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# Photo-biocatalytic one-pot cascades for the enantioselective synthesis of 1,3-mercaptoalkanol volatile sulfur compounds

Kate Lauder,[a] Anita Toscani,[a] Yuyin Qi,[b] Jesmine Lim,[b] Simon J. Charnock,[b] Krupa Korah,[a] and Daniele Castagnolo*[a]

**Abstract:** The synthesis of enantiomerically pure 1,3-mercaptoalkanol volatile sulfur compounds via a one-pot photo-biocatalytic cascade reaction is described. Two new KRED biocatalysts with opposite enantioselectivity have been discovered and proved to be efficient on a wide range of substrates. A one-pot cascade reaction combining the a photocatalytic thio-Michael addition with a biocatalytic ketoreduction in aqueous medium results in a green and sustainable approach to access enantiopure 1,3-mercaptoalkanols in excellent ee and yields.

Volatile sulfur compounds (VSCs) constitute a wide class of structurally different chemicals which may contribute to both agreeable and disagreeable flavor and aroma of foods and beverages.[1-8] Aromas involving VSCs include tropical fruit,[4] guava,[5] onions,[6] cheddar cheese,[7] wine[1a] and beer.[8] The majority of VSCs found in foods and beverages exist as chiral isomers[9] and their olfactory perception may depend on their diastereomeric and enantiomeric configuration,[10] such as for the chiral alcohols **1-3** (Figure 1). Since the stereodifferentiation of chiral VSCs may have a great impact on the flavor and aroma of foods, the identification of high-yielding, cheap and straightforward methods for their production in an enantiomerically pure form is highly desirable. From a chemical point of view, 20−30% of the VSCs are 1,3-mercaptoalkanols, making them the most important sulfur compounds with aroma activity.[4a,9,11] 1,3-Mercaptoalkanols can be obtained in enantiomerically pure form *via* preparative GC resolution of the corresponding racemic mixtures[9] or through chemical reduction of ketones using chiral auxiliaries[12] or metal catalysts.[13] However, these approaches suffer from limitations in terms of atom-economy sustainability, use of non-green solvents and catalyst recyclability. Greener biocatalytic approaches have been developed via lipase-mediated kinetic enzymatic resolution[14] or Baker's yeast-mediated reduction of carbonyl precursors[15] (Figure 1). Despite being enantioselective, these biotransformations remain unappealing at industrial level due to low yields and poor conversions.[16] The recent advancements in molecular biology and metagenomics have recently made a wide number of new enzymes accessible and suitable for a large variety of stereocontrolled organic reactions. Within this context, this work describes the identification and the development of two new highly selective keto-reductase (KRED) biocatalysts for the synthesis of enantiomerically pure 1,3-mercaptoalkanols with general structure **C**. In addition, a mild and efficient one-pot cascade sequence for the direct synthesis of **C** from readily available α,β-unsaturated carbonyls **A** has been developed by combining the KRED biocatalytic step with a photocatalyzed thio-Michael reaction (Figure 1).

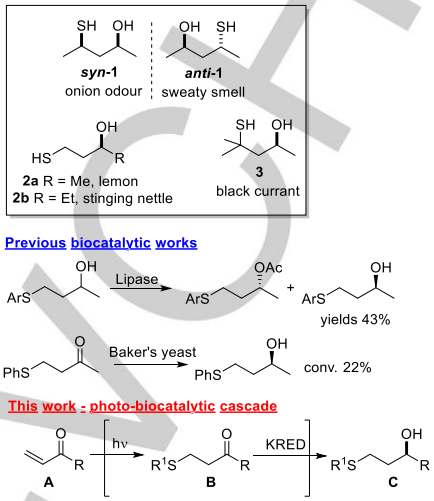


**Figure 1.** Examples of natural VSCs and biocatalytic approaches for the synthesis of VSCs

A set of mercaptoalcohols **6a-c** were initially synthesized from appropriate ketone **5** precursors (Scheme 1S),[17] and used as model substrates for the identification of appropriate biocatalysts among a pool of 384 KREDs, identified and isolated through a metagenomic approach,[18,19] from Prozomix's library. A qualitative kREDy-to-go assay combined with a spectrophotometric UV-Vis assay[20] was performed leading to the selection of five KRED enzymes (KRED290, 296, 311, 349, 363) able to promote the ketone **5** to alcohol **6** reduction and thus used in this work.

