuels is increasingly imminent. Sustainable production using rapidly renewable resources involves both challenges and opportunities for developing novel catalytic approaches towards the use of resources such as carbohydrates and lignin [1,2]. The high oxygen content in these substrates as compared to fossil compounds is accompanied by high functionality present in biomass [3]. Such abundant functionality in biomass raises the question, how novel processes can selectively transform the substrate to a product with selected functionality [3].

The most important value-added products accessible from carbohydrates include 5-hydroxymethylfurfural (HMF) [4,5]. HMF is being investigated by several academic and industrial groups as a promising precursor of polymers, resins, pharmaceuticals, fuel additives and solvents [2]. Depending on its quality, market values in the range of (2-300 USD/kg) have been described [6,7]. Hence, a production of highly pure compound is desirable for profitability. Processes of production have included transformations of carbohydrates using Lewis acidic salts and water as an obvious green solvent [6]. In addition, water is a more promising option for HMF purification than high-boiling organic solvents or ionic liquids [8-10].

While glucose is the cheaper and hence economically more attractive substrate than fructose, HMF yields from glucose in water have left room for improvement. Such improvement should be based on reliable carbon balances, but reported carbon yields often imply a significant amount of unidentified compounds in the reaction mixtures. The quantity of these compounds would help close the carbon balance of the processes, while their identity would be indicative of reaction mechanisms that are accessible under the given reaction conditions. The nature of byproducts in the reaction mixture also affects purification strategies in order to obtain high quality, high value product [6].

Lewis acidic salts coordinate to the aldehyde group of glucose and thus permit an intramolecular 1,2 hydride transfer that leads to reversible glucose to fructose isomerization. The reversible reaction also leads to the formation of mannose [11-13]. In addition, CrCl_3 in water can catalyze 1,5 hydride transfers that convert D-glucose to L-sorbose. Only certain species are suggested to be active for catalysis, most notably

$[\text{Cr}(\text{H}_2\text{O})_5\text{OH}]^{2+}$ [10]. Nevertheless, the catalytic reaction remains incompletely understood, as witnessed by poor carbon balances in the conversion and by the detection of unidentifiable carbohydrate byproducts in the conversion [14]. These shortcomings indicate that better understanding of homogeneous Lewis acid catalysis may pave the way to improving both homogeneous and heterogeneous Lewis acid catalysts in carbohydrate conversion [14].

In the current study, we aimed at gaining a comprehensive overview of hitherto unidentified pathways in the conversion of sugars, specifically those that are accessible in the CrCl_3 -catalyzed conversion of glucose in aqueous solution. Using *in situ* spectroscopy on the unpurified reaction mixture, we identify various compounds that shed light on the conversions of glucose in aqueous solutions of Lewis-acidic salts.

Scheme 1. Reactions of CrCl_3 -catalyzed glucose conversion in aqueous solution discussed herein.

2 Results and Discussion

We employed NMR spectroscopy to sense uncharted chemistries in CrCl_3 -catalyzed glucose conversion. NMR spectroscopy is non-selective and thus permits an unbiased assessment of post-reaction mixture composition. Approaches that are more widely used in metabolic research were adapted, including the use of authentic reference standards, database and literature mining as well as the ability to determine chemical structures in complex samples from high-field NMR data without the knowledge of the analyte sum formula. Two-dimensional assignment spectra were used to identify structural motifs and their arrangement to NMR spin systems in the molecules of the reaction mixture. To this end, multiplicity-edited variants of ^1H - ^{13}C HSQC and ^1H - ^{13}C HMBC spectra, as well as ^1H - ^1H TOCSY and ^1H - ^1H COSY spectra

were recorded. These approaches identified a variety of unexpected compounds - and hence reaction pathways - in the well-studied reaction. The identification of novel byproducts should aid the measurement and management both of carbon balances and of product quality in Lewis acid catalyzed carbohydrate conversions.

