Synlett K. Lauder, D. Castagnolo Synpacts

Photo-Biocatalytic Cascades for the Synthesis of Volatile Sulfur Compounds and Chemical Building Blocks

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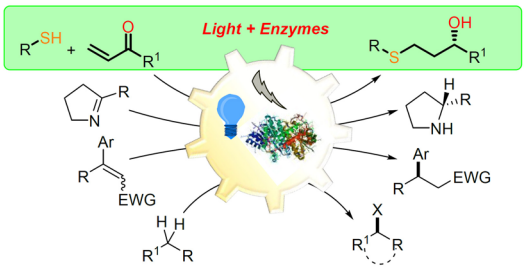

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Abstract Biocatalysis is a branch of catalysis that exploits enzymes to perform highly stereoselective chemical transformations under mild and sustainable conditions. This *Synpact* highlights how biocatalysis can be used in the synthesis of chiral 1,3-mercaptoalkanols, an important class of compounds responsible for the flavours and aromas of many foods and beverages. The identification of two ketoreductase (KRED) enzymes able to reduce prochiral ketone precursors enantioselectively to 1,3-mercaptoalkanols bearing a C–O stereocentre is presented. In addition, the combination of a photocatalytic thia-Michael reaction to access prochiral ketones with subsequent KRED-biocatalysed reduction in a one-pot cascade is presented. Photo-biocatalysed cascades represent one of the new and most intriguing challenges in synthetic chemistry, because the combination of different catalytic methodologies in domino processes offers unique opportunities to outperform sequential reactions with a high degree of selectivity and the avoidance of the need to isolate reaction intermediates.

Key words biocatalysis, ketoreductase, photobiocatalytic cascade, photocatalysis, mercaptoalkanols

1 Introduction

Volatile sulfur compounds (VSCs) are a currently untapped class of compounds that contribute to the distinctive flavours and aromas of a wide range of foods and beverages, including garlic, bread, cheese, meat, wine, and beer, usually at parts-per-million or even parts-per-billion levels.[1–3] Due to the low concentration of VSCs occurring naturally, their extraction from natural sources in industrially relevant quantities may be tough.

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Daniele Castagnolo obtained his Master's degree and Ph.D. in pharmaceutical chemistry from the University of Siena in 2006, working under the guidance of Professor Maurizio Botta. During his doctoral studies, he joined the research group of Professor Johann Mulzer at the University of Vienna as a visiting Ph.D. student. He carried out his postdoctoral studies at the Helsinki University of Technology in the group of Professor Petri Pihko, again at the University of Siena, as a research fellow, and then at the University of Manchester with Professor Jonathan Clayden. He began his independent research at Northumbria University, Newcastle upon Tyne, in 2012 as a lecturer, and in 2015, he moved to King's College London, where he is currently a senior lecturer in pharmaceutical and organic chemistry. His research interests are focused on the development of novel biocatalysed reactions for the synthesis of drug-like compounds and sulfur volatile compounds, as well as on the development of new antimicrobial agents.

Currently, more than a hundred structurally different VSCs have been found in foods and beverages and, from a chemical point of view, about 20–30% of these are 1,3-mercaptoalkanols, suggesting that this is probably the most important class of sulfur compounds with flavour and aroma

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activity.[4,5] Most mercaptoalkanols exist as chiral isomers bearing either a C–O or a C–S stereocenter or both, and their configuration can often have a huge influence on the nature and intensity of their organoleptic properties.[6–8] As an example, the *syn*-diastereomers of 4-mercaptopentan-2-ol (**1**; Figure 1) have an onion odour, whereas the *anti*-diastereomers have a sweaty smell.[5] Similarly, (3*R*)-1-methoxyhexane-3-thiol [(*R*)-**4**] has an herbaceous, onion-like character, whereas the (*S*)-**4** enantiomer has a repulsive odour reminiscent of armpit sweat.[9] In contrast, whereas both enantiomers of 3-mercaptohexyl acetate **3** have a similar blackcurrant-like aroma, the odour intensities are distinctively different. As shown in Figure 1, (*R*)-**5** has a low odour threshold of 0.0063 ng/L compared with (*S*)-**5**, whose threshold is over two magnitudes larger, at 0.72 ng/L.[6] On the other hand, the flavour profiles of the racemates are a combination of those of the single enantiomers, both in terms of threshold and character. Because the different stereoisomers might have a great impact on the flavour and quality of foods, it is evident that chemical methodologies able to afford VSCs with excellent enantioselectivities are highly desirable.