The phenylthio-pentan-2-one **5a** was first treated with the five selected KRED biocatalysts in PBS (200 mM, pH 7.0) at 37 °C, using isopropyl alcohol (IPA) as cofactor recycling agent (Table 1). The conversion of **5a** into alcohol **6a** and the enantiomeric excess (ee) were determined by HPLC (*entry 1*). Strikingly, a remarkable variability in both conversions and selectivity was shown. Although KRED 290, 296 and 363 led to alcohol **6a** in a low amount and poor ee (15%, 12% and 8% respectively), the *S*-enantiomer was formed as the only product. On the contrary, biocatalysts KRED311 and 349 fully converted **5a** into **6a** (99%) with excellent ee (99% and 97% respectively). Most interestingly, KRED311 led to the formation of the *R*-enantiomer **(*R*)-6a**, whilst KRED349 catalyzed the selective formation of the *S*-enantiomer **(*S*)-6a**. The absolute configuration of **(*R*)-6a** and **(*S*)-6a** was established by comparison of the $\alpha_D$ values of **6a** with those reported in the literature.[15] The scope of the reaction was then expanded to a set of different substrates **5** (Table 1). Methyl ketones **5b-f** were treated with KRED311 and 349 and fully converted into the corresponding alcohols **6b-f** with excellent ee (*entries 2-6*) and striking enantioselectivity. Similarly, ethyl-ketones **5g-m** were converted into the corresponding alcohols **6g-m** with excellent ee (>99%), although a slightly lower conversion was obtained for **(*R*)-6g** allegedly due to the steric hindrance of the ethyl group (*entry 7*). As a general trend, KRED311 leads to lower conversions (*entries 10-13*) than KRED349, which in this occasion proved to be the most efficient biocatalyst leading to (*S*)-alcohols with good to excellent conversions (>80%). Again, full and opposite enantioselectivity was observed.

[a] Ms K. Lauder, Dr A. Toscani, Ms K. Korah, Dr D. Castagnolo*
School of Cancer and Pharmaceutical Sciences
King's College London
150 Stamford Street, SE1 9NH, London, United Kingdom
E-mail: daniele.castagnolo@kcl.ac.uk
[b] Dr Y. Qi, Dr J. Lim, Dr S.J. Charnock
Prozomix Limited
Station Court, Haltwhistle, Northumberland
NE49 9HN, United Kingdom.

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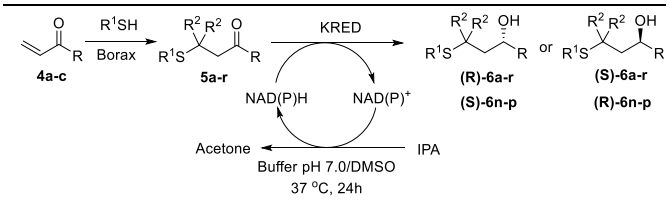
**Table 1. Biocatalytic synthesis of mercaptoalkanols 6a-r**