2.1 Detection and identification of anhydrosugars in aqueous reaction medium

For structural studies on unpurified reaction mixtures, NMR spectroscopy at high magnetic field (18.7 T magnetic field, 800 MHz ^1H Larmor frequency) was employed. The reaction mixture was produced by conversion of 10% (w/v) glucose in the presence of 17 mM $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ at 140 °C for one hour. NMR assignment spectra allowed us to identify the spin systems with chemical shifts shown in Figure 1. We assigned these spin systems to 1,6-anhydroglucofuranose (AGF) and 1,6-anhydroglucopyranose (AGP). Notably, the intramolecular dehydration products AGF and AGP were formed by reaction in aqueous solvent. Structural assignments to the anhydroglucoses were verified by comparison to published values for the purified, non-commercial AGF [15], while the pyranose form was identified by comparison to the spectra of authentic commercial levoglucosan standard. The peak resolving capacity of high-field 2D ^1H - ^{13}C NMR is above two million signals [16], hence the pattern of CH group signals permits analyte identification with excellent reliability.

Figure 1. Structure and chemical shift assignments of 1,6.-anhydroglucofuranose (AGF, left) and 1,6.-anhydroglucopyranose (AGP; right).

The spin system of AGF was identical to a previously reported, unidentified compound (but suspected hexose) from CrCl_3 -catalyzed glucose conversion in water under identical conditions. The bicyclic structure of the anhydrosugar explains the absence of other tautomers in this compound fractionated from product solutions of the reaction

[14]. Anhydroglucoses have previously been reported as potentially reactive byproducts in reaction pathways converting glucose to HMF in non-aqueous media [17-19]. The formation of these compounds as byproducts in aqueous solution on the other hand was less anticipated from computational predictions that suggested formation of these compounds in DMSO but not water [17]. In our experiments, AGF and AGP were detected at similar levels, albeit the substrate for AGP formation (the β -pyranose tautomer of glucose) is much more pronounced than the substrate for AGF formation (the β -furanose tautomer of glucose) in aqueous solution. This finding indicates a kinetic preference for the formation of the intramolecular furanoside as compared to pyranoside formation.

We repeated the reaction in DMSO instead of aqueous solvent to verify the higher propensity for formation of anhydroglucose under these conditions. Figure 2A shows a time series of *in situ* 1D ^{13}C NMR spectra visualizing the faster formation of AGF than of AGP at 110 °C. Subsequently, we added 17% (v/v) water to the product mixture derived in DMSO from the experiment shown in Figure 2A and followed the hydrolysis of anhydroglucose by *in situ* NMR spectroscopy at ambient pressure and 95 °C temperature (Figure 2B). The resultant time courses of AGF and AGP concentrations indicate that AGP was more resilient to hydrolysis than AGF. AGF and especially AGP levels have been found to decrease in

Figure 2. *In situ* NMR spectroscopy of AGF and AGP formation in DMSO (A) and of AGP and AGF hydrolysis upon addition of 17% (v/v) H₂O (B). Lines in (B) are a guide to the eye. Reaction conditions: 10% (w/v) glucose at 110 °C, 17 mM CrCl₃·6H₂O; reaction at 110 °C (A) subsequent hydrolysis in 17% H₂O, 83% DMSO, 95 °C (B) for the indicated time.

post-reaction mixtures upon addition of 17% water to the CrCl₃-catalyzed glucose conversion in DMSO. The resilience of AGP to hydrolysis under these conditions indicates that levels are decreased because AGP is hardly formed (rather than being hydrolyzed) in the presence of water [19]. In DMSO without addition of water, AGP and AGF can amount to significant byproducts of HMF (~40% of HMF; see Fig. 1S in the Electronic Supplementary Materials).

2.2 Formation of intermolecular acetals

An overview of hemiacetals and acetals that were present in the CrCl₃-catalyzed conversion in aqueous solution and in DMSO, respectively, is provided in Figure 3. Beyond AGF and AGP, the formation of disaccharides could be observed both in aqueous solution and - to a higher degree - in DMSO. Disaccharide formation is the result of intermolecular acetal formation of glucose, while AGF and AGP formation results from intramolecular acetal formation.

