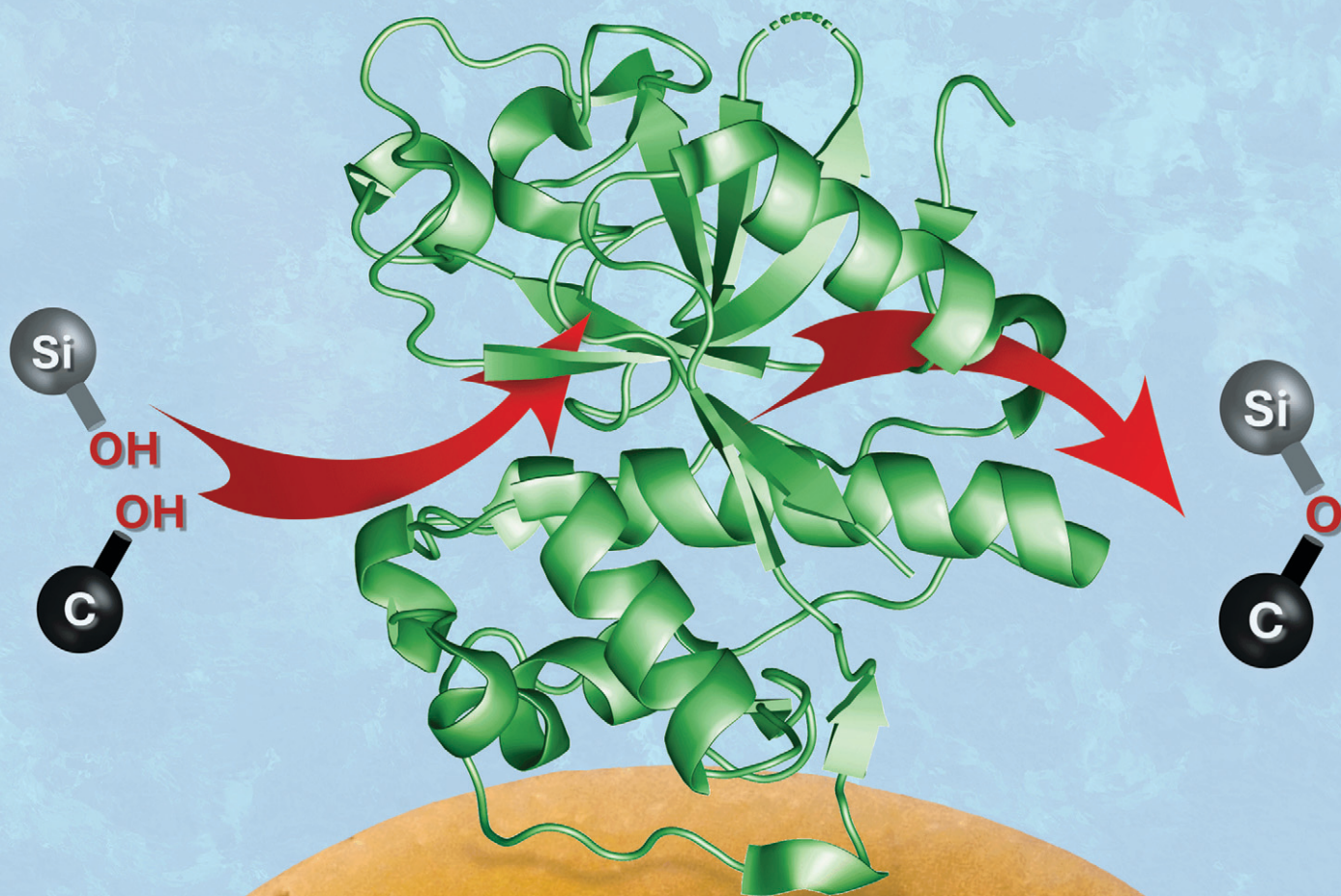


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**PAPER**

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# Investigating silicatein selectivity and specificity in silicon–oxygen bond condensation and metathesis†

