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## COMMUNICATION

## Mixing Chemo- and Biocatalysis for Rare Monosaccharide Production by Combining Aldolase and N-Heterocyclic Carbene Gold Catalysts

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**Chemo- and biocatalysis for multistep reactions were successfully combined to synthesize polyhydroxylated monosaccharides. Gold N-heterocyclic carbene, catalysing a green hydration, was coupled to an aldolase to create two stereocenters via a C-C bond formation in stereoselective and total economy atom fashions starting from simple and achiral compounds.**

Since many years, chemoenzymatic hybrid catalysis is the subject of great attention as it paves the way for the preparation of new molecules that are difficult to obtain through conventional synthetic strategies.<sup>1–4</sup> Hybrid catalysis combines biocatalysis, based on the specific activities (chemo-, stereo- and regioselectivity) of enzymes that catalyze complex reactions under soft working conditions (ambient temperature, atmospheric pressure, neutral pH, aqueous solvent) not easily reproduced by chemists,<sup>5</sup> with the efficiency of chemocatalysis, giving access to a large diversity of molecules, particularly small molecules or biomolecules, that may be produced at the industrial scale. It is highly unlikely that both catalytic processes may replace each other while combining both will offer new developments in synthetic chemistry. A one-pot synthesis based on cascade reactions should optimize the synthetic process in terms of time and resources,<sup>6</sup> avoiding protection/de-protection and even purification steps, leading to high yields, economic and environmental benefits, sustainable requirements that are promoted by the green chemistry concepts. However, implementation of hybrid catalysis is facing a hard challenge concerning the compatibility of both connected reactive systems often involving fragile enzymes and robust transition metal catalysts.<sup>7–9</sup> Operating conditions must be found to optimize the cascade pathway, to insure the chemical stability of substrates and products, and to

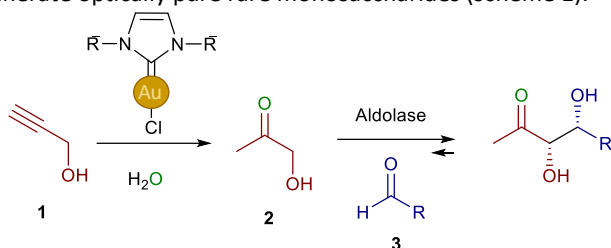
maintain the intrinsic catalytic activities of both catalysts, by avoiding their deactivation one by the other or by the substrates, the intermediates, the products or any possible co-solvents.

In the last decade, catalysis by gold complexes has emerged as a powerful tool for chemical synthesis through the activation of unsaturated hydrocarbons. Alkynes, for instance, can lead to a great variety of reaction as Rupe rearrangement, cycloisomerization, redox isomerization, Meyer Schuster rearrangement and hydration.<sup>10,11</sup> Alkyne hydration, a reaction transforming an alkyne into a ketone, is recognized as a typical example of atom economy principle.<sup>12</sup> Initially developed by Teles seminal work,<sup>13</sup> this gold(I) catalysed reaction have gained great interest over decades. The initial catalytic system consists in phosphines-based gold complexes and requires rather harsh conditions (sulfuric acid). Later, Marion et al.<sup>14</sup> reported that *N*-heterocyclic carbene (NHC) could efficiently replace the phosphine ligand. The chloride ligand is usually removed from the gold atom by addition of a proper scavenger (AgSbF<sub>4</sub>...). More recently, Gautier et al. reported that water soluble NHC-AuCl complexes could perform the hydration reaction in water, without silver scavenger or pH control and at a relatively low temperature (65°C), making the process greener and probably compatible with biological based material.<sup>15</sup> Therefore, we hypothesized that the ketones generated during this hydration reaction could be converted by various biocatalysts such as dehydrogenases, transaminases, transferases or aldolases, leading to functionalized chiral molecules with a high added value. To our knowledge, only two examples have been described in the literature converting the ketones, both concerning the use of dehydrogenases.<sup>16,17</sup> However, aldolases would be particularly interesting in this context of green chemistry since they also function, like the hydration reaction, with a total economy of atoms. Importantly, no cofactor needs to be regenerated and the reaction equilibrium is largely in favour of the product. More generally, only few examples of hybrid catalysis using the aldolisation reaction can be found in the literature<sup>18–21</sup> and even less concern biocatalysed

