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Galactose Oxidase Model: Biomimetic Enantiomer-Differentiating Oxidation of Alcohols by a Chiral Copper Complex

Santosh Kumar Alamsetti, Sreedevi Mannam, Pandi Mutupandi, and Govindasamy Sekar*[a]

Dedicated to Professor Vinod K. Singh on the occasion of his 50th birthday

Galactose oxidase (GO) is a copper-containing fungal enzyme that oxidizes alcohols to their corresponding aldehydes with concomitant reduction of molecular oxygen.[1] Its crystal structure reveals a unique mononuclear copper site with two nitrogen atoms (from histidine imidazole groups) and two oxygen atoms (from tyrosine groups) as donor atoms, plus an exogenous water or acetate molecule in a distorted square-pyramidal coordination.[2] The GO enzyme contains chiral copper in its active site that results from the histidine and tyrosine residues (Y495 and Y272). This enzyme has so far inspired several research groups to design a variety of synthetic analogues.[3,4] However, all the ligands in the GO models reported so far have been either achiral[3] or racemic,[4] and it is important to mention that in most cases the ligands employed are not readily available and have to be synthesized by tedious multi-step syntheses.

Further, enantiopure alcohols are very important structural units for the synthesis of a wide range of natural products, chiral ligands, and biologically active compounds.[5] Generally, enantiopure secondary alcohols are synthesized by the enzymatic kinetic resolution of racemic secondary alcohols through acylation/deacylation reactions,[6] nonenzymatic kinetic resolution,[7] or enantioselective reduction of ketones.[8] The aerobic oxidative kinetic resolution (AOKR) of secondary alcohols is a feasible alternative and ranks high amongst the easiest methods to synthesize enantiopure secondary alcohols. Although excellent catalytic methods are available for the achiral alcohol oxidation process, it is surprising that relatively very few catalytic enantioselective examples of ubiquitous alcohol oxidation exist. Recently, chiral Ru,[9] Pd,[10] Mn,[11] V,[12] and Ir[13] catalysts were developed for oxidative kinetic resolution to produce optically active secondary alcohols. However, these metal salts are either expensive or they provide poor selectivity. Also, the chiral ligands are not readily available and must be arduously synthesized in most cases. On the other hand, to the best of our knowledge chiral copper-catalyzed oxidation, which is an economic, mild, and biomimetic functional model of the mononuclear copper enzyme GO, has not been reported in the literature to date.

There are several problems associated with the synthetic analogues of GO reported so far. First, most of the ligands are not readily available, so they require laborious multistep syntheses and rigorous reaction conditions to form complexes with copper salts because phenolic groups do not coordinate well with copper due to their inherent weak-field ligand status in the spectrochemical series. This is a disadvantage of the relatively harder nature of oxygen donor ligands. Also, in the case of oxidative kinetic resolution, chiral metal salts are either expensive[9–10,13] or they provide poor selectivity.[11] To combat these facts, we aimed at synthesizing an enantiopure analogue of GO from an easily and readily available source to subsequently mimic GO's activity not only in primary alcohol oxidation but also as enantioselective catalysts for AOKR of racemic secondary alcohols. As a part of our ongoing research towards copper-catalyzed oxidation chemistry,[14] we envisioned binam (1,1′-binaphthyl-2,2′-diamine) as a suitable ligand for our purpose owing to its ready availability and relative ease of coordination compared with other oxygen-based ligands.

Enantiopure (*R*)-binam was treated with $Cu(OTf)_2$ in toluene at room temperature for one hour to give a (*R*)-binam–Cu complex. The X-ray crystal structure of this synthetic complex is reported here (Figure 1). $[Cu\{(R)\text{-binam}\}_2][OTf]_2$ has a distorted octahedral geometry in which Cu^{II} is coordinated by four nitrogen atoms (from the two

[a] S. K. Alamsetti, S. Mannam, P. Mutupandi, Dr. G. Sekar
Department of Chemistry
Indian Institute of Technology Madras
Chennai, Tamil Nadu, 600036 (India)
Fax: (+91) 44-2257-4202
E-mail: gsekar@iitm.ac.in