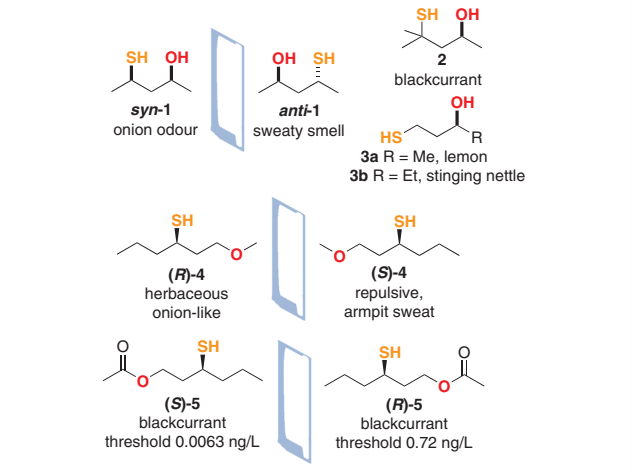
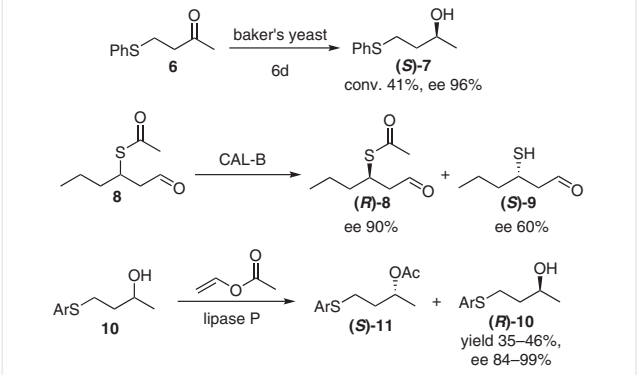


Figure 1 VSCs with a 1,3-mercaptoalkanol backbone and their respective flavouring and aroma properties

Mercaptoalkanols bearing an enantiopure C–S stereocenter, such as **1**, **4**, and **5** can be synthesised by using lithium reagents in the presence of chiral auxiliaries such as (–)-sparteine;[10] by the enantioselective thia-Michael additions using appropriate organocatalysts[11] or lanthanides complexes;[12] or through S_N2 reactions between thiols and enantiopure sulfonyloxy nitriles.[13] Mercaptoalkanols bearing a C–O stereocenter, such as **1**–**3**, can be obtained in enantiomerically pure forms by preparative GC resolution of the corresponding racemic mixtures[14] or through chemical reduction of ketone precursors by using chiral auxiliaries[15] or with chiral metal catalysts.[16] However, most of these approaches suffer from limitations in terms of atom economy and sustainability, the use of non-green solvents, a lack of recyclability of the catalysts, or, in some cases, harsh reaction conditions. In fact, chiral auxiliaries are required in stoichiometric quantities and therefore have low atom economy, whereas organocatalysts must often be synthesised by multistep sequences that might not adhere to the principles of green chemistry.[17]

2 Biocatalytic Synthesis of 1,3-Mercaptoalkanols

Biocatalysis is a relatively new, but already robust, strategy for synthesising stereodefined molecules by exploiting the intrinsic chirality of enzymes to catalyse chemical reactions.[18] However, biocatalytic approaches to access mercaptoalkanols are very limited in number and involve either kinetic enzymatic resolution of racemic substrates[19] by using lipase enzymes or reduction of carbonyl precursors mediated by baker's yeast (Scheme 1).[20] Nevertheless, the low yields and poor conversions of these biotransformations make them unappealing at the academic and industrial levels. The main limitation of the enzymatic kinetic resolution reaction is represented by the yields, which can only reach a maximum of 50% for each enantiomer. On the other hand, to the best of our knowledge, no examples of dynamic kinetic resolution of 1,3-mercaptoalkanols, which would lead to yields of >50%, have been reported to date.



Scheme 1 Biocatalytic approaches to 1,3-mercaptoalkanols

Similarly, the reduction of the prochiral ketone **6** with baker's yeast led to (*S*)-**7** with moderate conversion, despite its excellent enantioselectivity. Baker's yeast contains various enzymes that could potentially compete for the same substrate, thereby lowering the reaction yield.