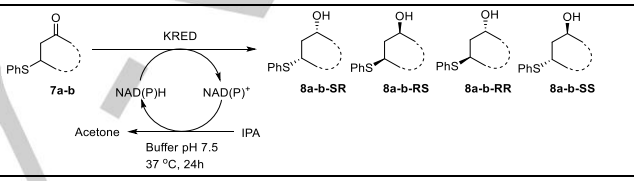



| Entry | SM | R | $R^1$ | $R^2$ | KRED | Alcohol | Conv. (%)[a] | ee %[b] (enan.)[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | | 290 | | 22 | 15 (S) |
| | | | | | 296 | | 25 | 12 (S) |
| *1* | **5a** | $CH_3$ | Ph | H | 311 | **6a** | >99 | 99 (R) |
| | | | | | 349 | | 99 | 97 (S) |
| | | | | | 363 | | 7 | 8 (S) |
| *2* | **5b** | $CH_3$ | Bn | H | 311 | **6b** | 99 | 99 (R) |
| | | | | | 349 | | 99 | 92 (S) |
| *3* | **5c** | $CH_3$ | Allyl | H | 311 | **6c** | 97 | 99 (R) |
| | | | | | 349 | | 98 | 98 (S) |
| *4* | **5d** | $CH_3$ | 2F-Ph | H | 311 | **6d** | 99 | 99 (R) |
| | | | | | 349 | | 99 | 99 (S) |
| *5* | **5e** | $CH_3$ | 4Me-Ph | H | 311 | **6e** | 93 | >99 (R) |
| | | | | | 349 | | 94 | >99 (S) |
| *6* | **5f** | $CH_3$ | 4Br-Ph | H | 311 | **6f** | 82 | 99 (R) |
| | | | | | 349 | | 54 | 99 (S) |
| *7* | **5g** | Et | Ph | H | 311 | **6g** | 67 | 99 (R) |
| | | | | | 349 | | >99 | 99 (S) |
| *8* | **5h** | Et | Bn | H | 311 | **6h** | 90 | 99 (R) |
| | | | | | 349 | | 92 | 99 (S) |
| *9* | **5i** | Et | Allyl | H | 311 | **6i** | 98 | 99 (R) |
| | | | | | 349 | | 97 | 99 (S) |
| *10* | **5j** | Et | 2F-Ph | H | 311 | **6j** | 63 | 99 (R) |
| | | | | | 349 | | 80 | 99 (S) |
| *11* | **5k** | Et | 2Cl-Ph | H | 311 | **6k** | 44 | 99 (R) |
| | | | | | 349 | | 50 | 99 (S) |
| *12* | **5l** | Et | *n*Pr | H | 311 | **6l** | 28 | 99 (R) |
| | | | | | 349 | | 86 | 99 (S) |
| *13* | **5m** | Et | 4Br-Ph | H | 311 | **6m** | 44 | 99 (R) |
| | | | | | 349 | | 66 | 99 (S) |
| *14* | **5n** | Ph | Ph | H | 311 | **6n** | 0 | 0 |
| | | | | | 349 | | 98 | 95 (R) |
| *15* | **5o** | Ph | Bn | H | 311 | **6o** | 8 | 99 (S) |
| | | | | | 349 | | 71 | 37 (R) |
| *16* | **5p** | Ph | Allyl | H | 311 | **6p** | 0 | 0 |
| | | | | | 349 | | 97 | 52 (R) |
| | | | | | 311 | | 0 | 0 |
| *17* | **5q** | $CH_3$ | Ph | $CH_3$ | 349 | **6q** | 0 | 0 |
| | | | | | 101 | | 81 | 99 (R) |
| | | | | | 311 | | 0 | 0 |
| *18* | **5r** | $CH_3$ | Bn | $CH_3$ | 349 | **6r** | 0 | 0 |
| | | | | | 101 | | 75 | 99 (R) |

[a]Calculated by HPLC using a Chiralpak IC column. [b]Calculated by HPLC using a Chiralpak IC column or by GC using a β-DEX™325 column. [c]Absolute configuration was established by comparison of the $\alpha_D$ values of **6a** with the value reported in the literature