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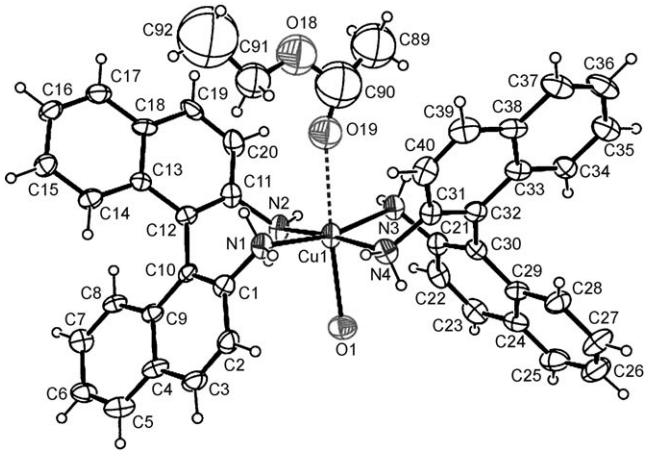


Figure 1. X-ray structure of the GO enzyme model, $[Cu^{II}\{(R)\text{-binam}\}_2]$, (CCDC 677060) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Ellipses were drawn at the 30% probability level). Ethyl acetate is in the sixth position and shows a weak van der Waals interaction (2.566 Å) with the central copper.

(*R*)-binam molecules), one water molecule occupies an axial position, and the other axial position is occupied by an ethylacetate molecule through a weak van der Waals interaction (the bond length between Cu^{II} and ethylacetate oxygen is 2.566 Å[15]). The complex crystallizes in a triclinic crystal system with space group *P*1 and unit cell dimensions of $a=$ 10.1523(4), $b=13.6844(5)$, $c=18.4478(9)$ Å; $\alpha=111.692(2)$, $\beta=96.544(3)$, $\gamma=92.518(2)°$; $Z=1$, cell volume = 2355.60(17) Å^3. The solution-state EPR spectrum of (*R*)-binam–Cu at 77 K supports a distorted octahedral structure because its $g_{\parallel}$ value (2.17) is significantly larger than its $g_{\perp}$ (1.99; see Figure 2).

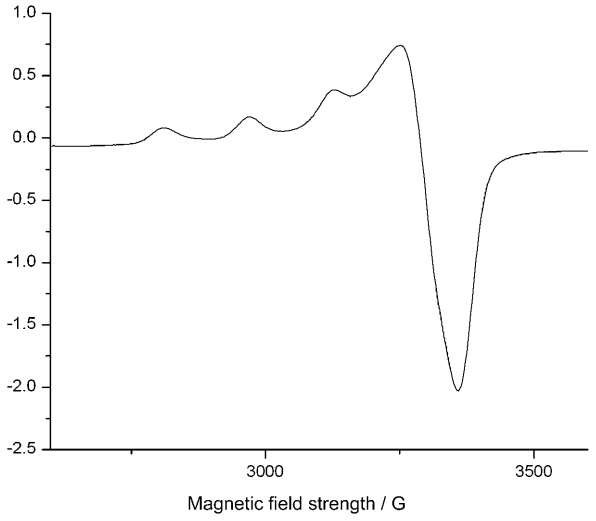
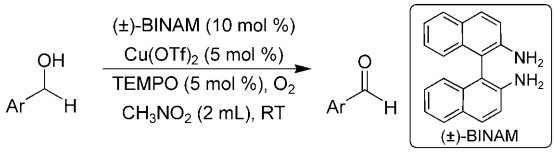


Figure 2. Solution-state EPR spectrum of $[Cu^{II}\{(R)\text{-binam}\}_2]$ in acetone at 77 K.

To mimic GO, oxidation of *p*-methoxybenzylic alcohol by $[Cu\{(\pm)\text{-binam}\}_2][OTf]_2$ with 5 mol% of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in nitromethane under an O_2 atmosphere was carried out and the reaction proceeded smoothly at room temperature to give an isolated yield of 95% of the corresponding benzaldehyde (Table 1, entry 4).

Table 1. (±)-binam–$Cu(OTf)_2$-catalyzed oxidation of primary alcohols.