Within this context, we started to explore novel biocatalytic green strategies to synthesise enantiopure mercaptoalkanol VSCs. In particular, our initial efforts were focused on the identification of enzymatic methods to access 1,3-mercaptoalkanols bearing C–O stereocenters, related to the flavouring agents **2**, **3a**, and **3b**. Previous work by Liu

and Cohen[20] showed that the prochiral ketone **6** could be reduced enantioselectively by baker's yeast reductases to give (*S*)-**7**. Consequently, we decided to screen the Prozomix's library of ketoreductases (KREDs), also known as alcohol dehydrogenases, with the aim of identifying appropriate enzymes able to convert ketones into enantiopure mercapto alcohols such as **7**. We identified 384 KRED enzymes present in the Prozomix library through a metagenomic approach. Instead of carrying out 384 biocatalytic reactions to identify the KREDs most suitable for substrate **6**, a colorimetric screening was initially carried out. The colorimetric kREDy-to-go assay, developed by Prozomix, consists of four 96-well plates containing a different KRED enzyme in each well, together with the cofactors NAD^+/$NADP^+$ and an ene-reductase (ERED) enzyme as a cofactor-recycling enzyme. Each KRED converts the racemic alcohol **7** into the corresponding carbonyl compound **6**, while simultaneously reducing $NAD(P)^+$ to NAD(P)H. The ERED regenerates the $NAD(P)^+$ by oxidation of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-2*H*-tetrazol-3-ium chloride (INT) present in each well. INT was thus converted into INT formazan which has a characteristic red colour, permitting the identification of those biocatalysts able to react with substrate **6** (Figure 2). Even though we were interested in the ketone-to-alcohol reduction, the kREDy-to-go assay proved to be useful as an initial screen to select a first panel of KREDs able to accommodate the mercapto-derivatives **6** and **7** in their catalytic pocket. A first group of 35 KRED enzymes was thus identified through the assay.

