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COMMUNICATION

One-pot Chemoenzymatic Deracemisation of Secondary Alcohols Employing Variants of Galactose Oxidase and Transfer Hydrogenation

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Supporting information for this article is given via a link at the end of the document.

Abstract: Enantiomerically enriched chiral secondary alcohols serve as valuable building blocks for drug intermediates and fine chemicals. In this study the deracemisation of secondary alcohols to generate enantiomeric pure chiral alcohols has been achieved by combining enantio-selective enzymatic oxidation of a secondary alcohol, by a variant of GOase (GOase M_{3-5}), with either non-selective ketone reduction via transfer hydrogenation (TH) or enantio-selective asymmetric transfer hydrogenation (ATH). Both the enzymatic oxidation system and the transition-metal mediated reduction system were optimised to ensure compatibility with each other resulting in a homogeneous reaction system. 1-(4-nitrophenyl)ethanol was generated with 99% conversion and 98% *ee* by the deracemisation method, and it has been extended to a series of other secondary alcohols with comparable results.

Deracemisation reactions, in which a racemate is converted into either single enantiomer, are attractive processes since they overcome the 50% conversion limit of kinetic resolution (KR) and therefore represent an important approach for the synthesis of enantio-pure compounds[1-4]. Previous work has shown that a variant of the enzyme galactose oxidase (GOase M_{3-5}) is capable of oxidising a wide range of chiral secondary alcohols to the corresponding ketones with high enantioselectivity[5]. Various variants of GOase have found numerous applications in areas including enantio-selective oxidation of atropisomers[6-7] and amino alcohols[8], glycoprotein labeling[9], converting alcohols to nitriles[10], or to carboxylic acids by a "through oxidation" process[11]. The process aspects for GOase applications have also been thoroughly reviewed[12]. In this paper we have investigated the deracemisation of secondary alcohols by combining GOase mediated oxidation with transition metal catalysed reduction. Previous reports have shown that it is possible to obtain enantio-pure secondary alcohols in high conversions by either employing one[13] or two[14-16] microbial systems, an organocatalytic system and a microbial system[17], a transition metal catalyst with an enzyme by deracemisation[18] or dynamic kinetic resolution (DKR) [19-21], and by stereoinversion[22]. One example for the deracemisation of secondary alcohols employing a combination of enzymes and transition metal catalysts was reported by Mutti *et al*[18]. They employed an iridium metal catalyst, for the non-selective oxidation, with an enzyme, ADH-A, for the asymmetric reduction, to achieve deracemisation of secondary alcohols, affording a 99.9% yield and a moderate 40% *ee*.

During the process of screening for a suitable reducing agent to work in conjunction with GOase, we observed that classical reducing agents such as sodium borohydride and borane-ammonia complex rendered complete loss of activity of the enzyme. This may be because the active copper centre present in GOase is reduced by the reducing agents. Consequently, we turned our focus to TH and ATH using transition metal catalysts (Scheme 1) that we have previously reported. These TH catalysts are highly efficient in mediating reduction of ketones to secondary alcohols[23-25]. Moreover, these catalysts are soluble in water, active at neutral pH, and stable in air, suggesting that they could be ideal candidates for combining with enzymes for the deracemisation of secondary alcohols.

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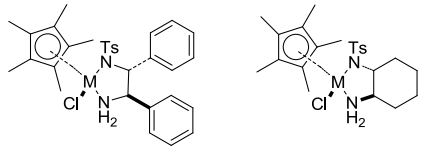
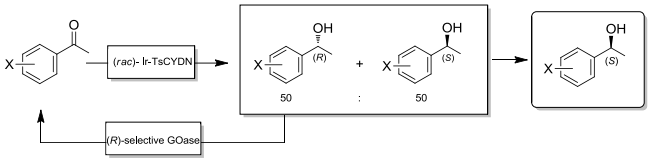


1 2

M-TsDPEN (M = Rh, Ir) M-TsCYDN (M = Rh, Ir)

Scheme 1. Examples of transition metal catalysts used in ATH

Herein we demonstrate the deracemisation of secondary alcohols by combination of GOase M_{3-5} catalysed enantio-selective oxidation system with a non-selective reduction by TH (Scheme 2), affording both high *ee* and conversions (up to 99%). We selected the substrates 3'-fluoro-acetophenone and 4'-nitro-acetophenone as model substrates based on the low enantio-selectivity observed with ATH, and the high activity shown by GOase for oxidation of the corresponding secondary alcohols.