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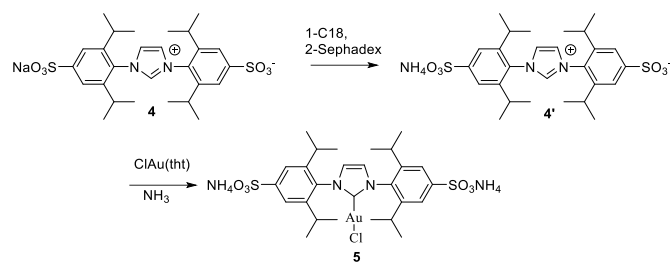
aldolisation reaction,<sup>22</sup> while this is a key reaction in organic synthesis. In this work, we propose to combine two original catalysts on the rise in their respective fields, a NHC-AuCl catalyst to catalyse a hydration reaction, and an aldolase to generate optically pure rare monosaccharides (scheme 1).



**Scheme 1.** Hydration reaction on propargyl alcohol **1** catalysed by NHC-AuCl, followed by FSA-catalysed aldolisation reaction between ketone **2** and aldehyde **3**, in a one-pot two-steps manner.

Among the different existing aldolases,<sup>23–26</sup> fructose-6-phosphate aldolase (FSA) has been chosen. It is the most recently discovered aldolase (in 2001) at the origin of a new family of aldolases called dihydroxyacetone (DHA)-aldolases, because DHA was the first nucleophilic substrate characterised for this enzyme. It is a class I aldolase, i.e., the nucleophile acts in the mechanism in the form of an enamine, formed thanks to the presence of a lysine in the active site (to note, class II aldolases correspond to the use of an enolate as a nucleophile). FSA allows the stereoselective formation of monosaccharides of (3*S*,4*R*) configurations. It is a thermostable enzyme with an optimum pH of 8.5.<sup>27</sup> Its role in the metabolism is not yet known, but in a very original way, it accepts different nucleophiles as substrates.<sup>26</sup> Actually, the best nucleophile is hydroxyacetone (HA), an unstable commercial molecule that should be distilled before use. Direct access to this methylketone moiety can be achieved by hydration of the propargyl alcohol (Scheme 1). In this context, the application of NHC-AuCl catalysts has already been reported in the literature.<sup>15</sup> We were interested in catalyst **5** (scheme 2) because the synthesis of ligand **4** is well described and **5** is negatively charged, like the enzyme, which could eventually allow their co-immobilisation on the same cationic support in the future. We applied the synthesis proposed by Plenio to obtain the imidazolium.<sup>28</sup> Quantitative <sup>1</sup>H NMR<sup>29,30</sup> indicated a purity of 56% on crude ligand **4** (Scheme 2). Purifying the crude mixture by reverse chromatography (C18 column) increased the purity to 70%. A subsequent purification on Dowex ion exchange resins failed probably due to interactions between the polymer of the stationary phase and the catalyst, disturbing the elution. Finally, using a crosslinked dextran-based resin (Sephadex: bicarbonate form) a final 90–95% purity was reached after elution with NH<sub>4</sub>HCO<sub>3</sub> (0.5 M). Ammonium carbonate was used because in the next step catalyst **5** is synthesized using the ammonia protocol<sup>31</sup>, thus avoiding the formation of a cation mixture. A final step using chloro(tetrahydrothiophene)gold(I)<sup>32</sup> and aqueous ammonia as base, in an ethanol/water mixture, afforded the expected Au-NHC **5** with a yield of 77% and in 94% purity, with no need for further

purification. We tested **5** (0.75 mol%) on an aqueous solution of propargyl alcohol (c=0.5 M) and find out that a complete conversion is achieved in 90 min at 60°C.