Whilst the substrates **5n-p** bearing bulkier substituents were poorly converted by KRED311, with only the exception of the benzyl derivative **(*S*)-6o** obtained in low amount but with excellent ee (99%), KRED349 proved to be significantly more efficient at affording alcohols **6n-p,** also with excellent 95% ee (*entry 14*). In all cases, opposite *R/S* enantioselectivity was observed with KRED311 catalyzing the formation of *S*-enantiomers and KRED349 affording the *R*-enantiomers.[21] Because of the presence of two bulky methyl substituents at C4, the alcohols **6q-r** were not obtained when KRED311-349, as well as 290, 296 and 363, were used. Surprisingly, alcohol dehydrogenase ADH101[22] reduced the ketones **5q-r** to alcohols **6q-r** with good conversion and excellent ee (99%) (*entries 17-18*), affording the *R*-enantiomer. The selectivity of the KRED biocatalysts on ketones **7a-b** bearing a stereocentre on the sulfur atom was also investigated (Table 2). The reduction of the cyclic ketone **7a** with $NaBH_4$ led to the diasteroisomers **8a** as a racemate with a 90:10 *syn/anti* ratio (*entry 1*).[23] The biocatalytic reduction of **7a** with KRED311 showed similar diastereoselectivity (85:15 *syn/anti* ratio) and excellent enantioselectivity, leading to *syn*-**8a-*SR*** isomer with 99% ee (*entry 2*),[24] whilst the *anti*-**8a** diasteroisomers were formed with 33% ee. Although KRED349 showed lower diastereoselectivity (60:40 *syn/anti* ratio), *syn*-**8a-*RS*** was formed with 83% ee (*entry 3*), confirming the enantiopreference of KRED349 for the *S*-enantiomer. Finally, the biocatalysts ADH101 and ADH152[22] showed good diastereo- and enantioselectivity (*entry 5*).

**Table 2. KRED biocatalysed reduction of chiral ketones 7a-b**



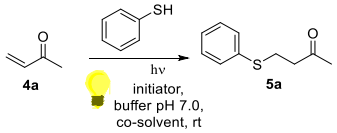

| Entry | Ketone | Reducing agent/enzyme | Conv. (%)[a] syn/anti | 8a-b SR:RS/RR:SS % (ee)/(ee)[b] % |
|---|---|---|---|---|
| *1* | | $NaBH_4$ | 90/10 | 45:45/5:5 (0)/(0) |
| *2* | | KRED311 | 85/15 | 85:0/10:5 (99)/(33) |
| *3* | **7a** | KRED349 | 60/40 | 5:55/18:22 (83)/(10) |
| *4* | | ADH101 | 23/76 | 20:3/36:40 (73)/(5) |
| *5* | | ADH152 | 87/13 | 72:15/6:7 (65)/(7) |
| *6* | | $NaBH_4$ | 60/40 | 30:30/20:20 (0)/(0) |
| *7* | **7b** | KRED311 | 58/42 | 58:0/42:0 (99)/(99) |
| *8* | | KRED349 | 69/31 | 13:56/3:27 (61)/(80) |

[a]Calculated by $^1$H NMR or HPLC using Chiralpak IC or IG columns. [b]Calculated by HPLC using a Chiralpak IC or IG columns.

The KRED-biocatalyzed reduction of **7b**, precursor of the VSC 4-mercaptopentan-2-ol **1**,[9] was also explored. The treatment of **7b** with KRED311 led to 60:40 *syn/anti*, similarly to $NaBH_4$ (*entries 6-7*). However, the biotransformation proved to be highly enantioselective leading to **8b-*SR*** and **8b-*RR*** in 99% ee. Similarly, the use of KRED349 showed good enantioselectivity affording isomers **8b-*RS*** and **8b-*SS*** with 61% and 80% ee respectively (*entry 8*).

Once the efficacy and the enantioselectivity of the KRED311/349 biocatalysts was proven, we decided to develop a more sustainable one-pot protocol to access mercaptoalkanols **6** directly from alkenes **4.**