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Silyl ethers are an important group of compounds containing Si–O bonds with a variety of applications, but their formation currently relies on reagents that are undesirable from a sustainability perspective. This study is a further investigation of the biocatalytic silylation of alcohols using silanols or silyl ethers as the silyl donor, with the recombinant enzyme silicatein- $\alpha$  as the catalyst. It was found that the model enzyme-catalysed reactions gave better conversion of phenol to its corresponding phenoxy silane compared to the aliphatic *n*-octanol. The enzyme was selective for phenols and did not catalyse disiloxane formation. In addition, it was observed that the optimum temperature for the enzymatic conversion was 75 °C. The enzyme also showed superior catalysis compared to conventional small molecule base catalysts such as imidazole and triethylamine.

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## Introduction

Silyl ethers are widely used as protecting groups for a variety of nucleophiles in organic synthesis.<sup>1–3</sup> Their introduction into the molecule of interest typically employs the corresponding silyl chloride, triflate or hydride reagents.<sup>1,3</sup> However, these compounds are energy-intensive to produce and their use results in the generation of stoichiometric amounts of hazardous or environmentally undesirable by-products. In principle, a more energy- and atom-efficient route to the formation of silyl ethers would be through the condensation of their corresponding silanol and alcohol. This approach would use starting materials that are safe to handle and release only water as the by-product. Biocatalytic approaches have been previously reported for the manipulation of the silicon–oxygen bond with a range of hydrolases including lipases, phosphatases (phytases) and muramidases (lysozymes).<sup>4–6</sup> However, the reported conversions were modest with regard to the formation of the silyl ethers from silanols.

Demospongiae are a class of marine sponges whose exoskeletons consist of inorganic silica. This exoskeleton is produced through a biosilification process (*i.e.*, condensation of silicic acid) catalysed by a family of

enzymes called the silicateins.<sup>7,8</sup> The  $\alpha$ -isoform of the silicatein (Sil $\alpha$ ) from *Suberites domuncula* has been extensively studied and it has been found that, apart from being able to catalyse the condensation of silicates into silica, this enzyme is also capable of catalysing the hydrolysis and condensation of a range of organosiloxanes and silyl ethers.<sup>9–12</sup> Here, an investigation using a trigger factor-Sil $\alpha$  fusion protein (recombinantly produced in *E. coli*) to catalyse the condensation of triethylsilanol with a range of phenols and aliphatic alcohols showed that phenols were generally more reactive than aliphatic alcohols.<sup>11</sup> However, this initial survey of substrates did not address the specificity of this biocatalyst or the time course of the reactions.

This present study therefore aimed to further investigate the effectiveness of silicatein-catalysed Si–O bond manipulation. Here, a more detailed examination of the reaction progress, substrate preference and product distribution were carried out; followed by comparative analyses against small molecule catalysts to confirm enzyme-specific catalysis. In addition, silyl transfer reactions were investigated, as an alternative to condensation reactions.

## Results and discussion

### Silicatein-catalysed silyl ether condensation

To further characterise these biocatalytic silyl condensation reactions, a more detailed analysis of the product distribution was carried out on the model condensation reaction between triethylsilanol (TES-OH) and either phenol

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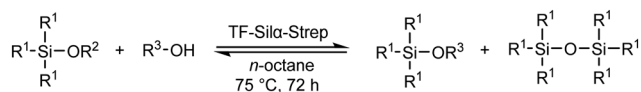


or *n*-octanol, which was catalysed by the previously reported Sil $\alpha$  fused to a trigger factor at the N-terminal and a strep II tag at the C-terminal (henceforth referred to as TF-Sil $\alpha$ -Strep).<sup>13</sup> As before, the reactions were conducted in neat *n*-octane using the lyophilised enzyme at 75 °C, and a 5 mol. eq. excess of triethylsilanol relative to the alcohol (Scheme 1, where R<sup>1</sup> = ethyl, R<sup>2</sup> = H, and R<sup>3</sup> = *n*-octyl or phenyl).