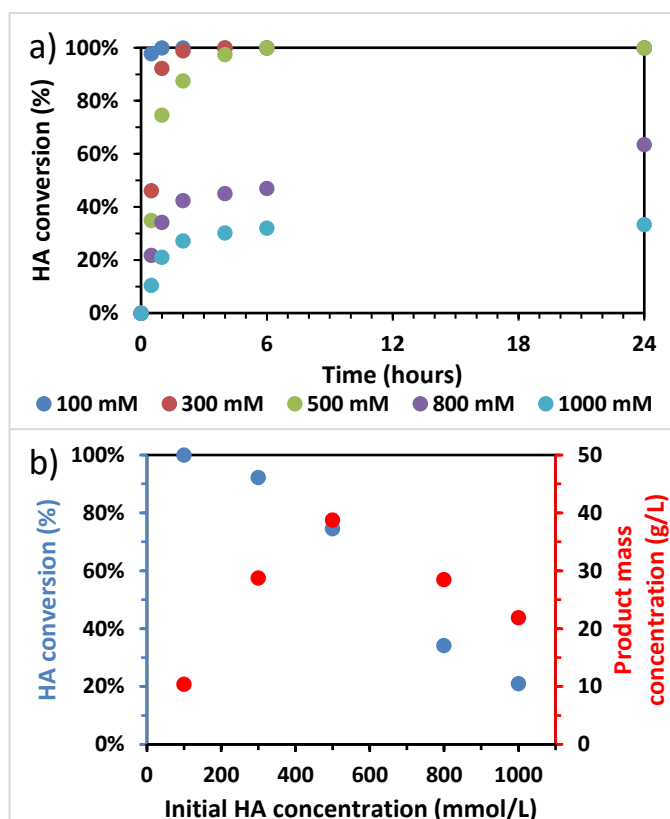


**Scheme 2.** Catalyst ligand purification steps required before synthesis of the catalyst.

The next step was to find the right working conditions to make the two catalysts compatible. Indeed, reaction solvent (water) and temperature (60°C), the usual conditions applied for carbenes gold catalysis, are the only compatible parameters to consider a coupling with thermostable FSA. In contrast, the catalysts have been used at different pH and concentrations: neutral pH and up to 100 mM substrate concentration for FSA<sup>33–35</sup> vs pH 3 and up to 1 M for the gold catalyst.<sup>15</sup> In addition, other putative cross effects, particularly concerning FSA and/or FSA substrates on gold catalyst and vice-versa have been studied, from the perspective of a one-pot reaction.

#### FSA compatibility

Firstly, for industrial purpose, FSA behaviour towards high substrate concentration has been investigated at analytical level, using HA and formaldehyde in a model reaction. When varying the concentration range from 0.1 to 1 M in stoichiometric amounts of both substrates, FSA revealed to be efficient up to 0.5 M since a total conversion was observed by spectrophotometric monitoring of HA disappearance, after 4h (Figure 1a). However, beyond this value, at 0.8 and 1 M, conversion rate dropped to 63 and 33% respectively after 24 h. In addition, at 1 M substrates concentrations, a slight reaction progress was detected from 6 to 24 h reaction time, which can be explained by enzyme denaturation. The quantity of product obtained after one hour was also represented when varying substrates concentrations. Again, the best result was obtained when using 0.5 M of both reactants (Figure 1b), which corresponds to an increase of 5 to 10 times compared to the usual concentrations, then reaching acceptable values for possible industrial applications.

