Catalytic enantioselective syn hydration of enones in water using a DNA-based catalyst

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The enantioselective addition of water to olefins in an aqueous environment is a common transformation in biological systems, but was beyond the ability of synthetic chemists. Here, we present the first examples of a non-enzymatic catalytic enantioselective hydration of enones, for which we used a catalyst that comprises a copper complex, based on an achiral ligand, non-covalently bound to (deoxy)ribonucleic acid, which is the only source of chirality present under the reaction conditions. The chiral β-hydroxy ketone product was obtained in up to 82% enantiomeric excess. Deuterium-labeling studies demonstrated that the reaction is diastereospecific, with only the syn hydration product formed. So far, this diastereospecific and enantioselective reaction had no equivalent in conventional homogeneous catalysis.

Although nature is remarkably adept at routinely using water as a nucleophile in the enantioselective synthesis of chiral molecules, this remains a major challenge to modern synthetic chemistry, especially in aqueous media. An important transformation in this respect is the asymmetric conjugate addition of water to α,β-unsaturated ketones, which provides chiral β-hydroxy ketones, a key structural motif in many natural products. Hydratase enzymes, such as fumarase and enoyl-CoA hydratase, achieve this enantioselective transformation in anti- or syn-selective fashion, albeit with generally high substrate specificity. In contrast, despite significant progress in aqueous-phase catalysis, including catalytic asymmetric synthesis, so far the enantioselective hydration of enones has eluded homogeneous catalysis. Here we present the first non-enzymatic diastereospecific and enantioselective hydration of α,β-unsaturated ketones with and in water that results in chiral β-hydroxy ketones from the syn addition of water, with up to 82% enantiomeric excess (e.e.).

Strategies are available for the catalytic asymmetric synthesis of the β-hydroxy carbonyl compounds, most notably the hydrogenation of β-keto esters and the aldol and oxo-Michael reactions. For the oxo-Michael addition, an enantioselective formal hydration of enones was achieved by conjugate addition of an oxygen nucleophile, such as an oxime, followed by reduction to yield the β-hydroxy ketone. The phosphine-catalysed conjugate addition of water to access racemic β-hydroxy carbonyl compounds has also been reported. To the best of our knowledge, no examples of the enantioselective conjugate addition of water in water that results in chiral β-hydroxy ketones from the syn addition of water, with up to 82% enantiomeric excess (e.e.).

The (deoxy)ribonucleic acid (DNA)-based catalytic system presented here overcomes several challenges to the enantioselective conjugate addition of water, including the intrinsic reversibility of hydration and the poor nucleophilicity of water under neutral conditions. That many chiral catalysts require anhydrous conditions to function optimally further complicates this reaction, which makes a DNA-based catalyst more attractive.

DNA-based asymmetric catalysis, a concept we introduced recently, proves to be a powerful approach to achieving asymmetric catalysis in water. The DNA-based catalyst consists of a catalytically active copper(II) complex (Cu–L), which is positioned in close proximity to the DNA helix through non-covalent interactions. Salmon testes DNA (st-DNA), which is natural DNA that consists of duplex fragments approximately 2,000 base pairs long, is generally used as the DNA source. In taking this approach, the inherent chirality of DNA was employed to achieve high enantioselectivities in several key C–C bond-forming reactions, such as the copper-catalysed Diels–Alder, Michael addition and Friedel–Crafts alklylation reactions. Enantioselective fluorinations and allylic aminations using DNA-based catalysts have also been reported. In our studies of the transformations of enones catalysed by Cu–L/st-DNA, we discovered, serendipitously, the first examples of enantioselective conjugate addition of water in water that result in the enantiomerically enriched β-hydroxy ketone product.

Results and discussion
The model reaction in the present study is the hydration of α,β-unsaturated 2-acyl imidazole 1a to give the β-hydroxy ketone 2a (Fig. 1). Using the Cu2a complex of 4,4′-dimethyl-2,2′-bipyridine (Cu–L) and st-DNA (the DNA-based catalyst that provided the highest enantioselectivities in all C–C bond-forming reactions reported to date), 2a was obtained with a modest 19% e.e. In contrast, the highest enantioselectivities were obtained with the first generation of ligands, which comprise a 9-aminoacridine intercalating moiety connected to an aminomethylpyridine metal-binding domain by a spacer (Fig. 1). The best results were obtained using 2L2, with 55% conversion and 72% e.e. after 24 hours for the R-enantiomer of 2a (Table 1, entry 2). Generally, lower conversions and enantioselectivities were obtained with the related ligands 1L3–1L5 (Table 1, entries 3–5). The absolute configuration of the hydration product was established by converting 2a into the corresponding β-hydroxy carboxylic ester, described previously (see Supplementary Information). This corresponds to the attack of water from the re-face of the enone. A series of control experiments confirmed that the enantioselectivity was induced by hydration of the alkene and was not the result of an enantioselective retro-aldol/aldol reaction (see Supplementary Information).