Scheme 2. Deracemisation of secondary alcohols generated from TH of ketones.

To investigate the compatibility of the oxidation system and the reduction system, the effect of each component of the system on the other components was initially examined. TH of ketones requires both the transition metal catalyst and the hydrogen donor sodium formate (HCOONa), whereas the biocatalytic oxidation of alcohols requires the enzyme GOase, oxygen, catalase and horseradish peroxidase (HRP). Firstly a series of biocatalytic oxidation reactions were performed in the presence of various concentrations of the metal catalyst (*rac*)-Ir-TsCYDN (Table 1).

Table 1. Optimisation of biocatalytic oxidation of secondary alcohols in the presence of (*rac*)-Ir-TsCYDN.

Entry	Time [h]	(*rac*)-Ir-TsCYDN [mM]	S/C (with Ir catalyst)	*ee* [%]	Enzyme concentration [µM]
1	18	0.2	250	100	14.6
2	18	0.4	125	100	14.6
3	18	0.8	62.5	88	14.6
4	18	1.2	41.7	50	14.6
5	24	0.8	62.5	100	29.2
6	24	1	50	100	29.2
7	24	1.6	31.3	100	29.2
8	24	2	25	96	29.2

Reaction conditions: 50 mM 3'-fluorophenylethanol, 0.2-2 mM (rac)-Ir-TsCYDN, 14.6 – 29.2 µM GOase, 22 µM HRP, 0.4 µM catalase, 37˚C, 900 rpm, total volume: 0.5 mL in water.

The catalyst (*rac*)-Ir-TsCYDN was prepared by combining the metal complex $[(Cp^*IrCl_2)_2]$ and the ligand racemic TsCYDN in distilled water as previously reported[23]. This solution was then used directly in the TH reaction. From Table 1, it can be seen that the presence of a transition metal catalyst has a significant effect on the biocatalytic oxidation reaction. At 14.6 µM enzyme concentration, only a minimum of 125 substrate/catalyst ratio (S/C) can be used without loss of *ee* (Table 1, Entry 1-4). However, this metal catalyst concentration is too low for high conversions in the TH reaction. As a result, the concentration of the enzyme was increased to 29.2 µM to allow a higher concentration of metal catalyst. Indeed, with a S/C of 25, only 4% loss of *ee* was observed (Table 1, Entry 8). Therefore, S/C ratios close to 25 – 30 and 29.2 µM GOase concentration were employed in subsequent deracemisation reactions.

We also explored the effect of concentration of sodium formate on the activity of GOase (Supporting information, Table S2). It turned out that the addition of HCOONa had a negative effect on the biocatalytic oxidation reaction and the higher concentration of sodium formate, the more *ee* decreased for the production of chiral alcohols. For example, by increasing the concentration of HCOONa from ca. 0.5 M to 1.76 M, a significant 27% loss of *ee* was observed. Therefore, in the following deracemisation reactions, the concentrations of HCOONa were restricted to near ca. 0.5 mM.

Next, we studied the impact of the components of the enzymatic oxidation system on the TH system. The major components that may potentially affect the performance of the reduction system are oxygen bubbling (by means of bubbling oxygen through the reaction mixture), which is used to provide the oxidant for the bio-oxidation by the requisite enzymes, namely catalase, HRP and GOase. The presence of the three enzymes was found to have little effect on the TH system. However, oxygen has been reported to serve as a competing hydrogen acceptor via direct reaction of the metal hydride intermediate with molecular oxygen. [24, 26] By performing the ketone reduction using transition metal catalysts with and without oxygen bubbling, we confirmed that conversions were reduced by up to 30% when oxygen was present (Supporting Information, Table S1). Elimination of oxygen bubbling only resulted in a 5% loss of *ee* in the bio-oxidations reactions and therefore, no oxygen bubbling was employed for the optimised reaction conditions in the following studies.