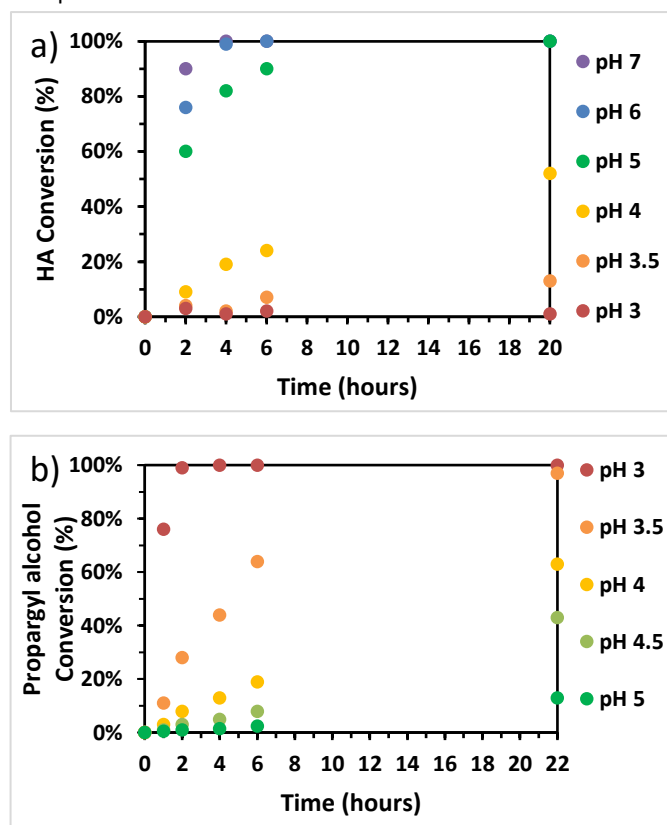


**Figure 1.** a) FSA catalysed conversion of hydroxyacetone (HA) and formaldehyde for various initial concentrations over time, b) Conversion and product mass concentration after one hour of reaction according to the starting concentrations of substrates. Conditions: 2 mg/mL FSA, hydroxyacetone and formaldehyde as substrates in stoichiometric amount, in a 1 mL final water volume, pH 7, room temperature.

Then, pH effect on FSA was assessed. This enzyme is known to have a broad pH profile of activity, from 6 to 12, with an optimum at 8.5, but no detail was reported concerning its activity over time at a pH lower than 6. When involving HA plus formaldehyde as the couple of substrates, as suspected, FSA loses activity while decreasing the pH. Indeed, the pH profile of the biocatalysed aldolisation reaction (Figure 2a) shows that the conversion rate was 100% at pH 7 and 6 after 4h whereas a slight decrease was observed at pH 5 with a 82% conversion rate for the same reaction time. A major drop of activity happened below pH 5, with only 19% at pH 4 and only traces of activity at pH 3.5 and 3. With a longer reaction time, i.e. 20h, 52% of conversion could be obtained at pH 4. It can be concluded that it is possible to use FSA up to pH 5 but more acidic conditions exclude a full conversion over a 24h reaction time. This was evidenced when recording the evolution of circular dichroism (CD) spectra of FSA as a function of the pH of the solution. The spectrum of FSA at pH 7 presented a positive band around 193 nm and negative bands at 209 nm and 222 nm (see SI). This form of spectrum is characteristic of a predominant  $\alpha$ -helix structure which is in accordance with Thorell et al.<sup>36</sup> who found the subunit of FSA folds into an  $\alpha/\beta$  barrel.<sup>28</sup> These characteristic peaks were less and less visible as the pH of the

solution decreased. Thus, the secondary structure of FSA was altered for pH below 4, which could explain the decrease in the activity of the enzyme at these pH values. Moreover, in near-UV region, the tertiary structure of FSA was also impacted by the pH of the solution as the shape and magnitude of CD spectrum changed with acidification (see SI). The magnitude of the major positive peak around 260 - 280 nm, attributed to tyrosine and phenylalanine residues,<sup>37</sup> decreased indicating a change in the aromatic amino acid environment upon alteration of FSA. This enzyme denaturation is correlated to the effect of pH on FSA activity we observed, and pH 5 appears to be the minimum pH allowing to keep the structuring of FSA.