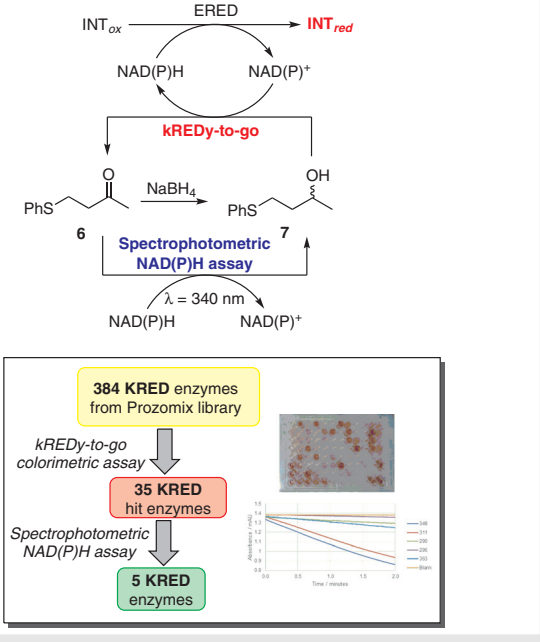


Figure 2 Screening of the KREDs from Prozomix library

However, because the assay was only able to detect the alcohol-to-ketone oxidation qualitatively, a spectrophotometric assay using the selected enzymes was carried out to identify those KRED biocatalysts able to promote the reverse ketone-to-alcohol reduction. The 35 hit KREDs were then screened against the ketone substrate **6**. The spectrophotometric assay exploits the NAD(P)H absorbance to ascertain the KRED activity qualitatively. If an enzyme is capable of reducing the carbonyl moiety, the NAD(P)H cofactor is converted into $NAD(P)^+$. Crucially, at 340 nm, only the oxidized NAD(P)H is detected. Thus, the ketone **6** was treated with the KRED biocatalysts and the catalytic cofactor NAD(P)H; no cofactor-recycling system was introduced into the reaction mixture. The decrease in the absorbance of NAD(P)H over time ultimately discriminates which enzymes are capable of reducing the ketone **6** to the alcohol **7**.[21] Five KRED enzymes from the Prozomix library, namely KREDs 290, 296, 311, 349, and 363, were found to promote the ketone-to-alcohol biotransformation and were therefore used in subsequent screening experiments on various ketone substrates. The third and final stage of screening involved small-scale reactions of the ketone **6** with the five hit KREDs. Ketone **6** was treated with each KRED in phosphate buffer (pH 7) at 37 °C, and glucose and glucose dehydrogenase (GDH) were employed to regenerate the cofactor NAD(P)H. All the reactions were analysed by chiral HPLC to determine the conversions of the reactants and the enantioselectivity. KRED363 resulted in the lowest conversion (7%) and enantioselectivity (8% ee), whereas KRED290 and KRED296 showed slightly improved conversions (22–25%) and enantioselectivities (15–12% ee). In all cases, (*S*)-**7** was obtained as the major enantiomer. Remarkably, KRED311 and KRED 349 resulted in complete conversion of **6** into **7** with 99 and 97% ee, respectively. Interestingly, whereas KRED311 selectively gave the *R*-enantiomer (*R*)-**7**, the *S*-enantiomer (*S*)-**7** was obtained from KRED349. An overview of the screening is shown in Figure 2. In summary, from among the 384 KRED enzymes of Prozomix library, two biocatalysts with opposite enantioselectivity were identified.

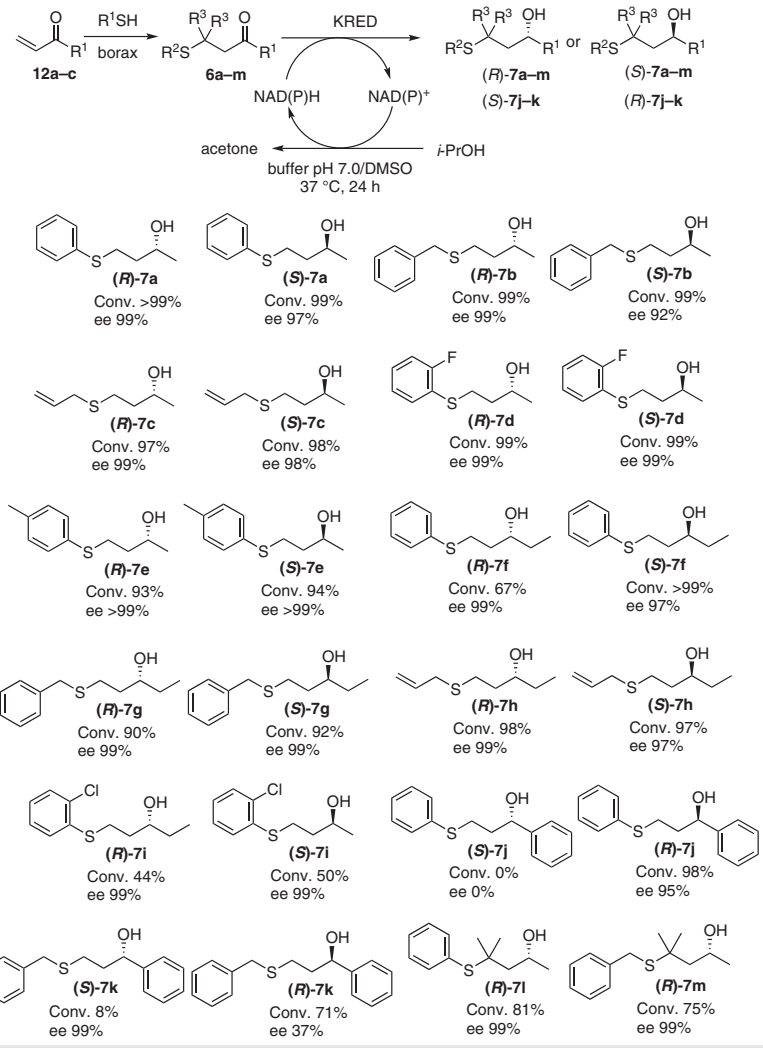
The substrate scope of these biotransformations was then investigated. The recycling systems for these enzymes was modified, and the KRED co-substrate isopropanol was preferred because of its ready availability and to avoid the use of GDH and the consequent generation of gluconic acid, which might have interfered with the biocatalytic cycle and altered the pH of the reaction.