Since the GOase reaction appeared to be more sensitive to the effect of the TH components, rather than vice-versa, further optimisation of the TH system was conducted.

Initially, various metal - ligand combinations were inspected for ketone reduction (Supporting information, Table S3). Both (*rac*)-Rh-TsCYDN and (*rac*)-Ir-TsCYDN were selected as the optimal catalysts for applications in further deracemisation rections .

Table 2. Optimisation of metal catalysts concentrations.

Entry	Time [h]	Metal catalysts	S/C	Alcohol [%]
1	3	(*rac*)-Rh-TsCYDN	100	77
2	3	(*rac*)-Rh-TsCYDN	83	81
3	3	(*rac*)-Rh-TsCYDN	71	84
4	1	(*rac*)-Rh-TsCYDN	31	79
5	3	(*rac*)-Rh-TsCYDN	31	99
6	3	(*rac*)-Ir-TsCYDN	100	87
7	3	(*rac*)-Ir-TsCYDN	83	89
8	3	(*rac*)-Ir-TsCYDN	71	93
10	3	(*rac*)-Ir-TsCYDN	63	99
11	3	(*rac*)-Ir-TsCYDN	50	99
12	1	(*rac*)-Ir-TsCYDN	31	97
13	3	(*rac*)-Ir-TsCYDN	31	99

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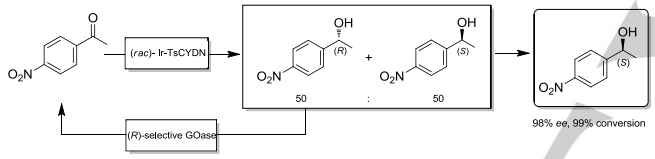
Reaction conditions: 25 mM 4'-nitro-acetophenone, 37˚C, 900 rpm, 0.2 - 0.8 mM (*rac*)-Ir-TsCYDN/(*rac*)-Rh-TsCYDN, 588 mM HCOONa (24 equiv.), total volume: 0.5 mL in water.

To further identify optimum S/C ratios for the transition metal catalysts to be employed in deracemisations, a range of reactions were performed with various concentrations of the catalysts at S/C ratios ranging from 31-100. The purpose of these studies was to identify the maximum concentration of metal catalysts that could be used to sufficiently reduce the ketone without impairing the activity of the enzyme.

It was found that with S/C ratios ranging from 71-100, neither (*rac*)-Rh-TsCYDN nor (*rac*)-Ir-TsCYDN was able to catalyse the complete reduction of the ketone substrate (Table 2). However, 99% conversion to the alcohol was obtained when (*rac*)-Ir-TsCYDN was used with S/C ratios ranging from 31-63, or with (*rac*)-Rh-TsCYDN with a S/C ratio of 31. Entries 4 and 12 show that at a S/C ratio of 31, the reaction using (*rac*)-Rh-TsCYDN showed lower conversions at 1 h compared to (*rac*)-Ir-TsCYDN, with 18% less alcohol produced, although the conversions were comparable at 3 h. With the objective of reducing the overall reaction time of the deracemisation reactions, (*rac*)-Ir-TsCYDN was identified as the best catalyst to perform the TH reaction in conjunction with the enzymatic oxidations by GOase (Table 3).

Table 3. Deracemisation of 1-(4-nitrophenyl)ethanol generated by TH of the ketone.



Time [h]	*ee* [%]	Alcohol [%]
1.5	1*	99
	Addition of GOase	
3	94	78
6	96	81
24	96	92
48	98	99

Reaction conditions: 1). Reduction. 25 mM 4'-nitro-acetophenone, 37˚C, 900 rpm, 0.8 mM (rac)-Ir-TsCYDN (S/C=31), 588 mM HCOONa (24 equiv.), total volume: 0.5 mL in water. 2). Oxidation. 29.2 µM GOase M_{3-5}, 22 µM HRP, 0.4 µM catalase.