The results showed that the enzyme did catalyse condensations with phenol with a conversion of 86% after 72 h, compared to 23% obtained with the negative control where the enzyme was omitted (Table 1, ESI† Fig. S1). In contrast, the enzyme did not give any significant increase in product formation in the analogous reaction with *n*-octanol, where the enzymatic reaction gave a conversion that was essentially the same as the negative control (3.0 vs. 2.6%). These results were consistent with the previous report<sup>11</sup> that showed phenols were generally preferred over aliphatic alcohols.

Condensation reactions involving silanols can produce their corresponding disiloxanes as a side-product since self-condensation is thermodynamically favourable.<sup>6,14,15</sup> However, it was found that the Sil $\alpha$  enzyme did not catalyse disiloxane formation, whereby the amounts found in the enzymatic reactions were not significantly higher than the trace amounts (~1%) found in the reactions where the enzyme was omitted (Table 1, ESI† Fig. S1). This result indicated that the enzyme selectively catalysed only the silyl ether condensation.

To further assess the enzyme preference for either aromatic or aliphatic alcohols, a competition experiment was conducted where both phenol and *n*-octanol were concurrently supplied and the product distribution profiles over 96 h were analysed (Fig. 1, ESI† Table S1). In general, the reactions appeared to reach completion at ~72 h, with little further conversion at 96 h (Fig. 1A). Consistent with the above result, the phenyl silyl ether (TES-OPh) formed much of the product, with ~62% net conversion (*i.e.* conversion of the catalysed reaction minus the uncatalysed reaction, Fig. 1B) after 72 h. In comparison, only a very small amount of the *n*-octyl silyl ether (TES-OOc) was formed above that of the control reactions where the enzyme was omitted (~1% net conversion). Even when accounting for the fact that the phenol was more reactive than the octanol (as seen in the uncatalysed reaction), the enzyme increased the conversion of TES-OPh by nearly 4-fold (85.9 vs. 23.1% for the catalysed and uncatalysed reactions, respectively, at 96 h), compared to TES-OOc where there was essentially no improvement between the catalysed and uncatalysed reactions.



**Scheme 1** General scheme for silyl ether formation catalysed by TF-Sil $\alpha$ -Strep.

**Table 1** Product conversions after 72 h for the enzyme-catalysed condensation of phenol or *n*-octanol with triethylsilanol. The percentage conversion for the silyl ether was calculated based on the molar quantity of alcohol (1.26 mmol). The percentage conversion for the disiloxane was calculated relative to the quantity of silanols (two moles of silanol produced one mole of disiloxane giving a theoretical maximum yield of ~3.17 mmol). The variance shown indicates the standard error of the mean. TES = triethylsilyl, OOc = *n*-octyloxy, and OPh = phenoxy

| Substrate         | Product              | Conversion (%) |               |            |
|-------------------|----------------------|----------------|---------------|------------|
|                   |                      | Enzymatic      | Non-enzymatic | Net        |
| Phenol            | TES-OPh              | 85.7 ± 5.4     | 23.0 ± 1.4    | 63.2 ± 5.6 |
|                   | (TES) <sub>2</sub> O | 1.0 ± 0.1      | 1.1 ± 0.3     | ~0.0       |
| <i>n</i> -Octanol | TES-OOc              | 3.0 ± 0.5      | 2.6 ± 0.2     | 0.4 ± 0.3  |
|                   | (TES) <sub>2</sub> O | 1.8 ± 0.1      | 1.6 ± 0.1     | 0.2 ± 0.1  |