**Table 3. Photocatalytic thio-Michael addition**



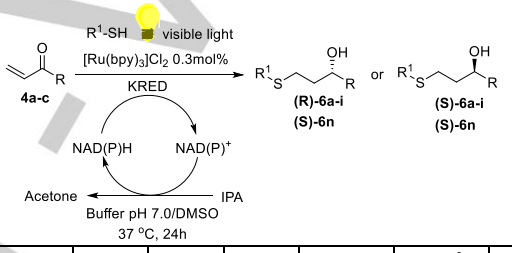

| Entry | Light hν | Initiator | Cosolvent 5% v/v | Additive[a] | Time | Conv. (%)[b] |
|---|---|---|---|---|---|---|
| *1* | Green LED | Eosin Y | Hexane | Pyridine | 2 h | 0 |
| *2* | Blue LED | $[Ru(bpy)_3Cl_2]$ | DMSO | - | 5 min | 95 |
| *3* | Blue LED | $[Ru(bpy)_3Cl_2]$ | DMF | - | 5 min | 90 |
| *4* | Blue LED | $[Ru(bpy)_3Cl_2]$ | IPA | - | 5 min | 85 |
| *5* | Blue LED | $[Ru(bpy)_3Cl_2]$ | DMSO | Aniline | 5 min | 99 |
| *6* | Blue LED | $[Ru(bpy)_3Cl_2]$ | DMF | Aniline | 5 min | 99 |
| *7* | Blue LED | $[Ru(bpy)_3Cl_2]$ | IPA | Aniline | 5 min | 99 |
| *8* | Blue LED | $[Ru(bpy)_3Cl_2]$ | DMSO | p-Toluidine | 5 min | >99 |
| *9* | **Visible** | **$[Ru(bpy)_3Cl_2]$** | **DMSO** | **-** | **5 min** | **>99** |
| *10* | Visible | $[Ru(bpy)_3Cl_2]$ | DMSO | p-Toluidine | 5 min | >99 |
| *11* | - [c] | $[Ru(bpy)_3Cl_2]$ | DMSO | - | 3 d | 52 |

[a]50mol% of additive were used. [b]Determined by $^1$H NMR. [c]In the dark

Mercaptoketones **5** were initially synthesized from **4** with Borax under basic conditions (pH 9)[17] which are incompatible with the biocatalytic reaction conditions (pH 7). Thus, we explored an alternative photocatalytic thiol-ene approach[25] to access ketones **5** in neutral aqueous medium. The photocatalytic Michael addition of thiophenol to vinyl ketone **4a** in phosphate buffer solution (PBS) at pH 7.0 was first investigated (Table 3). The use of green LED light in the presence of Eosin Y[26] proved to be ineffective (*entry 1*) and no ketone **5a** was obtained after 2h. On the contrary, when **4a** was reacted with PhSH under blue LED light using 0.3mol% of $[Ru(bpy)_3Cl_2]$ as initiator and no additives, the thioketone **5a** was formed in few minutes. Excellent conversion (95%) was obtained when DMSO was used as cosolvent (*entry 2*) and was therefore preferred over DMF and IPA (*entries 3-4*). Additives like aniline or *p*-toluidine (50mol%) also proved to be beneficial, leading to **5a** with >99% conversion within 5 minutes (*entries 5-8*). Surprisingly, the photocatalytic formation of **5a** also proceeded under visible light affording **6a** in a few minutes, with full conversion and no additives (*entry 9*). The latter conditions were therefore employed in the following studies. The combination of the visible light-catalyzed thio-Michael reaction with the biocatalytic ketone reduction was finally investigated as a one-pot process (Table 4). Vinyl ketones **4a-c** were suspended in PBS at pH 7.0 and treated with thiols **5** and catalytic $[Ru(bpy)_3Cl_2]$. The photocatalytic thio-Michael addition is instantaneous leading to the ketone intermediate **5** in <5min. The simultaneous addition of KRED, NAD(P)H and IPA to the reaction mixture resulted in the reduction of **5** into the enantiopure alcohols **6** within 24 hours with excellent yields and ee (Table 4).

The one-pot photo-biocatalytic cascade reaction was finally investigated *via in situ* NMR. Because of the complexity of the reaction mixture, a $^{19}$F NMR was performed in place of $^1$H NMR in order to clearly monitor the cascade process without the interferences arising from the solvent and the enzyme recycling system.