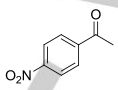
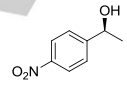
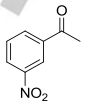
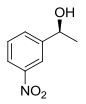
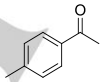
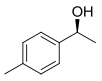
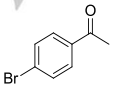
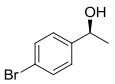
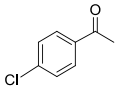
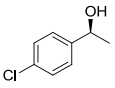
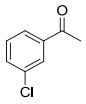
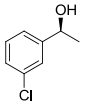
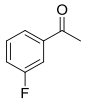
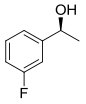
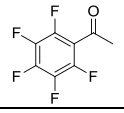
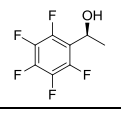
**1% ee may be due to error or impurities.*

The reaction was initiated by firstly performing the non-selective reduction step on the ketone substrate 4'-nitro-acetophenone with the conversion to the racemic alcohol reaching 99% after 1.5 h. Subsequently, GOase was added, and the *ee* increased to 94% during next 1.5 h as a result of enantio-selective oxidation by GOase. After a longer period of time both *ee* and the alcohol composition progressively increased to 98% and 99% respectively (Table 3), leaving only (*S*)-enantiomer of the alcohol in the reaction mixture. At this point there was trace amount of ketone or (*R*)-enantiomer of the alcohol remaining as shown from the HPLC traces of the final reaction mixture (Figure S9).

To demonstrate the generality of this method, a range of substrates were deracemised using the optimised reaction conditions.

As shown in Table 4, the deracemisation system was successfully applied for the production of a range of enantio-pure chiral secondary alcohols. In general, *meta*-substituted aryl ketones are typically difficult substrates for asymmetric reduction by ATH with transition metal catalysts, affording maximum selectivities of approximately 90% *ee* typically. [26] A notable improvement in *ee* was observed with the *meta*-substituted substrates (Table 4, entry 2, 6 and 7) by deracemisation compared to ATH, representing the advantage of the current combined system. In addition, the electron deficient substrate pentafluoro-acetophenone (Table 4, entry 8) gave a very good *ee* and conversion, demonstrating that the deracemisation process is highly tolerant of various substrates with different substituents.

Table 4. Deracemisation of a range of secondary alcohols.

Entry	Substrates	Products	Time [h]	*ee* [%]	Alcohol [%]
1			48	98	99
2			48	99	70
3			48	99	81
4			48	99	88
5			24	99	25
6			48	91	99
7			48	99	90
8			48	89	92

Reaction conditions: 1). Reduction. 25 mM substrates, 37 °C, 900 rpm, 0.8 mM (rac)-Ir-TsCYDN (S/C = 31), 588 mM HCOONa, total volume: 0.5 mL. 2). Oxidation. 29.2 µM GOase M_{3-5}, 22 µM HRP, 0.4 µM catalase.

In addition to the deracemisation reactions employing the (*rac*)-Ir-TsCYDN catalyst, boosting the enantio-selectivity with ATH by (*S*)-selective catalysts was also examined. The ATH by the (*S*)-selective Rh-TsDPEN has been previously applied in the reduction of a wide range of ketone substrates with generally high selectivity (*ee* > 94% for over 20 examples); but in some cases a lower *ee* was observed. For example, an *ee* of 88% was obtained for the reduction of 4'-nitro-acetophenone by the (*S*)-selective Rh-TsDPEN as reported by Wu et al[26]. However, deracemisation

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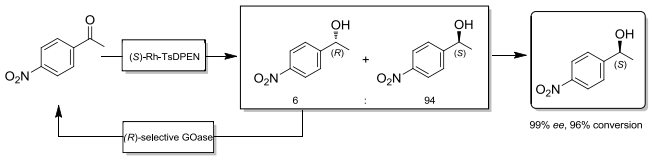
reactions employing the (*S*)-selective Rh-TsDPEN metal catalyst combined with GOase achieved excellent *ee* as well as conversions for the chiral alcohol products (Scheme 3).



Scheme 3. Deracemisation employing (*S*)-selective Rh-TsDPEN.