Cellulose has previously attracted some interest as a byproduct in the CrCl₃-catalyzed glucose

conversion in DMSO [18,19]. However, cellobiose was here found to be only one of the glucopyranosyl-glucopyranosides formed. The 1-4 linked cellobiose and maltose (4-O-β-D-glucopyranosyl-D-glucose and 4-O-α-D-glucopyranosyl-D-glucose, respectively) were formed in lower amounts than for instance the 1-6 linked disaccharides gentiobiose and isomaltose (6-O-β-D-glucopyranosyl-D-glucose and 6-O-α-D-glucopyranosyl-D-glucose, respectively). Integration of respective signals in the ¹H-¹³C HSQC spectra of Figure 3 indicated that gentiobiose and isomaltose are formed at levels that are 6-fold higher than those of cellobiose and maltose. Furthermore, all other glucopyranosyl-glucopyranosides that can be formed from reaction between two glucoses (trehaloses, kojibiose, sophorose, nigerose and laminaribiose) were detectable. In analogy to the formation of AGF and AGP in aqueous solution, disaccharide formation could also be detected in aqueous medium, albeit at lower levels than in DMSO (Figure 3). All disaccharide signals were identified by comparison to high-resolution ¹H-¹³C HSQC spectra of authentic standards [20].

Figure 3. Surface plot of ¹H-¹³C HSQC spectra on post-reaction samples of glucose conversion in aqueous solution (top) or in DMSO (bottom). Reaction conditions: 10% (w/v) glucose, 17 mM CrCl₃·6H₂O, 6 mL 90% H₂O/10% D₂O (top) or 99% d₆-DMSO/1% DMSO (bottom), 140 °C for 1 hour in water and/or 30 min in DMSO.

2.3 Branched C6-carbohydrates

Previous mechanistic studies had speculated on the possible presence of branched carbohydrates in aqueous glucose conversion catalyzed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$. In fact, the suspected C6-sugar identified herein as AGF had been assumed to be a branched chain hexose [14].

The signals of the branched chain hexose hamamelose (2-C-(hydroxymethyl)-D-ribose) were herein detected in the post-reaction mixture of glucose conversion by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in water as indicated in Figure 3 (top). In solution, hamamelose occurs as an equilibrium of α - and β -furanose and pyranose forms with comparable populations. Hence, hamamelose could be identified by comparison of the ^1H - ^{13}C HSQC signals to the pattern of tautomer signals from an authentic standard (Figure 4). In addition to hamamelose, 2-C-(hydroxymethyl)-L-lyxose could be detected in the aqueous reaction mixture, albeit at smaller amounts and predominantly from its pyranose form (Scheme 2). Signals were identical to the 2-C-(hydroxymethyl)-L-lyxose ^1H - ^{13}C HSQC signals after reacting sorbose with 0.2% (w/v) ammonium heptamolybdate tetrahydrate.

Figure 4. Spectral region from the ^1H - ^{13}C HSQC of the reaction mixture displayed in Figure 3 top. The reaction mixture is displayed in blue, authentic standards of hamamelose and mannose are displayed in red and light grey, respectively. Reaction conditions: 10% (w/v) glucose, 17 mM $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 6 mL 90% H_2O , 10% D_2O , 140 °C for 1 hour.

Scheme 2. Branched chain sugars detected upon conversion of glucose with CrCl_3 .

Hamamelose and 2-C-(hydroxymethyl)-L-lyxose can be formed by Bilik-type carbon shifts from fructose and sorbose, respectively. The Bilik-type carbon shift has been widely described for the direct conversion of glucose to mannose by concurrent C2-C3 bond cleavage and C1-C3 bond formation resulting in an intramolecular C1-C2 carbon shift [21-24]. For ketoses, the concurrent C2-C3 bond cleavage and C2-C4 bond formation leads to the formation of the branched chain ketoses (Scheme 3).

Formation of the branched C6-carbohydrates by a mechanism akin to Scheme 3 was corroborated by using D-[1- ^{13}C] glucose as substrate. The ^{13}C label was preferentially incorporated into the 2-hydroxymethyl groups of hamamelose, as expected from the displayed mechanism (see Fig. 2S in the Electronic Supplementary Materials). Alternatively, branched C6-carbohydrates could have been formed by aldol condensation of smaller linear sugars. Branched sugars have thus been discussed as prospective value-added compounds or precursors to value-added chemicals formed from smaller sugars [25]. Due to the reversibility of the Bilik reaction, and the likely irreversibility of fructose dehydration to HMF [17], branched sugars presumably interconvert with their respective ketose forms and serve as off-pathway intermediates for the formation of HMF. Consistent with this interpretation, hamamelose accumulated less in DMSO than in aqueous reaction medium (see e.g. Figure 3), probably due to the faster competing conversion of fructose to HMF in DMSO. This interpretation is consistent with previous reports showing that less fructose exists freely in the reaction system of DMSO as compared to aqueous solutions, as the high dehydration potential of DMSO favors subsequent reaction of fructose to HMF [18].