**Table 4. One-pot photo-biocatalytic cascade**




| Entry | Cmpd | R | $R^1$ | KRED | Conv. %[a] | ee %[a] (enant.) | Yields[b] (%) |
|---|---|---|---|---|---|---|---|
| *1* | **6a** | $CH_3$ | Ph | 311 | 99 | >99 (R) | 73 |
| *2* | **6a** | $CH_3$ | Ph | 349 | 99 | >99 (S) | 71 |
| *3* | **6b** | $CH_3$ | Bn | 311 | 99 | 99 (R) | 66 |
| *4* | **6b** | $CH_3$ | Bn | 349 | 99 | 97 (S) | 54 |
| *5* | **6c** | $CH_3$ | Allyl | 311 | 99 | >99 (R) | 43 |
| *6* | **6d** | $CH_3$ | 2F-Ph | 311 | 98 | 99 (R) | 68 |
| *7* | **6g** | Et | Ph | 311 | 97 (48h) | >99 (R) | 45 |
| *8* | **6g** | Et | Ph | 349 | 95 | >99 (S) | 60 |
| *9* | **6h** | Et | Bn | 311 | 98 | 99 (R) | 40 |
| *10* | **6i** | Et | Allyl | 311 | 99 | 99 (R) | 49 |
| *11* | **6n** | Ph | Ph | 349 | 98 | 95 (S) | 38 |

[a]Calculated by HPLC using a CHIRALPAK IC column. [a]Isolated yields. Compounds were purified by flash chromatography

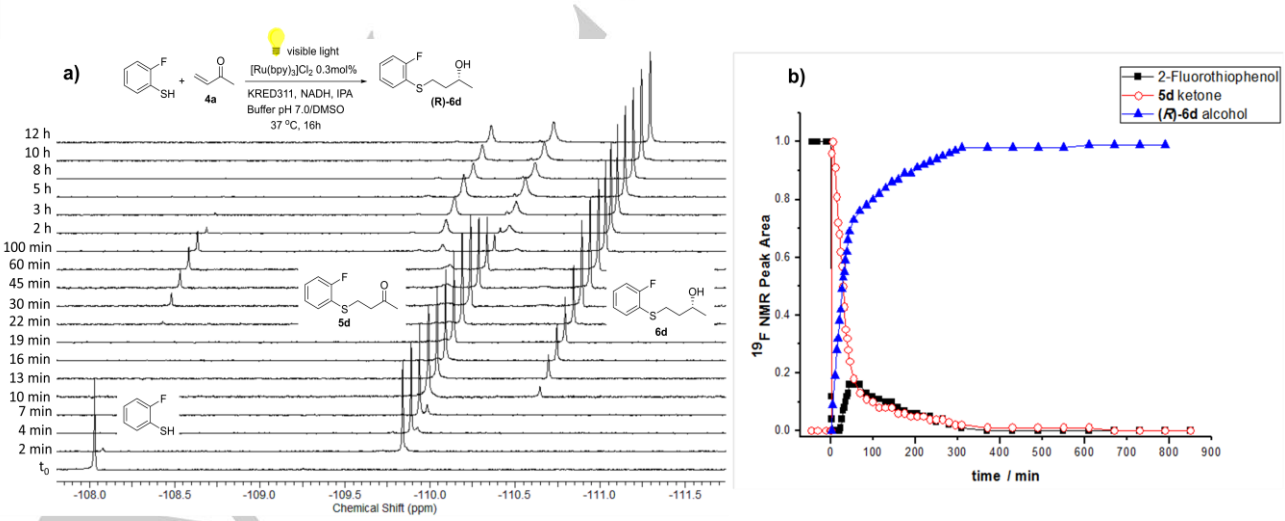



**Figure 2.** a) *In situ* $^{19}$F NMR stacked spectra of the photo-biocatalytic cascade reaction; b) kinetic profile of the reaction showing the disappearance of the 2-fluorothiophenol (—■—), the formation and subsequent disappearance of the ketone **5d** (—○—) in correspondence to the appearance of **6d** (—▲—).

