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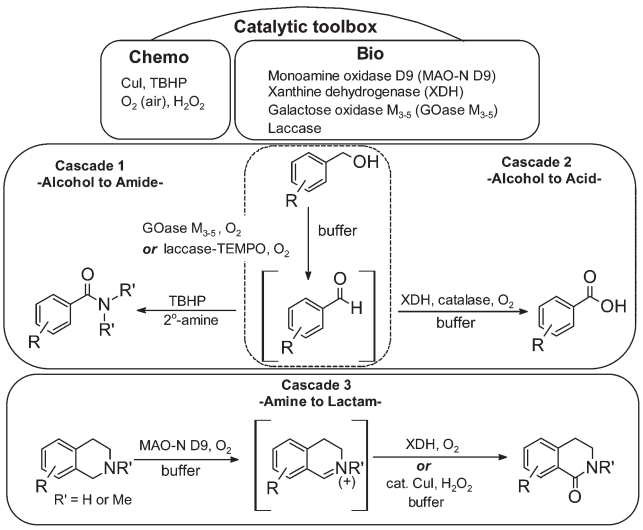
Catalytic bio–chemo and bio–bio tandem oxidation reactions for amide and carboxylic acid synthesis†

Beatrice Bechi,‡[a] Susanne Herter,‡[a] Shane McKenna,[b] Christopher Riley,[b] Silke Leimkühler,[c] Nicholas J. Turner*[a] and Andrew J. Carnell*[b]

A catalytic toolbox for three different water-based one-pot cascades to convert aryl alcohols to amides and acids and cyclic amines to lactams, involving combination of oxidative enzymes (monoamine oxidase, xanthine dehydrogenase, galactose oxidase and laccase) and chemical oxidants (TBHP or CuI(cat)/H_2O_2) at mild temperatures, is presented. Mutually compatible conditions were found to afford products in good to excellent yields.

Amides, lactams and carboxylic acids are ubiquitous functional groups in organic chemistry found in natural products, pharmaceuticals and a wide range of synthetic polymers. Amide bond formation can be achieved using activated carboxylic acid derivatives or an increasingly elaborate range of coupling reagents.[1] However, these methods can be expensive and involve the use of toxic and atom inefficient reagents, increasing their environmental E factor.[2] Due to their widespread application in synthetic organic chemistry, there is a great deal of interest in new sustainable and environmentally benign alternatives for generating both carboxylic acids[3] and amides.[4]

The approach described here exploits the increasing range of oxidative enzymes that can work under ambient conditions in aqueous buffer and use aerial oxygen as the electron acceptor, hence representing an ideal alternative to traditional oxidants. The ability to tune enzyme activity and substrate specificity using protein engineering and directed evolution strategies[4b,5] has resulted in the creation of biocatalysts that can be used *in vitro* in catalytic cascade pathways on unnatural substrates.[6] This approach allows combination of enzymes (bio–bio)[6a] and of enzymes with chemocatalysts (bio–chemo),[6a,7] extending the range of sustainable chemistry possible. In this paper, we demonstrate three new one-pot tandem cascade reactions using combinations of enzymes and chemocatalysts for: oxidative coupling of aryl alcohols with amines to give amides (cascade 1), conversion of aryl alcohols to carboxylic acids (cascade 2) and transformation of cyclic amines to lactams (cascade 3) (Scheme 1).



Scheme 1 Catalytic bio–chemo and bio–bio tandem oxidations.

Our objectives were realised by combination of enzymes and chemocatalysts that can work cooperatively under mild aqueous conditions, avoiding the use of organic solvents, hazardous and toxic chemicals as well as heavy metal catalysts associated with a minimisation of energy and waste production.