Both in aqueous solution and in DMSO, the combined amount of carbon that is detected in carbohydrates different from glucose, mannose and fructose is comparable to the level of HMF in the experiments of Figure 3. Hence, the less canonical pathways of carbohydrate conversion described herein can impact strongly on the carbon balance of the catalyzed reaction.

Scheme 3. Plausible mechanism for the conversion of ketoses into branched carbohydrates with a migration of the ketose C1 carbon to 2-hydroxymethyl groups.

2.4 Formation of a variety of C6-carbohydrates through cleavage/condensation

Ketoses are absent in the hemiacetal spectral region (Figure 3), but can be conveniently detected in the primary alcohol region of 2D ^1H - ^{13}C HSQC spectra. Figure 5 displays the primary alcohol spectral region including signals from ketoses and aldoses formed in aqueous solution. As expected, fructose and sorbose were among the ketoses detected in the reaction. Less expected was the presence of smaller amounts of tagatose, the keto-isomer of galactose. In parallel to tagatose, galactose could be detected both from its C1 signal (Figure 3) and from its C6 signal (Figure 5) in ^1H - ^{13}C HSQC spectra. Other C6 sugars such as altrose, idose and allose could be detected by comparison to authentic standards, albeit at low amounts (see Fig. 3S in the Electronic Supplementary Materials). These findings are consistent with the presence of C3 sugars (especially dihydroxyacetone) in the reaction mixture as a possible precursor for the variety of C6 sugars and a likely intermediate in subsequent cleavage/condensation reactions of glucose.

Diverse hexose reaction products have previously been reported when using dedicated retro-aldol and 1,2 carbon shift catalysts for the conversion of aldohexoses [23]. Overall, CrCl_3 -catalyzed conversion of glucose induces the formation of a diverse ensemble of mono- and disaccharides, branched carbohydrates and anhydrosugars, even though the formation of these products was not optimized by any means in the current study.

Figure 5. Spectral region of primary alcohol groups in ^1H - ^{13}C HSQC, showing ketose signals for fructose, sorbose and tagatose at decreasing amounts, in addition to aldose and anhydrosugars as indicated.

2.5 Dehydration reactions different from HMF formation

Signals outside the spectral region of carbohydrates were evident in NMR spectra of post-reaction mixtures. Such signals included the expected signals from HMF and levulinic acid (see Fig. 4S and 5S in the Electronic Supplementary Materials). The presence of unexpected compounds was evident through the presence of various olefinic, aldehyde or aliphatic hydrogen NMR signals. Figure 6 displays the spin system of byproduct (2E)-2,4-pentadienal in the aqueous reaction mixture. The ^1H NMR signals are displayed through their correlations in a ^1H - ^1H TOCSY spectrum. The chemical structure can be determined unambiguously against the reaction mixture background through sequential assignments of a characteristic aldehyde group and four olefinic groups including a terminal CH_2 group. LC-MS analysis confirmed the presence of a compound with the molecular weight of pentadienal in the reaction mixture (see Fig. 6S in the Electronic Supplementary Materials). The chemical identity of the compound was additionally verified through comparison to published chemical shift values [26]. Like anhydrosugars, unsaturated compounds including (2E)-2,4-pentadienal are early intermediates in the pyrolysis of biomass [27]. The formation of such products thus appears accelerated in the presence of catalytic amounts of CrCl_3 at 140 $^\circ\text{C}$ in aqueous solution.

Figure 6. ^1H - ^1H TOCSY showing the spin system of (2E)-2,4-pentadienal. The assignment of the compound in water is displayed.