The catalyst concentration could be lowered to 3 mol% in copper (ratio of base pairs DNA/Cu–L2, 6:1) with only a small decrease in the enantiomeric excess (Table 1, entry 6), albeit the conversion did...
not reach the same level, even after prolonged reaction. When the reaction was performed in the absence of ligand, but in the presence of st-DNA and Cu(NO₃)₂, the S-enantiomer of 2a was obtained with 42% e.e. (Table 1, entry 7). This is the opposite enantiomer of st-DNA and Cu(NO₃)₂, the reaction was performed in the absence of ligand, but in the presence of st-DNA. Figure 1 shows the reaction scheme of the DNA-based catalyst and general reaction scheme of the catalytic enantioselective hydration of a variety of α,β-unsaturated 2-acyl-(1-alkyl)imidazole substrates.

**Table 1 | Reaction optimization and substrate scope.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product</th>
<th>Ligand</th>
<th>Reaction time (h)</th>
<th>Conversion (%)</th>
<th>e.e. (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>L₁</td>
<td>24</td>
<td>14</td>
<td>19 (R)</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2a</td>
<td>L₂</td>
<td>24</td>
<td>55</td>
<td>72 (S)</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2a</td>
<td>L₃</td>
<td>24</td>
<td>20</td>
<td>24 (R)</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2a</td>
<td>L₄</td>
<td>24</td>
<td>36</td>
<td>55 (R)</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2a</td>
<td>L₅</td>
<td>24</td>
<td>24</td>
<td>20 (R)</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2a</td>
<td>L₂</td>
<td>72</td>
<td>33</td>
<td>62 (R)</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2a</td>
<td></td>
<td>24</td>
<td>20</td>
<td>42 (S)</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2b</td>
<td>L₂</td>
<td>7</td>
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<tr>
<td>9</td>
<td>1c</td>
<td>2c</td>
<td>L₂</td>
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<td>3</td>
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<td>1d</td>
<td>2d</td>
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<td>2e</td>
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</tr>
<tr>
<td>12</td>
<td>2f</td>
<td>2f</td>
<td></td>
<td>24</td>
<td>0</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Standard conditions: 5°C, 20 mM MES buffer, pH 6.5, 15 μM 1 (1 mM), 1.3 mg ml⁻¹ st-DNA (2 mM base pairs). 0.39 mM ligand, 0.3 mM Cu(NO₃)₂ unless noted otherwise. *Determined by ¹H NMR spectroscopy. †Determined by HPLC using a chiral stationary phase. ‡0.14 mg ml⁻¹ st-DNA, 0.039 mM ligand, 0.03 mM Cu(NO₃)₂; n.d. = not determined.
was induced between R–2a and S–2a. Tentatively, this could result from the formation of diastereomeric complexes with Cu–L2/DNA.

The stereochemical course of the hydration reaction was elucidated further by carrying out the transformation with D2O as solvent. The reaction in D2O was slower than that in H2O, but the equilibrium shifted towards the product: after three days 40% conversion and 79% e.e. was found and after seven days the conversion increased to 90% and 3a was obtained with 73% e.e. (Fig. 3). The presence of an equilibrium isotope effect explains the higher conversion and enantioselectivity found in D2O; apparently, 3a is more stable than 2a, and hence the contribution of the dehydration reaction relative to the hydration pathway is smaller.

The 1H NMR spectrum of 3a in CDCl3 shows that it contains one deuterium at the α-carbon (Fig. 3). This further supports a hydration mechanism, because a retro-aldol/aldol mechanism would give rise to complete deuteration at the α-position.

The appearance of the signal for the α-protons of 2a is the result of two different vicinal couplings of the diastereotopic protons. The rotation around the C2–C3 bond is restricted in β-hydroxy ketones because of the formation of an intramolecular hydrogen bond between the β-alcohol and the keto moiety, which is supported by infrared spectroscopy and concentration-dependent 1H NMR spectroscopy (Supplementary Figs S8,S9). This results in a chair-like conformation, in which the bulky t-butyl moiety can be assumed to occupy the equatorial position25. The geminal coupling constant between the two α-protons is 15.7 Hz. The two vicinal coupling constants of 9.4 and 2.3 Hz between the α-protons and the β-proton involve the anti and the gauche protons, respectively.