### Effect of reaction temperature on phenol condensation

The effect of temperature on product conversion was then investigated, using TES-OH and phenol for the model reaction. These reactions were conducted over the course of 96 h at 22 (ambient temperature), 50, 75 and 95 °C (Fig. 2A, ESI† Table S2). It was observed that reactions carried out at 75 °C gave the fastest and highest conversions, with the reaction having reached completion after 72 h. This result held even when considering the net conversion, which was ~62% in this case (Fig. 2B). In comparison, the reactions at 95 and 50 °C had not yet reached completion even after 96 h, and effectively no conversion was observed at any time point when heating was not applied (<1% net conversions at 22 °C). These results are in agreement with a previous report that showed good conversion rates were achieved at 75 °C using TF-Sil $\alpha$ -Strep on phenols<sup>11</sup> and hexahistidine-tagged TF-Sil $\alpha$  on *n*-octanol.<sup>10</sup>

Even under the best conditions noted above, it was found that absolute conversions never exceeded 88%. This result was not due to the excessive formation of the disiloxane side-product, which never exceeded ~1% gross conversions (Table 1). Instead, it may reflect the equilibrium position of the reaction, since TF-Sil $\alpha$ -Strep can also catalyse the reverse reactions, *i.e.* hydrolysis or silyl transfer (see below).

### Analysis of non-specific catalysis

Further verification reactions were carried out to check if the observed catalysis is indeed due to the specific action of the enzyme and not due to the other excipients in the lyophilisation preparation that could, in principle, contribute to general acid–base catalysis. The condensation of triethylsilanol and phenol was again carried out at 75 °C (Scheme 1, R<sup>1</sup> = ethyl, R<sup>2</sup> = H, and R<sup>3</sup> = phenyl) and analysed after 24 h in the presence of only the lyophilised additive mixture comprising potassium salts and 18-crown-6, or each additive individually. The results showed that only the fully constituted formulation that included the enzyme gave any significant conversion (Fig. 3A). Neither the mixture of lyophilisation additives nor any of its individual components gave any meaningful conversion (<1% in all cases). It has





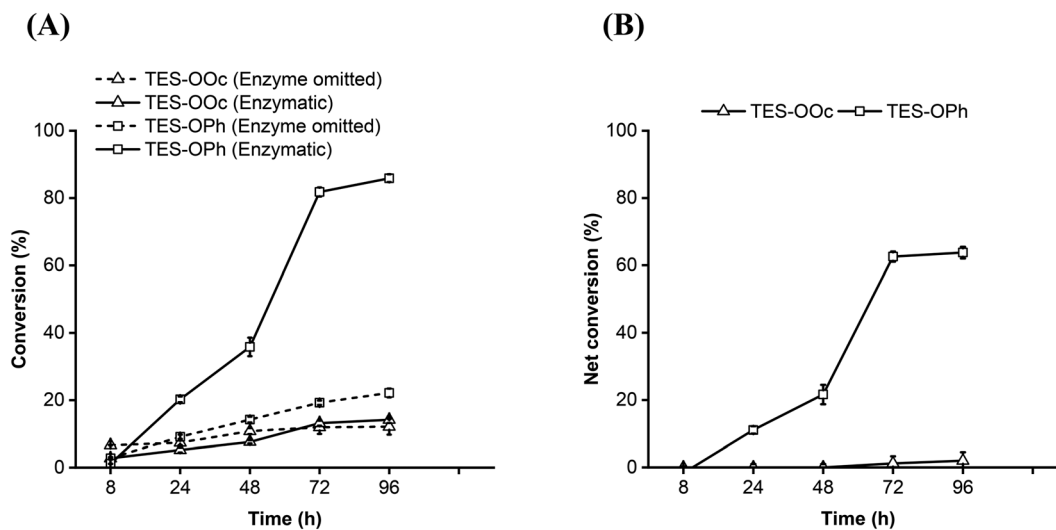


Fig. 1 Graphs of product conversion (A) and net conversion (B) against time for the condensation of phenyl and octyl silyl ethers in a mixed reaction. The error bars shown indicate the standard error of the mean.