(1) Alcohols to aldehydes to amides (cascade 1)

Recently, there has been a great deal of interest in synthetic organic chemistry in developing catalytic oxidative amidation

[a]*School of Chemistry, Manchester Institute of Biotechnology, University of Manchester, 131 Princess Street, Manchester, M1 7DN, UK. E-mail: nicholas.turner@manchester.ac.uk; Fax: +44 (0)161 2751311; Tel: +44 (0)161 3065173*

[b]*Department of Chemistry, University of Liverpool, Crown Street, Liverpool, L69 7ZD, UK. E-mail: acarnell@liv.ac.uk; Fax: +44 (0)151 7943500; Tel: +44 (0)151 7943534*

[c]*Institute of Biochemistry and Biology, University of Potsdam, Maulbeerallee 2, D-14476 Potsdam, Germany. E-mail: sleim@uni-potsdam.de; Fax: +44 331/977-5128; Tel: +49 331/977-5603*

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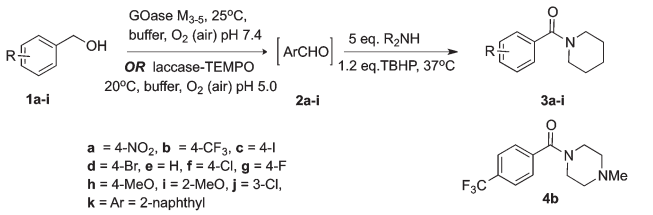
‡These authors contributed equally to the work.

reactions to couple aldehydes with amines. The reactions are thought to proceed by oxidation of the imine or hemi-aminal intermediates and are catalysed by transition metals (Rh, Ru, Pd, Fe),[8] *N*-heterocyclic carbenes,[9] Cu,[10] Cu–Ag[11] and lanthanides.[12] Stoichiometric terminal oxidants required are *tert*-butyl hydroperoxide (TBHP) or aqueous 70% TBHP (T-HYDRO), H_2O_2, or oxone. In some cases, it is possible to start with the alcohol, which undergoes oxidation to the aldehyde *in situ*.[4c,13,14] Yields for oxidative amidation of benzaldehydes are generally good (46–96%), although aliphatic and heteroaryl aldehydes give lower yields and require higher reaction temperatures. Thus, mild catalytic conditions that can run at ambient temperature without the need to use amine HCl salts[10] or a large excess of the aldehyde would be an attractive tool for future chemistry.

We have previously developed variants of *F. graminearum* galactose oxidase (GOase), such as GOase M_{3-5}, that show a remarkable ability to oxidise secondary and primary benzylic alcohols to their respective ketone and aldehyde products and H_2O_2 as by-product.[15] The combination of laccase from *T. versicolor* with the redox mediator TEMPO[16] can be employed to achieve the same transformations. We now report the application of both biocatalysts in a one-pot tandem reaction with different amines (5 eq.) and TBHP (1.2 eq.) to convert benzylic alcohols to aldehydes (1st step) and subsequently to the tertiary amides (2nd step) (Table 1, Tables S1 and S2†). The reactions were run sequentially as one-pot-two-step processes since the GOase M_{3-5} and laccase were found to be sensitive or inhibited by the amines or TBHP required in the second step. As GOase produces within its catalytic cycle one mole H_2O_2 per mole of alcohol substrate being oxidised, we attempted to use this natural *in situ* generated by-product in the amide formation step in place of addition of TBHP. The results, however, suggested the amount of enzymatically generated H_2O_2 to be insufficient for oxidation of the aminal intermediate to yield the desired amide products **3a–k** and **4b**.

The temperature for the one-pot amide formation was maintained at 20–37 °C. In the second step, in which the assumed aminal intermediate is oxidised to the amide, the tandem reactions worked optimally at higher initial substrate concentrations (50–80 mM) which were found to be best tolerated by the laccase–TEMPO system employed for the 1st step (aldehyde formation). Thus, the highest conversions (9–91%) and isolated yields (22–91%) of amides were obtained using the laccase–TEMPO combination. Different benzyl alcohol substrates exhibited a concentration-dependent effect on the efficiency of conversion to the respective amide when comparing the two biocatalytic systems. Substrates such as *para*-nitrobenzyl alcohol **1a** gave high conversion to amide **3a** at lower concentrations (10 mM) used in combination with GOase M_{3-5}. In contrast, alcohols **1c–d** and **1f–i** showed distinct variation in yields when comparing the GOase M_{3-5} (10 mM) and laccase–TEMPO system (80 mM). In general, alcohols with electron-withdrawing substituents revealed a pronounced propensity for amide formation, whereas yields declined with electron-donating groups. Strictly speaking, although the first step for aldehyde formation from benzyl alcohols was quantitative in both the GOase M_{3-5} and laccase–TEMPO systems (Tables S1 and S2†), the amide forming second step was clearly identified to determine yields of amide products due to the concentration of aldehyde present. Most examples presented herein involved piperidine as a model amine, although we were pleased to find that our method can be extended to the formation of tertiary amide **4b**, a feature frequently found in drug molecules.