Entry	Alcohol	Product	Time [h]	Yield[a] [%]
1	$C_6H_5CH_2OH$	C_6H_5CHO	22	71
2	*o*-NO_2-$C_6H_4CH_2OH$	*o*-NO_2-C_6H_4CHO	24	71
3	*p*-Cl-$C_6H_4CH_2OH$	*p*-Cl-C_6H_4CHO	25	60
4	*p*-OMe-$C_6H_4CH_2OH$	*p*-OMe-C_6H_4CHO	20	95
5	*p*-NO_2-$C_6H_4CH_2OH$	*p*-NO_2-C_6H_4CHO	32	81
6	*m*-NO_2-$C_6H_4CH_2OH$	*m*-NO_2-C_6H_4CHO	22	86
7	*m*-OMe-$C_6H_4CH_2OH$	*m*-OMe-C_6H_4CHO	19	50
8	3,4,5-$(OMe)_3$-$C_6H_2CH_2OH$	3,4,5-$(OMe)_3$-C_6H_2CHO	17	84

[a] Isolated yield.

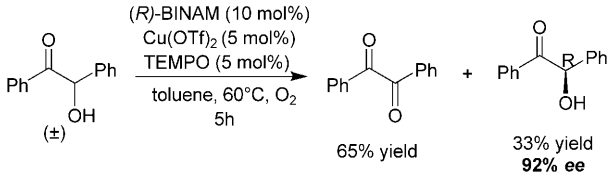
The reaction is catalytic, only 5 mol% of $[Cu\{(\pm)\text{-binam}\}_2][OTf]_2$ complex was required for the complete conversion of the alcohol. Here, molecular oxygen is used as the sole oxidant and water is obtained as the ultimate byproduct. This makes our process eco-friendly and green as well. To investigate the scope of our catalyst, the oxidation reaction was extended to several other primary alcohols, which were oxidized to the corresponding aldehydes at room temperature and the results obtained are summarized in Table 1. Oxidation here is very selective because over-oxidized product (carboxylic acids) was not observed in any case.

Our main objective was to use our enantiopure GO model as an efficient catalyst in the synthesis of biologically important organic molecules through oxidation reactions. Enantiopure benzoin (2-hydroxy-1,2-diphenylethanone) is an important intermediate in the synthesis of a potent anticancer agent[16] and has generally been synthesized by enzymatic hydrolysis with benzaldehyde lyase (BAL) or benzoylformate decarboxylase (BFD) enzyme.[17] Other methods include enantioselective benzoin condensations by using polycyclic triazolium salt or its analogues as catalysts, which again has the drawback of having to be synthesized in many steps.[18] By avoiding these problems, we have synthesized enantiomerically enriched benzoins for the first time to the best of our knowledge by nonenzymatic kinetic resolution with $[Cu(binam)_2][OTf]_2$ as the catalyst in the oxidation reaction.

At the outset, (±)-benzoin was subjected to AOKR with 5 mol% of enantiopure (*R*)-binam, 5 mol% of $Cu(OTf)_2$, and 5 mol% of TEMPO in toluene at 60 °C. In this reaction, molecular oxygen is used as a stoichiometric oxidant. The

reaction proceeded well and gave isolated yields of 84% for the ketone product and 15% for recovered benzoin, which was obtained in 90% enantiomeric excess (*ee*) in 7 h. A wide range of copper salts were screened with (*R*)-binam in toluene, and (*R*)-binam–$Cu(OTf)_2$ turned out to be the complex of choice for oxidative kinetic resolution because the other copper salts gave poor results. Then the reaction was screened in several solvents to obtain the recovered alcohol with good yield and very high optical purity. Among the solvents screened, toluene turned out to be the best solvent.

Next, we studied the effect of the ratio of (*R*)-binam and $Cu(OTf)_2$ in toluene and found that when 10 mol% of (*R*)-binam and 5 mol% of $Cu(OTf)_2$ was used, the reaction gave yields of 65% for benzil and 33% for recovered benzoin in 92% *ee* in 5 h (Scheme 1). This result clearly shows that an