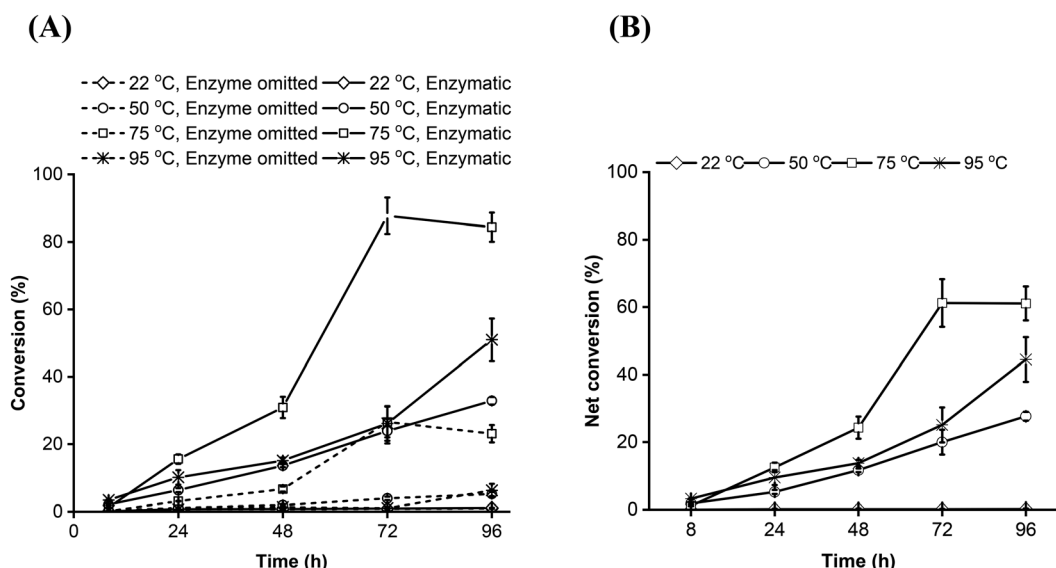


Fig. 2 Graphs of product conversion (A) and net conversion (B) against time for the condensation of phenyl silyl ether at different reaction temperatures. The error bars shown indicate the standard error of the mean.

already been shown that the enzyme that had been deliberately heat-denatured prior to lyophilisation also gave conversions that were no better than the additives alone.<sup>10,11</sup> Therefore, these results overall confirm that the observed silylations are the result of enzyme-specific catalysis.

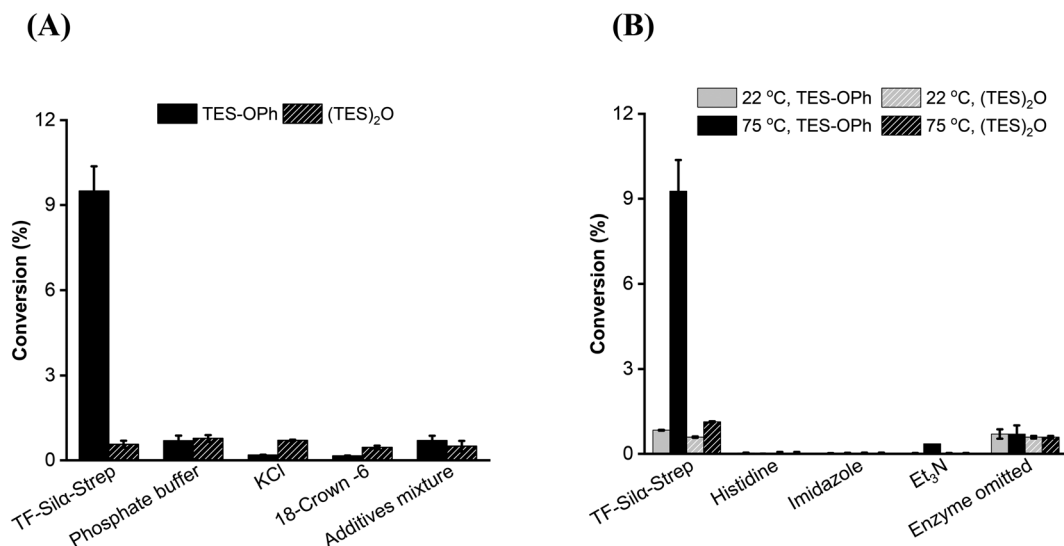
Next, a comparison of enzyme catalysis with that of small molecule bases that are commonly used in synthetic chemistry such as imidazole, triethylamine ( $\text{Et}_3\text{N}$ ) and histidine (present in peptide catalysts)<sup>16</sup> was carried out. These experiments were carried out at equivalent molar concentrations of the small molecule catalysts to the enzyme (*i.e.* 67  $\mu\text{M}$ ) at 22 °C and 75 °C. The results show that all the comparator small molecules gave negligible conversions