The most indicative results of the biocatalytic reduction of ketones **6** into alcohols **7** are summarised in Scheme 2. Ketone precursors were in turn obtained through borax-catalysed thia-Michael addition of thiols to vinyl ketones **12a–c**. Initially, the substitutions in the R^1-position were scrutinised, with the thiophenol group replaced by aliphatic and variously substituted aromatic moieties. Then, the size of the R group was increased from methyl through ethyl to

phenyl. Finally, the protons in the R^2 positions were replaced with methyl groups. KRED biocatalysts were effective for a wide range of 1,3-mercaptoalkanols, particularly for those bearing Me and Et R-groups. However, for the Ph-substituted ketones **6j** and **6k**, no conversion was observed in the case of KRED311, whereas slightly lower conversions and ee values were obtained with KRED349, probably due to the steric hindrance of the substrates. Neither KRED was able to reduce substrates **6l** and **6m**, which have dimethyl substitutions in the β-position of the ketone, suggesting that the active site might be constricted in this region. However, the alcohol dehydrogenase ADH101 from the Johnson Matthey library proved able to convert the substrate **6l** and **6m** with good conversion and excellent ee (99%). In this case, the (*R*)-enantiomer was selectively obtained. The absolute configuration for **7a** was determined by comparison with data reported in the literature.[19]

3 Photo-Biocatalytic Synthesis of 1,3-Mercaptoalkanols

One of the most intriguing challenges for chemists is represented by the possibility of combining chemocatalysis and enzymatic catalysis in a single reaction, due to problems of compatibility of the catalysts and the different reaction conditions in which these generally operate. A combination of chemo- and biocatalysis offers opportunities to outperform sequential transformations, and the development of one-pot multistep cascade reactions involving both metallo- or organocatalysts and enzymes would be highly appealing in terms of both selectivity and synthetic efficiency. Cascade reactions offer additional benefits regarding the greenness of the methodology, such as the avoidance of isolation and purification of reaction intermediates or the need for functional-group protection strategies.[24]



Scheme 2 Biocatalytic synthesis of mercaptoalkanols **7**[22]

The possibility of combining the thia-Michael reaction for the synthesis of ketones **6** with the enzymatic step in a cascade reaction was then explored. However, the borax-catalysed thia-Michael synthesis of **6** was carried out under conditions (non-neutral pH) incompatible with the biocatalytic reduction. Thus, merging the chemocatalytic thia-Michael reaction with the biocatalytic reaction in a one-pot protocol turned out to be unfeasible.

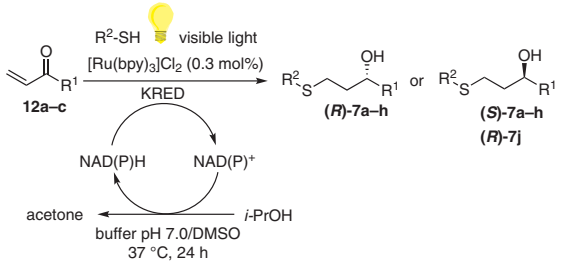
Visible-light photoredox catalysis represents an important tool for organic synthesis, and has become popular in the last two decades.[25] Photoredox-active metal complexes or organic dyes can be used to initiate photoinduced processes upon excitation with visible light. Such photocatalytic approaches can be carried out with cheap equipment and proceed through a radical mechanism permitting unique reactions to occur under mild conditions. Photocatalysis can be well exploited for the construction of C–S bonds through the reaction of thiols with alkenes (thio-ene photocatalysis).[26] Thus, the possibility of accessing the mercapto ketone **6** through a photocatalytic thia-Michael reaction under biocatalytic reaction conditions (buffer medium at pH 7) was investigated. Whereas the vinyl ketones **12a–c** and thiophenol reacted slowly in a DMSO/buffer mixture at pH 7,[27] it was found that the photoinitiator $[Ru(bpy)_3]Cl_2$ was able to catalyse the thia-Michael reaction with full conversions in less than five minutes under visible light under the same conditions. Thus, the photocatalysed thia-Michael and the biocatalysed KRED reduction were combined into a one-pot photo-biocatalytic cascade, as shown in Table 1. The vinyl ketone **12a–c** and the appropriate thiol were suspended in DMSO/buffer medium, to which the $[Ru(bpy)_3]Cl_2$ photoinitiator was added. After a few minutes, isopropanol, NAD(P)H cofactors, and the KRED enzyme was then added to the reaction mixture, leading to enantiopure mercaptoalkanols **7a–j** with excellent yields and enantioselectivities.