Table 1 Bio–chemo tandem conversion of alcohols **1** to amides **3** and **4**

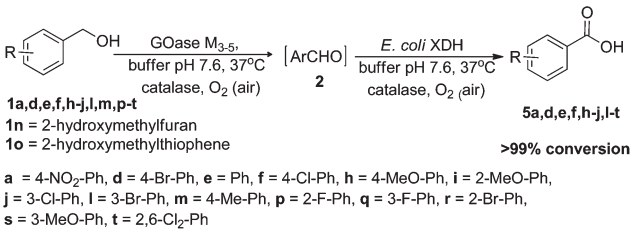


		Conversion to amide 3/4 [%]	
Alcohol **1**		GOase M_{3-5}-TBHP[a]	Laccase-TEMPO-TBHP[b]
1a	**3a**	100	91 (91)[c]
1b	**3b**	87	89 (57)
1c	**3c**	63	90 (60)
1d	**3d**	26	86 (73)
1e	**3e**	21	32
1f	**3f**	14	75 (53)
1g	**3g**	4	69
1h	**3h**	0	26 (22)
1i	**3i**	0	9
1j	**3j**	36	87 (41)
1k	**3k**	38	45 (35)
1b	**4b**[d]	—	(40)

[a] Reaction conditions: GOase M_{3-5} (7.25 μM), **1a–k** (10 mM) in sodium phosphate buffer (50 mM pH 7.4), 25 °C , 16 h, then piperidine (R_2NH) (5 eq.), TBHP (1.2 eq., 6.6% v/v), 37 °C, 24 h. [b] Reaction conditions: laccase (12 U), TEMPO (24 mM), **1a–k** (80 mM) in sodium citrate buffer (100 mM), 20 °C, 16 h, then piperidine (R_2NH) (5 eq.), TBHP (1.2 eq.), 37 °C, 24 h. [c] Isolated yields in parentheses. [d] R_2NH = *N*-methylpiperazine (5 eq.). Conversion to amides reported are based on HPLC peak areas at λ = 254 nm (Tables S1 and S2).

(2) Alcohols to carboxylic acids (cascade 2)

The oxidation of alcohols to carboxylic acids very often requires a stepwise process *via* the aldehyde and typically employs catalytic ruthenium or chromium and strong oxidants such as iodate or chlorite.[17] Direct catalytic oxidation of alcohols to carboxylic acids is relatively rare.[3a,18] Biocatalytic processes using whole cells and isolated enzymes are attractive tools for synthesis of carboxylic acids due to the mild and green conditions employed.[19] However, with whole cells, products often need to be continuously removed from the reaction due to toxicity of the intermediate aldehyde or acid. Therefore, *in vitro* cascades employing isolated enzymes equally offer a very attractive alternative approach. Examples include the use of alcohol



Scheme 2 Bio–bio cascade reaction for conversion of alcohols **1** to acids **5**. Reaction conditions: GOase M_{3-5} (1.3 mg mL^{-1}), alcohols **1** (1 mM) in sodium phosphate buffer (50 mM, pH 7.6), catalase (0.25 mg mL^{-1}), *E. coli* XDH (0.18 mg mL^{-1}), 37 °C, 16 h.

dehydrogenases and aldehyde dehydrogenases with recycling of the oxidised NAD^+ cofactor carried out by an oxygen-dependent NADH oxidase.[20] Whilst elegant, there is still the requirement for addition of cofactor and the auxiliary enzyme.