Propargyl alcohol, the substrate for the chemically catalysed hydration reaction (Scheme 1), was found to have a detrimental effect on FSA. Indeed, at 0.5 M in alcohol, aldolisation stopped completely at about 35% conversion after one hour of reaction time. CD measurements showed no enzyme denaturation as no change in the shape and magnitude of spectra was observed, which could be consistent with an inhibiting role for the alcohol. Inhibition constant calculation confirmed the hypothesis, corroborated by the curve profile obtained. Indeed, propargyl alcohol behave like a competitive inhibitor for FSA with an inhibition constant  $K_i$  of 16 mM (see SI). Nevertheless, since propargyl alcohol is involved in the first step of the cascade, it should disappear rapidly resulting in quite low concentrations, compatible with FSA.



**Figure 2.** Effect of the pH over time on a) FSA activity (conditions: 2 mg/mL FSA, 0.5 M HA and formaldehyde, 1 mL water, r.t.) and on b) the NHC-AuCl catalyst velocity (conditions:

3 mg/mL catalyst, 0.75 mol%, 0.5 M propargyl alcohol, water, 60°C).

Finally, interactions between the two catalysts have been considered. In the presence of NHC-AuCl complex, FSA activity seemed to be slightly slowed down. Indeed, while 100% conversion in 4h was reached during the biocatalytic step, without any organometallic catalyst, the rate dropped to 80% in its presence. However, more than 90% of conversion was attained in these latter conditions after 6h of reaction (see SI).

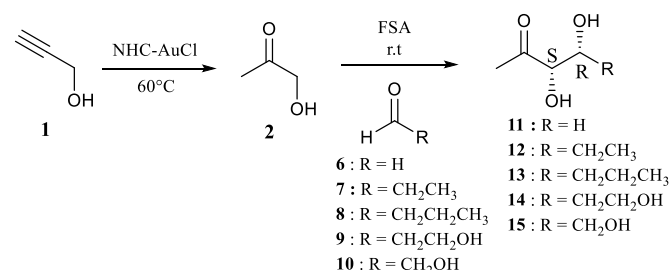
#### NHC-AuCl catalysts compatibility

On the catalyst side, reaction pH is also of importance. A pH profile of the hydration reaction was drawn (Figure 2b) showing that the conversion rate was 100% at pH 3 in 2h, but fell down to 25% for a slight pH increase (pH 3.5), even going to only 12% at pH 4 and then traces at pH 4.5. Longer reaction time did not increase a lot the reaction rate since 43% was obtained at pH 4.5 after 22 h. These results definitely preclude to apply a pH close to neutrality compatible with FSA.

By contrast, no disturbance was detected on the catalyst by the FSA electrophile component, i.e., formaldehyde, nor by the enzyme itself (see SI).

#### One-pot two-step implementation

These preliminary studies enabled to conclude that the strongest incompatibility of both catalysts concerns pH. This is a regular problem in hybrid catalysis where changes of pH, often accompanied by adjustment of the reaction medium, are to be considered.<sup>4</sup> Therefore in our case, only the pH will be modified. Thus, the only answer was to envisage a one-pot two-step sequence reactions. In the first step, propargyl alcohol (0.5 M) and the gold carbene catalyst were introduced into water. The hydration reaction of the alkyne took place at 60°C. Once completed, the pH was raised to 7, the enzyme and formaldehyde (0.5 M) were added and the second aldolisation step was carried out at room temperature. Finally, after the two-step reaction, i.e., about 8 h of reaction (2 h for hydration plus 6 h for aldolisation), the reaction medium was simply filtered on a Sephadex type anion exchange resin, allowing to discard both the gold catalyst and the enzyme. After elution with water, the solution was evaporated and the final product was recovered as a pure oil, in 86 % isolated yield.



**Scheme 3.** One-pot Two-step synthesis involving a chemo-catalyst (NHC-AuCl) and a stereoselective aldolase (FSA) for the preparation of several chiral aldols in water.