The kinetics of the photo-biocatalytic cascade were also studied through in situ ^{19}F NMR on compound **7d**. ^{19}F NMR was preferred to ^{1}H NMR because of the background interference caused by the aqueous medium, as well as the biocatalyst, cofactors, and recycling system. As shown in Figure 3, the photocatalysed reaction of 2-fluorobenzenethiol with methyl vinyl ketone was almost instantaneous following the addition of photoinitiator $[Ru(bpy)_3]Cl_2$. The KRED enzyme was then added to the reaction mixture after three minutes, together with isopropanol and the cofactor, leading to almost full conversion into the alcohol (*R*)-**7d** after about 10 hours.[28]

4 Photo-Biocatalysed Cascade Reactions

Photo-biocatalysed cascade reactions have acquired a growing interest in the last few years.[29] The possibility of combining biocatalysis with light for the sustainable synthesis of organic compounds is an attractive field of research. In fact, merging together various catalysts able to mediate complementary chemical reactions in a one-pot protocol can lead to the development of novel and more sustainable synthetic routes for the construction of challenging molecules, otherwise unobtainable by standard methods. Several works describing combinations of photocatalysis and biocatalysis have been recently reported (Fig-

Table 1 One-Pot Two-Step Photo-Biocatalysed Cascade to Yield 1,3-Mercaptoalkanols[23]



Entry	R^1	R^2	Product	KRED	Conv.[a] (%)	ee[a] (%)	Yield[b] (%)
1	Ph	Me	**7a**	311	99	>99 (*R*)	73
2	Ph	Me	**7a**	349	99	>99 (*S*)	71
3	Bn	Me	**7b**	311	99	99 (*R*)	66
4	Bn	Me	**7b**	349	99	97 (*S*)	54
5	All	Me	**7c**	311	99	>99 (*R*)	43
6	2-FC_6H_4	Me	**7d**	311	98	99 (*R*)	68
7	4-Tol	Et	**7f**	311	97[c]	>99 (*R*)	45
8	Ph	Et	**7f**	349	95	>99 (*S*)	60
9	Bn	Et	**7g**	311	98	99 (*R*)	40
10	All	Et	**7h**	311	99	99 (*R*)	49
11	Ph	Ph	**7j**	349	98	95 (*R*)	38

[a] Determined by HPLC using a ChiralPak IC column.
[b] Isolated yield.
[c] After 48 h.

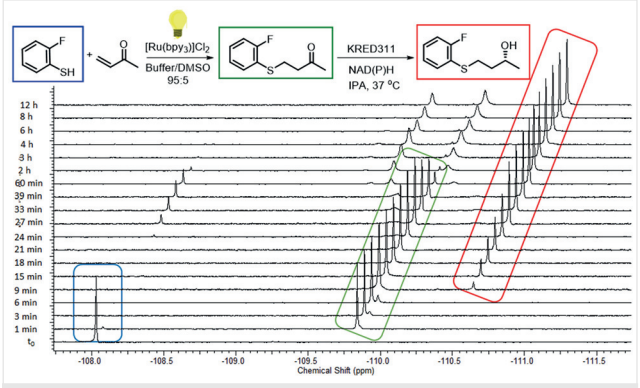


Figure 3 ^{19}F NMR in situ NMR of the photo-biocatalytic cascade

ure 4). Hartwig and Zhao developed an elegant photo-biocatalysed dynamic kinetic resolution reaction in which a light-activated photocatalyst catalyses the isomerization of aryl alkenes **13**, which, in turn, are converted into enantiomerically pure derivatives **14** by an ERED biocatalyst. The ERED is active on the *E*-isomer of alkene **13**, which is reduced enantiospecifically to the alkane **14** with high yields (60–96%) and high enantioselectivities (88–99% ee).[30] However, alkenes can often exist as mixtures of *E*- and *Z*-isomers and therefore, in the presence of such a mixture, the *Z*-alkene would remain unreacted. Also, the synthesis of *Z*-alkenes is sometimes favoured over the *E*-isomer. Thus, a combination of an Ir-catalysed photoisomerization with a biocatalytic reduction leads to enantiopure alkanes **14** from *E*/*Z*-alkene mixtures.