Since in this case the metal catalyst also contributes to the final *ee* of the product, the reaction conditions were less restrictive (lower concentrations of enzyme and transition metal catalysts can be used) compared to the reactions employing the racemic transition metal catalysts.

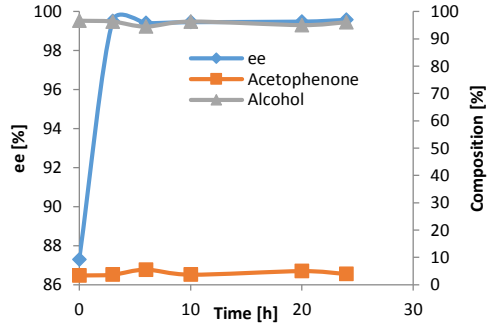


Figure 1. Deracemisation of 1-(4-nitrophenyl)ethanol generated by (*S*)-selective Rh-TsDPEN (Time = 0 h marked as the start time of the second oxidation step). *Reaction conditions: 1). Reduction. 50 mM 4'-nitro-acetophenone, 30 °C, 250 rpm, 0.2 mM (S)-selective Rh-TsDPEN (S/C = 250), 147 mM HCOONa, total volume: 0.5 mL. 2). Oxidation. 14.6 μM GOase $M_{3\text{-}5}$, 22 μM HRP, 0.4 μM catalase.*

In Figure 1, time = 0 h represents the start of the second step of the reaction (oxidation) after the reduction had completed, leaving 87% *ee* of the alcohol and <5% ketone in the reaction mixture. After addition of the components from the oxidations system, *ee* and conversions reached 99% and 96% after 3 h, respectively. These results were achieved with only 14.6 μM GOase at S/C = 250, which means that the concentrations of both enzymes and metal catalysts were lower than the deracemisations using the racemic metal catalyst (*rac*)-Ir-TsCYDN. In the end, the combination of GOase with (*S*)-selective Rh-TsDPEN leads to a 12% improvement in *ee* compared with performing only the reduction of the ketone by (*S*)-selective Rh-TsDPEN, which demonstrates the effectiveness of the deracemisation method.

In summary, we have successfully combined an enantio-selective enzyme GOase with a racemic metal catalyst (*rac*)-Ir-TsCYDN to achieve the deracemisation of secondary alcohols to highly enantiomerically enriched chiral alcohol products. By optimising each of the biocatalytic oxidation and chemocatalytic reduction steps, deracemisation was achieved by employing the enzyme GOase ((*R*)-selective) and a racemic transition metal catalyst. Outstanding *ee* and conversions were obtained. When the (*S*)-selective Rh-TsDPEN was applied in the deracemisation process, both *ee* and conversions were improved compared to employing ATH alone. The deracemisation system was also expanded to a range of secondary alcohols with varied functionalities. *ee* and conversions to some of the challenging/problematic substrates under sole TH/ATH conditions were also improved.

Acknowledgements

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Keywords: biocatalysis • chiral secondary alcohols • galactose oxidase • deracemisation • transfer hydrogenation

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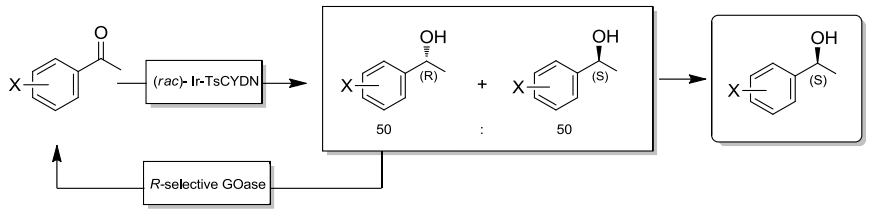

Chiral secondary alcohols were synthesized in up to 99% *ee* and 98% conversions by deracemisation methods. These methods can be achieved by employing an asymmetric oxidation of the alcohol substrates with a non-asymmetric or asymmetric reduction of the ketones in one-pot. The galactose oxidase $M_{3\text{-}5}$ variant was utilised as the biocatalyst for the oxidation of the alcohols, and Transfer hydrogenation (TH) or asymmetric transfer hydrogenation (ATH) were employed for the reduction of the corresponding ketones.

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