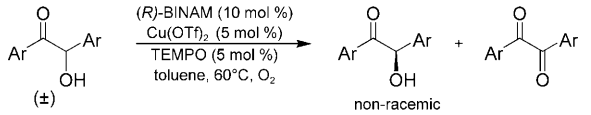


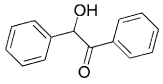
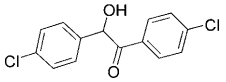
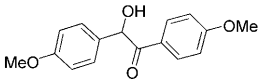
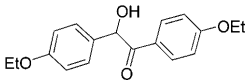
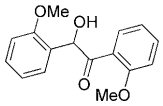
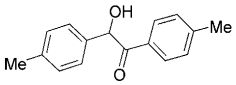
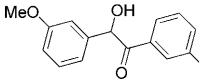
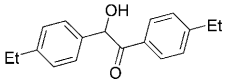
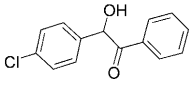
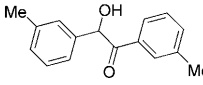
Scheme 1. The AOKR of (±)-benzoin by (*R*)-binam–Cu.

optimised 2:1 ratio of (*R*)-binam and $Cu(OTf)_2$ is the appropriate combination for effective catalytic activity and this ratio unequivocally corresponds to the ratio obtained from our crystal structure of GO model. In all reactions in this AOKR, the *S* enantiomer of racemic benzoin was oxidized faster to the corresponding benzil and the slower-reacting *R* enantiomer was recovered in a highly enantiomerically enriched form.

After optimizing the reaction conditions for the AOKR of racemic benzoin, we initiated detailed investigations into the scope of the $[Cu\{(R)\text{-binam}\}_2][OTf]_2$-catalyzed AOKR reaction with other benzoins, and the results obtained are summarized in Table 2. Again, the *S* enantiomer of the racemate was oxidized faster to the corresponding benzil and the slow-reacting *R* enantiomer of benzoin was recovered in an enantiomerically enriched form. The reactivity of the benzoins in our AOKR process was increased if the benzoin had an electron-withdrawing group, such as a chloro group at the *para* position. If the benzoin had one chloro group it took 4 h for a 70% conversion, whereas the presence of two chloro groups reduced the conversion time to only 0.5 h (Table 2, entries 1 vs. 3 vs. 12). On the contrary, the reactivity decreased when benzoins with electron-donating groups, such as methyl, methoxy, and ethoxy groups at the *para* position (Table 2, entry 1 vs. 4, 5, and 7). However, if the electron-donating group was in the *meta* position of benzoin, the decreased reactivity due to the *para* effect was suppressed (Table 2, entries 4 vs. 9 vs. 1). We observed that *ortho* substitution reduces the rate of reaction drastically and only in the case of *ortho*-substituted benzoin was poor enantioselectivity observed (Table 2, entry 6). We attribute this to the

Table 2. The AOKR of (±)-benzoins by $[Cu\{(R)\text{-binam}\}_2][OTf]_2$.



Entry	(±)-Benzoin	Time [h]	Benzil	Recovered benzoin		
			Yield[a] [%]	Yield[a] [%]	*ee*[b,c] [%]	Config.[d]
1		5	65	33	92	*R*
2		8	83	15	98	
3		0.5	63	28	98	*R*
4		12	65	25	93	*R*
5		14	60	29	84	*R*
6		144	68	25	28	*R*
7		10	60	37	76	*R*
8		12	71	20	95	
9		4	61	34	86	*R*
10		6	77	17	98	
11		16	78	20	95	*R*
12		4	76	24	90	*R*
13		8	70	24	84	*R*

[a] Isolated yield. [b] The ee was determined by using HPLC on a chiral column-Diacel ChiralPAK AS-H (see the Supporting Information). [c] The data given are from single experiments. [d] The configuration of recovered benzoins was determined by comparing the optical rotation value with the literature value (see the Supporting Information).

steric hindrance created at the *ortho* position. The *ee* of recovered benzoins was determined by HPLC on a chiral stationary phase (see the Supporting Information for full details). Although the exact role of TEMPO in this AOKR is unclear, we have a strong insight that TEMPO might act as a hydrogen acceptor during the catalytic cycle. A detailed mechanistic study is in progress.

Thus, we have developed for the first time an enantiopure model of the GO enzyme from commercially available compounds in a single step. This in situ-prepared GO model, $[Cu\{(R)\text{-binam}\}_2][OTf]_2$, can be used directly as an efficient catalyst for the oxidation of primary alcohols to the corresponding aldehydes by using molecular oxygen as the sole oxidant and with water being only byproduct. This enzyme

model has been extensively used for an enantioselective oxidation process (AOKR) to synthesize highly enantiomerically enriched benzoins. This result demonstrates the first chiral copper-catalyzed oxidative kinetic resolution of alcohols (benzoins) and the simplest method for the synthesis of highly important chiral benzoins. We are continuing to explore the enormous potential of chiral binam–Cu^{II} in the synthesis of other biologically important alcohol-containing molecules, and mechanistic studies of AOKR and the detailed results of these investigations will be reported in due course.