Ward's research group reported a photo-biocatalysed cascade for the synthesis of enantiopure pyrrolidines **17**.[31] A water-soluble Ir catalyst was combined with monoamine oxidase from *Aspergillus niger* (MAO-N) to convert a racemic mixture of amine **17** into the enantiomerically pure products. Imines **15** are initially transformed into the highly reactive radicals **16**, which, in turn, are converted into racemic amines **17**. Then, the MAO-N biocatalyst selectively oxidises one of the amine enantiomers into the imine **15**, and the cycle is repeated until only the pure amine (*R*)-**17** remains.

Yang et al. recently reported a light-mediated dynamic kinetic resolution of primary amines **18** by using *Candida antarctica* lipase B (CAL-B).[32] The photocatalysed process permitted the rapid racemisation of the amines **18**, while the CAL-B selectively acylated the *R*-enantiomers. In this way, the racemic amines could be converted into the (*R*)-amides **19**, which were obtained with up to 99% ee and high conversions.

Photocatalysis is not only used for promoting the isomerization of enantiomers. Ding et al. developed a photo-biocatalytic cascade to synthesise 2,2-disubstituted indol-3-ones **23** from 2-arylindoles **20** by the combined use of a $Ru(bpy)_3Cl_2$ photocatalyst and a wheat-germ lipase (WGL).[33] The photocatalyst promotes the oxidation of **20** to

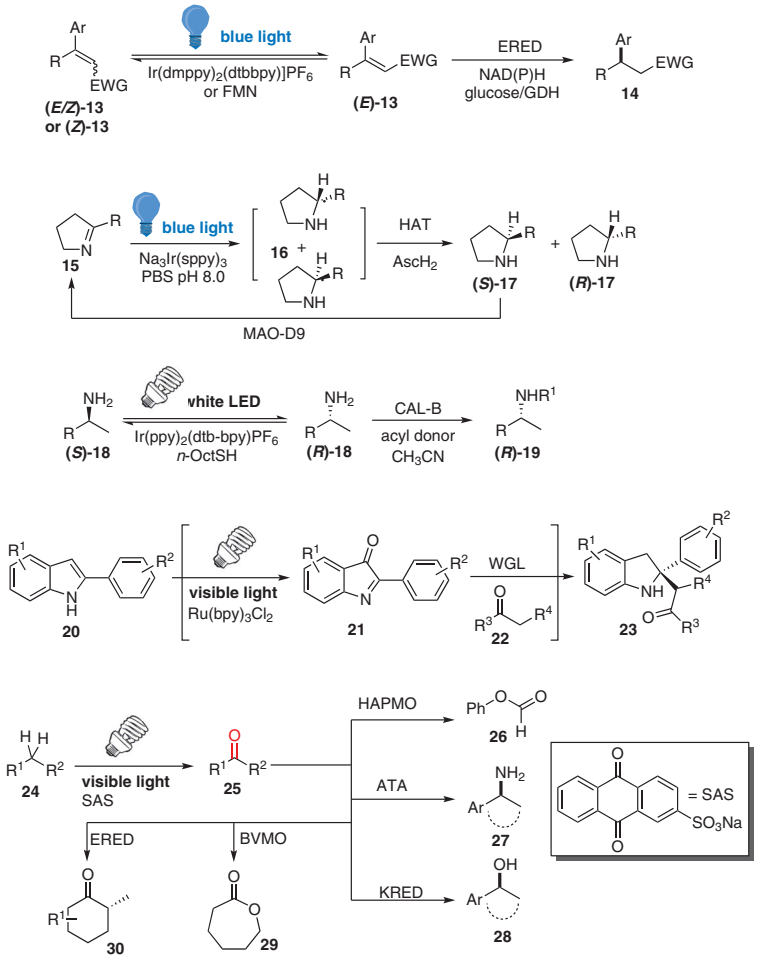


Figure 4 Photo-biocatalysed cascades for the synthesis of fine chemicals

yield the prochiral imine intermediate **21**, a suitable substrate for WGL. Then, the ketone reagent **22** reacts with **21** to yield indoles **23** with a stereodefined chiral quaternary carbon centre.