The reaction of 1a with D2O yielded monodeuterated 3a as a single diastereoisomer, with a vicinal coupling constant of 2.0 Hz, which indicates that the two vicinal protons are positioned in a

Figure 2 | Temporal evolution of enantiomeric excess and conversion.

a. The hydration of 1a into 2a over time. The enantiomeric excess (of R–2a) is depicted as open squares and the conversion of 1a into 2a as closed diamonds. b. The dehydration of 2a into 1a over time. The enantiomeric excess of the remaining substrate (S–2a) is depicted as open squares and the conversion of 2a into 1a as closed diamonds. Figure 2a shows the enantiomeric excess in the R-enantiomer, whereas Fig. 2b shows the enantiomeric excess in the S-enantiomer.

Figure 3 | Diastereospecificity of the catalytic hydration reaction.

a. Synthesis of 3a by hydration using D2O and catalysed by Cu–L2/st-DNA. b. Synthesis of 3b by hydration of deuterated substrate 4 (85% D) catalysed by Cu–L2/st-DNA. c. 1H NMR spectra of 2a (i), 3a (ii) and 3b (iii) in CDCl3 in the region 3.8–3.0 parts per million (ppm), and chair conformations and Newman projections used for the conformational analysis. Signals in the 3.2–3.0 ppm region arise from the α-protons, and signals at 3.7–3.8 ppm from the β-protons. In the spectrum of 2a (i), the geminal coupling constant between the two α-protons is 15.7 Hz. The two vicinal coupling constants of 9.4 and 2.3 Hz between the α-protons and the β-proton involve the anti and the gauche protons, respectively. The spectrum of 3a (ii) shows a single diastereomer with a vicinal coupling constant of 2.0 Hz, which demonstrates that D2O was added in a syn fashion. For the complementary experiment that gave rise to 3b, spectrum (iii) shows a large vicinal coupling constant of 10.0 Hz, which corresponds to the anti-orientation between the α- and β-protons. Im = 2-(1-methyl)imidazolyl.
Cu(NO$_3$)$_2$ in D$_2$O (that is, in the absence of DNA or ligand) also fashion. Interestingly, it was observed that reaction with only TTTTG)$_2$ and d(GCGCTATAGCGC)$_2$ in D$_2$O (82% e.e.). These optimum enantiomeric excess showed that sequences with central diastereospecificity, and ensures that both the hydroxyl group and the atom and the hydroxyl group were from the same water molecule as enoyl-CoA hydratase. For enoyl-CoA hydratase the hydrogen source of chirality present in the reaction and, hence, is responsible for the observed chiral induction; in the absence of DNA, no enantioselective hydration of L1(NO$_3$)$_2$. A 15 ml aqueous solution of the copper(II)–L1 complex (0.3 mM) and st-DNA (1.3 mg mL$^{-1}$) in 2-(N-morpholino)ethanesulfonic acid (MES) buffer (20 mM, pH 5.5) was prepared by mixing 10 ml of a st-DNA stock solution (12 mg ml$^{-1}$ st-DNA in 30 mM MES buffer, pH 5.5, prepared 24 hours in advance) with 5 ml of a filtered solution of Cu(NO$_3$)$_2$ (0.9 mM) and ligand L1 (1.2 mM) in water. 1a (2.9 mg) was added to the catalyst solution (15 µmol, final concentration 1 mM) dissolved in 30 µl of CH$_3$CN. The reaction was mixed by continuous inversion at $5\, ^\circ C$. The crude product was isolated by extraction with Et$_2$O (2 × 10 ml), drying on Na$_2$SO$_4$ and concentration in vacuo. The enantiomeric excess was determined by HPLC, using a chiral stationary phase. An analytically pure sample of 2a was obtained after column chromatography (SiO$_2$, hexanes:ethyl acetate).

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References


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Author contributions

A.J.B., B.L.F. and G.R. conceived the project; A.J.B., D.C. and G.R. designed the experiments; A.J.B., D.C., D.G. and F.R. performed the experiments and analysed the data. A.J.B., B.L.F. and G.R. co-wrote the paper. All authors discussed the results and commented on the manuscript.

Additional information

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