Then, the efficiency of the process was extended in obtaining other aldol adducts by varying the aldehyde component (Scheme 3). However, longer chain or branched chain FSA electrophiles were not converted as well as formaldehyde, even during one day of reaction. Nevertheless, with a simple increase in the amount of enzyme powder, from 2 to 4 mg/mL, at least 90% conversion was obtained with three (**7**, **8**, **9**) of the four aldehydes considered after a total of 7 h of reaction (2 h for hydration plus 5 h for aldolisation). These results also demonstrated that other aldehydes than formaldehyde could be used at a concentration of 500 mM. For glycolaldehyde **10**, 78% conversion was obtained after 24 h. A simple filtration on Sephadex followed by in vacuo evaporation, afforded the final products in 68-91% isolated yields (Table 1).

The various compounds prepared are rare carbohydrates or analogues and therefore of interest for the market devoted to food and human health. Many monosaccharides, including deoxysugars, have considerable chemotherapeutic potential.<sup>38</sup> For example, 1-Deoxy-D-xylulose **15**, is used as an intermediate in the biosynthesis of thiamine (vitamin B1)<sup>39</sup> and pyridoxal (vitamin B6).<sup>40</sup> In addition, this monosaccharide is involved in the non-mevalonate pathway, that is the major route towards volatile terpenoids in plants.<sup>41</sup> More generally, many monosaccharides, such as fructose or erythulose, are involved in a wide variety of biological processes.<sup>42</sup> Therefore, analogues like **11**, **12** and **14** could disturb some pathways and act as inhibitors of one or several constitutive enzymes, which could constitute new drugs. To note, **11**, **13** and **15** are commercially available, which in itself proves their interest.

We have successfully challenged a sustainable chemoenzymatic one-pot cascade reaction with an improved overall efficiency compared to the corresponding two separate steps. Indeed, for instance, HA, known as quite instable in solution, could be directly converted after its *in-situ* formation (no prior energy-demanding distillation). Starting from a simple achiral compound, used at a high concentration, we have succeeded to access to rare monosaccharides with two asymmetric carbons with a perfect control of their stereochemistries, in a total overall atom economy. This latter consideration can be illustrated through the E factor calculation as green metrics.<sup>43</sup> Indeed, for the five proposed syntheses, this E factor is always lower than 0.5, which represents a major advance compared to the more classical syntheses of these molecules displaying a E factor higher than 2 (see SI)

**Table 1.** Results for the tandem hydration/aldolisation reactions varying FSA electrophile, after 7 h of reaction time, including E factor. Conditions: 3 mg/mL, 0.75 mol% NHC-AuCl catalyst, 0.5 M propargyl alcohol, 60°C, pH 3, in water (1mL), then r.t, pH 7, 4 mg/mL FSA powder (50% glygly), 0.5 M aldehydes.

Aldehyde substrate	Product	Conversion rate (%)	Yield (%)	E factor
6	11	94	86	0.3
7	12	96	78	0.4
8	13	91	72	0.5
9	14	90	91	0.2
10	15	78 (in 24h)	68	0.5

## Conclusions

This work is a proof of principle highlighting that it is possible to bring together the two worlds of catalysis and biocatalysis, for the benefit of organic synthesis. It demonstrates the potential of aldolases to be used in hybrid catalysis. Implementation of a one-pot one-step reaction was unfortunately not possible, but finally not detrimental since it is not necessary to shift any equilibrium, generally a real problem in one-pot two-step experiments involving balanced reactions. We have shown the possibility to scale it up, and by this way, five optically pure monosaccharides were obtained with 68 to 91% yield, purified thanks to an easy and fast protocol, from simple and achiral compounds, involving reagents in strict stoichiometric amounts. We assumed that FSA, which is one of the most promising aldolases in terms of diversity of accepted substrates, was surprisingly weakly inhibited by gold unlike what is known.<sup>7,44</sup> On the other hand, the gold catalyst, was not inhibited, indicating that the 2 cysteine residues present in FSA did not interact with the catalyst. To go further, we are currently working on the co-immobilization of the two catalysts.

## Conflicts of interest

There are no conflicts to declare

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