The alkene **4a** was treated with 2F-phenylthiol and KRED311 under the conditions reported in Table 4 and the formation of ketone **5d** and alcohol **6d** was monitored at 37 °C. At $t_0$ the $^{19}F$ NMR shows the presence of the 2-fluorothiophenol (Figure 2). As soon as **4a** and the photoinitiator are added, the photocatalyzed reaction takes place and the ketone **5d** is formed within 3 minutes. The KRED311 was added, together with the NADH and IPA, just after the photoinitiator. At t=9 minutes, the formation of the alcohol **6d** can be observed. From the kinetic profile shown in Figure 2, it is clear that the *in situ*-generated ketone **5d** (-110.04 ppm) is almost fully converted (90% ca.) to the respective alcohol **6d** (-110.70 ppm) after 3 hours. Finally, after 5 h the ketone **5d** is reduced to **6d** with 97% conversion. According to the *in situ* NMR experiment, the reaction is completed after 12 h. As it can be seen from the $^{19}F$ stacked spectra, at t=2h, the formation of two broad peaks (-109.71 and -110.07 ppm) was observed. The signals were attributed to the intermolecular H-bonds of **6d** with the phosphate salts. To confirm this hypothesis, the reaction was stopped after 16 h and **6d** was extracted in EtOAc. The $^{19}F$ NMR of the crude extract in $CDCl_3$ showed only the peak of the alcohol **6d**, together with traces of the remaining excess of ketone **5d**. Alcohol **6d** was then re-suspended in phosphate buffer and stirred for 6 hours, before being analysed by $^{19}F$ NMR. Again, the formation of two broad peaks was observed confirming our assumption. The reason for the reappearance of the signal at -108.28 ppm of the 2F-thiophenol is yet not clear, although possible issues with the suspension of the compounds, as well as the stirring, could have contributed to its appearance. However, it is evident that the remaining 2-fluorothiophenol fully reacts with **4a** (added in slight excess) affording **5d**, which is in turn converted into the alcohol **6d**.

In conclusion, an efficient, mild and highly enantioselective one-pot photo-biocatalytic cascade protocol to access 1,3-mercaptoalkanols from α,β-unsaturated ketones has been developed. Two new KRED biocatalysts able to reduce the ketones **5** with opposite enantioselectivity and excellent ee have been identified. Both biocatalysts proved to be efficient on a wide range of ketone substrates including the chiral precursors **7a-b**. In addition, a photocatalytic synthesis of ketones **5** was developed and combined in a one-pot cascade with the KRED biocatalytic reaction, allowing the manufacturing of enantiopure 1,3-mercaptoalkanols **6** in a greener and more sustainable fashion. The single enantiomer derivatives **6** are currently being investigated for their olfactory and flavour properties.

## Experimental Section

Experimental details, procedures and copies of spectra are reported in the Supporting Information.

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**Keywords:** ketoreductase, photocatalysis, biocatalysis, mercaptoalkanols, volatile sulfur compounds

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[17] See Supporting Information for details on the synthesis of racemic **6a-c** (Scheme 1S) for kREADy-to-go assay.

[18] Details on the identification, isolation, cloning and purification of the KREDs are reported in the Supporting Information.

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[20] kReady-to-go and UV-Vis assays are described in the Suppoting Information.

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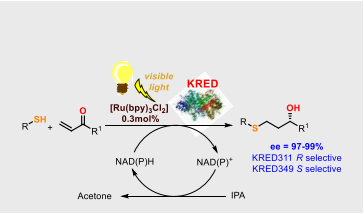
# COMMUNICATION

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*Kate Lauder,[a] Anita Toscani,[a] Yuyin Qi,[b] Jesmine Lim,[b] Simon J. Charnock,[b] Krupa Korah,[a] and Daniele Castagnolo*[a]*

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**Photo-biocatalytic one-pot cascades for the enantioselective synthesis of 1,3-mercaptoalkanol volatile sulfur compounds**