Aiming to expand the range of *in vitro* processes toward carboxylic acid synthesis, we have developed a cascade reaction using two oxidative enzymes, GOase M_{3-5} and xanthine dehydrogenase (XDH) from *E. coli*,[21] to achieve direct and clean conversion of aryl alcohols to acids *via* the *in situ* generated aldehyde (Scheme 2). XDH belongs to a family of molybdenum-dependent enzymes[22] and uses aerial O_2 as an electron acceptor in the absence of other mediators or cofactors. This enzyme family is receiving increasing attention in the drug metabolism field[23] but has never before been exploited in synthesis. Since the substrate specificity of *E. coli* XDH has not previously been reported, we initially screened a panel of *ca.* 65 aldehydes (Table S3†) using nitroblue tetrazolium (NBT), a redox active dye previously used to examine microorganisms for xanthine oxidase activity.[24] Substrate specificity of *E. coli* XDH appeared to be dictated by enzyme–substrate interactions since there were no obvious substrate electronic effects dictating reactivity. We selected the best hits from the NBT assay for more detailed analysis and were delighted to observe 81–100% conversion in 1–5 h. While most of the aldehyde substrates were oxidised by *E. coli* XDH to >90% conversion within 1 h, aldehydes **2d**, **2i** and **2m** revealed slower turnover, taking 5 h to reach 80–90% conversion. There is no structural information on *E. coli* XDH although related aldehyde oxidases are known to accept a wide range of substrates.[23] The aryl alcohols **1a**, **1d–1f**, **1h–j**, **1l–t**, corresponding to the best aldehyde substrates **2** for *E. coli* XDH, were then selected for a one-pot-one-step GOase M_{3-5}-XDH cascade approach resulting in *quantitative* conversion of 16 benzyl and heteroaryl alcohols to the corresponding carboxylic acids over 16 h (Scheme 2, Table S4†).

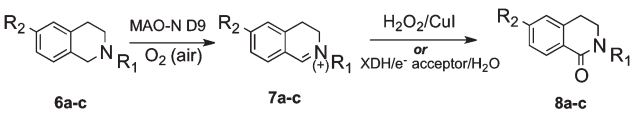
Following optimisation, the oxidation of 3-methoxybenzyl alcohol **1s** was run at 40 mM substrate concentration (Table S5 and Fig. S33†) showing complete conversion to the aldehyde by GOase M_{3-5} after 30 min, followed by slower conversion by *E. coli* XDH to reach 94% conversion to the acid **5s** (81% isolated yield) after 5 h. The addition of catalase to destroy the H_2O_2 generated by GOase M_{3-5} and delivering additional equivalents of O_2 was found to be essential for achieving high conversions. In order to facilitate increased substrate loading, current work is focussed on finding improved enzymes for both steps to increase rate and throughput.

(3) Cyclic amines to lactams (cascade 3)

Catalytic methods for the direct α-oxidation of amines to afford lactams are receiving a great deal of attention. However, most methods require high temperatures or environmentally undesirable stoichiometric reagents such as hypervalent iodine[25] or chlorite.[26] Use of bulk gold[27] and gold nanoparticle catalysts[28] have been reported but often require temperatures up to 100 °C in organic solvents[29] or the presence of 200 mol% NaOH.[28] Recently, use of a remarkable Ru-pincer complex (150 °C, sealed tube) has been reported for the oxidation that uses water as the oxygen source and produces hydrogen.[30]

Herein, we now present our initial results on the one-pot oxidation of cyclic amines to lactams under mild (37 °C) and aqueous conditions using two novel and related approaches (Table 2). Both of these methodologies use a variant of *A. niger*

Table 2 Tandem bio–chemo and bio–bio catalysed conversion of cyclic amines **6** to lactams **8**



Substrate	Conditions[a]	Conversion to lactam **8a–c** [%]
6a	A (MAO-N D9/CuI/air)	74
6a	B (MAO-N D9/XDH-E232V/Fe(III)/DCPIP/air)	91
6a	C (MAO-N D9/XDH-E232V/laccase/DCPIP/air)	54
6a	D (MAO-N D9/*E. coli* XDH/catalase/air)	94
6b	A	47[b]
6b	B	—
6b	D	—
6c	A	42[b]
6c	D[c]	100[b]