Experimental Section

General: Please see the Supporting Information for details of the materials and equipment used in this study.

Typical experimental procedure for primary alcohol oxidation: A mixture of (±)-binam (28.4 mg, 0.1 mmol) and $Cu(OTf)_2$ (18.05 mg, 0.05 mmol) in nitromethane (2 mL) was stirred at RT for 10 min, then TEMPO (7.82 mg, 0.05 mmol) was added to the reaction mixture. After stirring for 5 min, *para*-methoxybenzylalcohol (138 mg, 1 mmol) was added and the mixture was stirred under an O_2 atmosphere (by using an O_2 balloon) for 20 h at RT. After complete disappearance of *para*-methoxybenzylalcohol (monitored by TLC), the reaction mixture was concentrated under vacuum and the resulting residue was purified by column chromatography on silica gel (eluent hexanes/ethyl acetate) to obtain *para*-methoxybenzaldehyde as a colorless liquid (130 mg, 95%). $R_f = 0.67$ (hexanes/ethyl acetate, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.87$ (s, 1H), 7.82 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.4$ Hz, 2H), 3.87 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 190.7$, 164.6, 131.9, 129.9, 114.3, 55.6 ppm; IR (neat): $\tilde{\nu} = 2840$, 2741, 1679 cm^{-1}; HRMS: *m*/*z* calcd for $C_8H_9O_2$: 137.0603 $[M+H]^+$; found: 137.0598.

Typical experimental procedure for AOKR: A mixture of (*R*)-binam (28.4 mg, 0.1 mmol) and $Cu(OTf)_2$ (18.05 mg, 0.05 mmol) in toluene (2 mL) was stirred at RT for 10 min, then TEMPO (7.82 mg, 0.05 mmol) was added to the reaction mixture. After stirring for 5 min, benzoin (212 mg, 1 mmol) was added, then the mixture was heated to 60 °C under an O_2 atmosphere (by using an O_2 balloon) for 5 h. After cooling to RT, the reaction mixture was diluted with ethyl acetate and then washed with dilute HCl followed by water. The organic layer was dried over sodium sulfate, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (eluent: hexanes/ethyl acetate) to give the benzil (137 mg, 65%) and the recovered benzoin (70 mg, 33%).

Benzoin: $R_f = 0.49$ (hexanes/ethylacetate, 80:20); $[\alpha]_{25}^{D} = -76.0$ ($c = 1$ in acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$–7.96 (m, 2H), 7.52–7.57 (m, 1H), 7.39–7.44 (m, 2H), 7.34–7.37 (m, 4H), 7.27–7.33 (m, 1H), 5.98 (d, $J = 6$ Hz, 1H), 4.58 ppm (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.1$, 139.1, 134.0, 133.6, 129.3, 129.2, 128.8, 128.7, 127.9, 76.4 ppm; IR (neat): $\tilde{\nu} = 3418$, 1679, 1261, 1068 cm^{-1}; HRMS: *m*/*z* calcd for $C_{14}H_{12}O_2Na_1$: 235.0735 $[M+Na]^+$; found: 235.0727. The *ee* was determined to be 92% by using HPLC on a ChiralPAK AS-H column (5% *i*PrOH/hexanes, 1 mL min^{-1}, 220 nm): minor retention time: 11.2 min, major retention time: 18.1 min.

Benzil: $R_f = 0.70$ (hexanes/ethylacetate, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$–7.94 (m, 4H), 7.57–7.62 (m, 2H), 7.42–7.47 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 194.7$, 135.0, 133.3, 130.1, 129.2 ppm; IR (neat): $\tilde{\nu} = 3064$, 1656 cm^{-1}; HRMS (*m*/*z*): calcd for $C_{14}H_{10}O_2Na_1$: 233.0578 $[M+Na]^+$; found: 233.0585.

Acknowledgements

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Keywords: oxidation · chiral benzoins · enantioselectivity · enzyme models · kinetic resolution

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