The presence of unexpected byproducts can hint at the structure of the active catalyst species. In the case of CrCl_3 catalysis in water, $[\text{Cr}(\text{H}_2\text{O})_5\text{OH}]^{2+}$ was suggested as the most active Cr(III) species acting as a bifunctional Lewis acid-Brønsted base site [10]. Our aqueous reaction mixture contained a compound most likely representing 2-C-methyl-ribonolactone. A plausible pathway for the formation of this compound is depicted in Scheme 4. The compound is the result of a Lewis acid catalyzed aldose-to-ketose isomerization and subsequent Brønsted base catalyzed benzilic acid rearrangement [28]. Hence, the presence of this compound is consistent with the previously suggested activity of a bifunctional Lewis acid-Brønsted base site. The compound was identified through multiplicity edited ^1H - ^{13}C HSQC and ^1H - ^{13}C HMBC spectra identifying a lactone and tertiary alcohol carbon, as well as a secondary alcohol in the vicinity of a methyl group (Figure 7). Chemical shifts of the compound are strongly indicative of a five-membered ring and are consistent with assignments of the previously characterized purified compound [28].

Scheme 4. Plausible pathway towards 2-C-methyl-ribonolactone through isomerization, dehydration and base catalyzed rearrangement [28].

Figure 7. Structure of 2-C-methyl-ribonolactone and multiplicity edited ^1H - ^{13}C HMBC showing the connectivities from the methyl protons to quaternary carbons of tertiary alcohol and lactone (red sub-spectrum) and to the CH group of the secondary alcohol C3 (blue sub-spectrum).

2.6 Implications for monitoring pathways, carbon balances and product quality

Use of in situ NMR spectroscopy on unpurified reaction mixtures provides a means of detecting and identifying uncharted chemistries in CrCl_3 -catalyzed glucose conversion. Formation of anhydrosugars and other reactions occurring early in glucose pyrolysis were accelerated in the CrCl_3 -catalyzed reaction in water at 140°C . Likewise, branched carbohydrates, disaccharides and carbohydrates formed from subsequent cleavage-condensation reactions could be identified. In addition, a reaction product that could be indicative of the concerted action of Lewis acidic isomerization and Brønsted base catalyzed rearrangement supports the notion that these sites may play a concerted catalytic role. LC-MS was used as a complimentary method to validate the presence of compounds with the mass of pentadienal, dehydration products and disaccharides, in addition to HMF (see Fig. 6S in the Electronic Supplementary Materials).

Several pathways and compounds contribute to the carbon balance of the CrCl_3 -catalyzed reaction in water at 140°C (Figure 5S in the Electronic Supplementary Materials, with yields for 15 main compounds and compound classes listed in the figure caption). Unsurprisingly, product distributions are vastly altered when conducting the reaction in DMSO (Figures 3 and 1S). DMSO stabilizes the acyclic and five-membered furanose structure of fructose relative to the pyranose form [29-31], facilitates dehydration of fructofuranose to HMF and prevents the formation of levulinic acid, while favoring intra- and intermolecular acetal formation of glucose to anhydroglucose and disaccharides, respectively.

Beyond its impact on the carbon balance, the quantitative identification of byproducts has an important role in product purification and hence product quality. Byproduct yields were determined with a lower limit of quantification of ~0.2%, when using 10% (w/v) glucose substrate. As purity and price correlate, validating the purification of highly pure biomass derived compounds is highly desirable for the profitability of future bioeconomies.

3 Conclusion

In conclusion, the methodology and findings described herein identify byproducts without the need for purifying them. Use of high field *in situ* NMR spectroscopy in conjunction with reference compounds, literature mining and the use of two-dimensional assignment spectra emerges as an attractive approach to identify new reactions in biomass conversion [32,33]. This approach is particularly promising for identifying hitherto unknown compounds due to the ability to distinguish isomeric compounds, even in the absence of authentic reference standards. Reactivities described herein benefit the understanding of mass balances in HMF formation by providing insight into new classes of byproducts. In addition, the improved mapping of accessible reaction pathways will expedite future identification of impurities and will aid the development of purification strategies towards high-value HMF production from carbohydrates.