[a] Conditions A: **6a–c** (40 mM), MAO-N D9 (0.4 mg mL^{-1}), MOPS buffer (100 mM, pH 7.5), 10 eq. H_2O_2, CuI (1 mol%), 37 °C, 16 h. Conditions B: **6a–c** (1 mM), MAO-N D9 (1 mg mL^{-1}), XDH E232V (1.7 mg mL^{-1}), potassium phosphate buffer (100 mM, 0.1% EDTA, pH 7.6), DCPIP (10 mol%), $K_3Fe(CN)_6$ (1 eq.), 20 °C, 2 h. Conditions C: **6a** (1 mM), MAO-N D9 (1.1 mg mL^{-1}), XDH E232V (1.7 mg mL^{-1}) potassium phosphate buffer (100 mM, 0.1% EDTA, pH 7.6), DCPIP (10 mol%), *T. versicolor* laccase (0.6 mg mL^{-1}), 20 °C, 2 h. Conditions D: **6a** (1 mM), **6c** (10 mM), MAO-N D9 (1.1 mg mL^{-1}), *E. coli* XDH (0.37 mg mL^{-1}), sodium phosphate buffer (50 mM, pH 7.4), 20 °C, 2 h. [b] Addition of ammonia–borane prior to extraction and analysis. [c] Includes addition of catalase (0.1 mg mL^{-1}), reaction at pH = 8.0. Conversion to lactams reported are based on response factors obtained from NMR-HPLC correlations (ESI, chapter 5.4.1).

monoamine oxidase (MAO-N D9) to catalyse the oxidation of the cyclic amine **6** to the imine/iminium **7** (1st step). The second step uses *either* chemocatalysis (H_2O_2/cat. CuI) or biocatalysis (xanthine dehydrogenase (XDH)/electron acceptor) to yield the desired lactam **8**.

Our model substrate for initial studies on the tandem reaction was tetrahydroisoquinoline **6a** (THIQ) in view of the high activity displayed by the D9 variant of MAO-N (Table S6†). Thus, the corresponding imine dihydroisoquinoline **7a** (DHIQ) generated by the MAO-N-catalysed 1st step became the substrate for subsequent investigations on the chemo or biocatalytic lactam forming 2nd step. Following the chemocatalytic approach for the 2nd step, we were able to achieve 69% conversion of DHIQ **7a** to lactam **8a** using 10–20 equivalents of H_2O_2 with 1 mol% CuI at 37 °C.

We then searched for a biocatalytic approach making use of an enzyme that is capable of oxidising THIQ-derived imines/iminiums **7** to lactams **8**. The drug metabolism literature contains reports of molybdenum-dependent aldehyde oxidases that are capable of catalysing such oxygen-dependent conversions. However, recombinant mammalian aldehyde oxidases generally have quite low activity and have not been exploited synthetically.[31] A related bacterial enzyme, recombinant xanthine dehydrogenase (XDH) from *Rhodobacter capsulatus*, can be expressed in reasonable yields and activity. Moreover, variants of *R. capsulatus* XDH were examined and showed a shift in substrate specificity from the natural substrates xanthine and hypoxanthine towards aldehyde oxidase type substrates.[31] Hence, we investigated variant XDH-E232V from *R. capsulatus* and found good activity towards DHIQ **7a**. Interestingly, the wild-type XDH from *R. capsulatus* revealed no activity against this substrate. As *R. capsulatus* XDH has in general only low reactivity with oxygen and preferentially uses other electron acceptors, we screened a range of electron acceptors (Table S8†) and found that either a combination of the redox mediator DCPIP (10 mol%) and either 1 eq. $K_3Fe(CN)_6$ or *T. versicolor* laccase/aerial O_2 could drive the reaction yielding lactam **8a**. In effect, the XDH-E232V/DCPIP/laccase combination functions as an oxidase surrogate. In addition, we examined *E. coli* XDH, in which case aerial O_2 acts directly as the terminal electron acceptor. Simply adding *E. coli* XDH (0.04 mg mL^{-1}) to a solution of imine **7a** in NaPi buffer (50 mM, pH 7.4) with periodic shaking gave complete conversion to the corresponding lactam **8a** at 20 °C in 2 h. Having established chemocatalytic and biocatalytic methods for high conversion of imine **7a** to the lactam **8a** we set about combining both reaction types with the MAO-N conversion to establish the desired tandem reactions.