Finally, Hönhe, Schmidt, and their co-workers exploited photocatalysis to generate a range of prochiral ketones **25**, which were then transformed into a variety of derivatives **26–30** by using various biocatalysts.[34] Sodium anthraquinone-2-sulfonate (SAS) was used as photoinitiator to convert a series of alkanes **24** into ketones **25**. The latter were, in turn, treated with an appropriate biocatalyst [lyase, ERED, KRED, monooxygenase (CHMO or HAPMO), or amine transaminase] to generate compounds **26–30** in good conversions and with high enantioselectivities.

Despite these initial successes in the development of photo-biocatalysed cascades, a number of potential issues will need to be addressed in the near future, such as the interferences between the photocatalysed conditions and the redox cofactors, the mutual deactivation of some enzymes with the photocatalysts, and the occurrence of side reactions due to the presence of radical intermediates in the reaction media.

Also, the use of organo-photoredox catalysts,[26b] instead of the metal ones, might offer a greener and cheaper alternative and a better compatibility with the reaction conditions of biocatalytic transformations.

5 Conclusions

This *Synpact* article summarises the development of a novel photo-biocatalysed cascade for the synthesis of 1,3-mercaptoalkanol derivatives from readily available building blocks. The discovery of two new KRED enzymes able to catalyse the reduction of mercapto ketones with high enantioselectivity is described. In particular, the development of two screening approaches, a colorimetric and a spectrophotometric assay, for the rapid selection of the most-active KRED biocatalysts from a library of 384 enzymes is highlighted. The work then focused on the development of photo-biocatalytic cascade transformations that might permit the direct synthesis of key chemical compounds through a combination of photocatalytic and biocatalytic reactions in a one-pot process. An overview of the most recent and innovative photo-biocatalysed approaches for the synthesis of chemical building blocks is also presented.

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(22) **Biocatalytic Synthesis of Mercaptoalkanols 7; General Procedure**
A 1.5 mL microcentrifuge tube was charged with a solution of ketone **6** (0.03 mmol) in DMSO (50 μL), 200 mM phosphate buffer (pH 7.0; 650 μL), *i*-PrOH (50 μL), and NAD(P)H cofactor (0.001 mmol) in buffer (200 μL). (NADH was used with KRED311, and NADPH was used with KRED349.) A solution of the purified KRED stabilised in aq $(NH_4)_2SO_4$ solution was prepared for use by spinning down a 100 μL suspension at 8000*g* for 15 s, removing the aq $(NH_4)_2SO_4$ supernatant, and resuspending the pellet in buffer (50 μL). The resuspended KRED was added to the microcentrifuge tube, and the tube was placed on an environmental shaker at 160 rpm in a temperature-controlled room at 37 °C for 24 h. The mixture was then extracted with EtOAc (3 × 200 μL), dried ($MgSO_4$), and filtered through a 0.2 μM-pore-size filter. The EtOAc was removed in vacuo and the product was redissolved in the appropriate HPLC-grade solvent and injected into the HPLC to determine the percentage conversion and the ee.

(23) **Photo-Biocatalysed Cascade Synthesis of 1,3-Mercaptoalkanols: General Procedure**
But-3-en-2-one (0.0455 mmol, 1.0 equiv) and DMSO (50 μL) in 200 mM phosphate buffer (pH 7.0, 700 μL) were added to a vial containing the appropriate thiophenol or mercaptan (0.0455 mmol, 1.0 equiv). $Ru(bpy)_3Cl_2$ (0.000137 mmol, 0.3 mol%) was then added, and the mixture was stirred for 1 min. *i*-PrOH (1.31 mmol, 28.7 equiv) and NAD(P)H (0.00137 mmol, 0.03 equiv) were then added. (NADH was used with KRED311, and NADPH was used with KRED349.) A solution of the purified KRED stabilised in aq $(NH_4)_2SO_4$ solution was prepared for use by spinning down a suspension at 8000*g* for 15 s, removing the aq $(NH_4)_2SO_4$ supernatant, and resuspending the pellet in buffer (50 μL). The resuspended KRED was then added to the reaction mixture, which was shaken on an environmental shaker at 160 rpm in a heated room at 37 °C for 24 h. The mixture was then mixed with EtOAc (2 × 1 mL), and the mixture was spun in a microcentrifuge at 8000*g* for 1 min to remove traces of the enzyme. The organic layers were collected, dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by column chromatography [silica gel, EtOAc–hexanes (1:9)] to yield pure mercaptoalkanols **7**.

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