4 Experimental section

4.1 Chemicals

D₂O (99.9 atom % D), d₆-DMSO (99.9 atom % D), D-mannose (>99%), sorbose, tagatose, D-[1-¹³C] glucose (99 atom % ¹³C), 1,6-anhydro-β-D-glucopyranose (99%) and ammonium heptamolybdate tetrahydrate (99.98%) were obtained from Sigma-Aldrich. CrCl₃·6H₂O (>96%) was obtained from Merck. Hamamelose was obtained from Carbosynth. In order to detect 2-C-(hydroxymethyl) lyxose signals, sorbose was reacted with 0.2% (w/v) ammonium heptamolybdate tetrahydrate for 2 hours at 80 °C and observed NMR signals of 2-C-(hydroxymethyl)-L-lyxose signals were identified in the resultant mixture using previously assigned chemical shifts for the purified compound [34].

4.2 General procedure for catalytic experiments

Glucose was dissolved to 10% (w/v) in 6 mL of H₂O or DMSO. CrCl₃·6H₂O was added to a final concentration of 17 mM. Catalytic experiments were carried out in 15 mL Ace pressure tubes under magnetic stirring at 140 °C for up to 6 hours and samples of 500 μL volume were collected after 10, 30, 60, 120, 240 and 360 minutes.

D₂O was added to the aqueous reactions to a final concentration of 10% (v/v). For tracking the fate of D-[1-¹³C] glucose in aqueous solution, 500 μL of a mixture with standard concentrations (10% D-[1-¹³C] glucose and 17 mM catalyst) were transferred to a 5 mm NMR sample tube and reaction was tracked *in situ* at 95 °C overnight in a 600 MHz Bruker Avance III NMR spectrometer equipped with a BBO smart probe.

4.3 Assignment NMR spectra

Assignment spectra of reaction mixtures were recorded at 25 °C on a Bruker Avance III 800 MHz spectrometer equipped with a TCI cryoprobe. NMR spectra included standard and multiplicity edited ¹H-¹³C HSQC, ¹H-¹³C HMBC spectra as well as ¹H-¹H COSY and ¹H-¹H TOCSY spectra. Cr(III) lead to some line broadening especially in the ¹H dimension. Authentic reference compounds were dissolved to concentrations of 50 mM in D₂O or in d₆-DMSO prior to the acquisition of ¹H-¹³C HSQC spectra. All spectra were processed with extensive zero filling in both spectral dimensions using a shifted sine-bell apodization function and analyzed in Bruker Topspin 3.5 pl7. Chemical shifts were referenced relative to the anomeric signal of α-glucopyranose at 5.230 (¹H) and 92.990 (¹³C) ppm [20].

4.4 Data Fitting

¹³C T₁ relaxation times were measured on reaction mixtures using the inversion-recovery method with recovery delays of 0.1, 1, 5, and 60 seconds and an inter-scan relaxation delay of 300 seconds. Spectra were acquired on a Bruker Avance III 800 MHz spectrometer equipped with a TCI cryoprobe. Signal areas were integrated in Bruker Topspin 3.5 pl7 and fitted using proFit 6.2.9 (QuantumSoft, Zurich) as

$$A(\tau) = A(0)[1 - 2(e^{-\frac{\tau}{T_1}})],$$

where A(0) is the signal area derived for the relaxed (Boltzmann equilibrium) spin polarization, τ is the recovery delay and T₁ is the spin-lattice relaxation time. Cr(III) shortened relaxation times to below 1 second for most substrate, solvent and product ¹³C spins (see Fig. S5 in the Electronic Supplementary Materials). Hence, quantitative ¹³C spectra, for instance in reaction tracking (Figure 2), could be acquired with short recycle delays and high sensitivity.

4.5 LC-MS

LC-MS experiments were conducted using a Waters Acquity UPLC system connected to a Waters SQD2 mass spectrometer. The UPLC system contained a quaternary pump, an autosampler, a Waters HILIC column, a temperature-controlled column oven, and a diode array detector. Phase A was 0.1% formic acid (aq) and phase B was acetonitrile/water (95/5, v/v) with 0.1% formic acid. Positive and negative ESI modes were used. Data were acquired, processed and analyzed using the MassLynx version 4.1 software package.

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