Bio–chemo tandem catalysis

Combination of the CuI/H_2O_2 reaction conditions with the MAO-N D9 biocatalyst resulted in a one-pot conversion of **6a** to the lactam **8a** in 74% yield, implying high conversion catalysed by MAO-N D9 and at least as good performance by the copper catalyst, if not better, in the tandem reaction (conditions A, Table 2). The MAO-N enzyme produces H_2O_2 which may provide additional equivalents for the Cu-catalysed lactam forming 2nd step, thus slightly increasing the yield and showing a mutual benefit of combining these two steps. In addition, two related tetrahydroisoquinoline derivatives **6b** and **6c** from the initial screen with MAO-N D9 also underwent the tandem reaction (Table 2). As previously described,[6b] MAO-N variant D9 has an active site which is sufficient for accommodation of bulky substrates. However, compound **6b** produced a slightly lower activity (Table S6†), probably due to the position and nature of the NO_2-substitutent. Both of these substrates (**6b**, **6c**) are *N*-methylated and thus the substrate for the second step is an iminium. Although HPLC analysis of extracts indicated higher conversion, treatment of the reaction mixture with ammonia–borane prior to extraction showed the yields of **8b** and **8c** to be 47 and 42%, respectively.

Bio–bio tandem catalysis

The conditions developed using the *R. capsulatus* XDH-E232V variant and *E. coli* XDH for the conversion of DHIQ **7a** to the lactam **8a** matched well with those required for the MAO-N D9 oxidation. A combination of MAO-N D9 and XDH-E232V with the DCPIP (10 mol%)/Fe(III) (1 eq.) acceptor system gave an excellent 91% conversion to the lactam in 2 h (conditions B, Table 2). Moreover, laccase was also found to be applicable in place of Fe(III) in the tandem reaction (condition C). Thus the reaction uses 3 enzymes, buffer, catalytic DCPIP and aerial O_2 at 22 °C. We were also pleased to find that the *E. coli* XDH, which did not require any additional additives, could be coupled with MAO-N D9 to afford the lactam **8a** in 94% conversion (conditions D, Table 2). Substrate **6b** gave a complex product mixture with *R. capsulatus* XDH-E232V, whereas *E. coli* XDH was not able to catalyse the conversion of the iminium **7b** to lactam **8b**. In contrast, substrate **6c** (10 mmol scale) was converted quantitatively to the lactam **8c**. The addition of catalase was found to be necessary, presumably to destroy peroxide produced by the *E. coli* XDH reaction. Interestingly, the efficiency of the *E. coli* XDH reaction on **7c** appeared to be pH dependent as at pH 7.6 the overall conversion to lactam **8c** was 36%, whereas at pH 8.0 a quantitative conversion was achieved. In this case, we hypothesise that a greater proportion of the iminium **7c** exists in the pseudobase (hemiaminal) form at higher pH and that the latter may be the actual substrate for the enzyme.[23a]

Conclusions

We have demonstrated a toolbox of oxygen-dependent enzymes, which can be used in a simple and efficient fashion together or in combination with chemocatalysts or chemical reagents in aqueous one-pot biocatalytic tandem cascades to provide amides, carboxylic acids and lactams in good to excellent yield under very mild conditions (20–37 °C). The enzymes MAO-N D9 and GOase M_{3-5} have previously been developed for deracemisation of amines and resolution of secondary

alcohols. In the present work, each of these enzymes has been combined in a new way with xanthine dehydrogenases (XDHs) to create novel synthetic cascade reactions. The XDHs have been applied for the first time in preparative biocatalysis. They do not require addition of expensive cofactors and were highlighted to be ideally suited for combination with other oxidases. Evaluation of biocatalyst stability, immobilisation and recycling will facilitate scale up of these cascade processes. Work is currently ongoing to expand the range of mutually compatible and greener oxidative functional group transformations based on bio–bio and chemo–biocatalytic cascades.

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