(<1% in all cases) (Fig. 3B). It was also observed that disiloxane formation was also negligible in the small molecule-catalysed reactions, while the TF-Sil $\alpha$ -Strep selectively catalysed the formation of the silyl ether, in agreement with the results above.

### Biocatalytic silyl transfer reactions

To investigate whether the enzyme was capable of catalysing intermolecular silyl transfer (*i.e.* silyl transesterification) reactions, an experiment was conducted in a similar manner to the phenol condensation except that triethylethoxysilane (TES-OEt) was used as the silyl donor (Scheme 1,  $\text{R}^1 = \text{ethyl}$ ,





**Fig. 3** Histograms of TES-OPh and (TES)<sub>2</sub>O conversions for reactions involving: (A) the lyophilisation additive mixture (containing phosphate salts and crown ether) or the individual components of the mixture; or (B) various small molecule bases. In all cases, “TF-Sil $\alpha$ -Strep” represents the fully constituted reaction containing the lyophilised enzyme in the additive mixture. The percentage conversion for the disiloxane was calculated relative to the quantity of silanol. The error bars shown indicate the standard error of the mean.

R<sup>2</sup> = ethyl, and R<sup>3</sup> = phenyl). In general, it was found that the desired phenyl silyl ether was indeed formed (Fig. 4A, ESI† Table S3), while the negative controls where the enzyme was omitted gave essentially no conversions (<0.2%). However, the conversions were much lower compared to the analogous reaction using TES-OH, with a ~5% gross conversion after 96 h (ESI† Table S3) compared to ~84% with the silanol (Table 1). The reasons for this low conversion were unclear, but since the conversions appeared to approach a plateau after 96 h, it implies that the observed results may simply be a reflection of the final equilibrium position for this reaction.

Finally, an analogous reaction was carried out using trimethylethoxysilane (TMS-OEt) as the silyl donor to further investigate the effect of the substrate size in the transesterification. The results showed that the corresponding phenyl silyl ether was also formed, and the presence of the enzyme gave product conversions that were higher than when the enzyme was omitted (Fig. 4B, ESI† Table S3). It also gave better net conversions compared to TES-OEt (~20 vs. 3%) after 72 h (Fig. 4C, ESI† Table S3). In a similar manner to TES-OEt, the reaction appears to approach thermodynamic equilibrium after ~72 h.

It was also observed that the amount of disiloxane formed by both silyl donors was low and not significantly different from the amount in the reaction with triethylsilanol, consistent with the hypothesis that the enzyme selectively catalysed only the silyl ether condensation. This result implies that the enzyme only accepts a relatively small alkyl moiety as the partner to the silyl group (*i.e.* phenoxy or ethoxy accepted, while *n*-octyl, TES or TMS are not).

## Conclusions

In summary, an analysis of the role and effectiveness of TF-Sil $\alpha$ -Strep for catalysing silyl ether condensations and silyl transfers was carried out. In general, these enzymatic condensations showed a preference for the aromatic phenol over the aliphatic *n*-octanol, as evidenced by much higher conversions obtained for the phenol condensation; confirming the findings of the previous studies. An investigation into the reaction progression showed that reactions conducted at 75 °C for 72 h gave the best results. These conversions were directly attributable to the enzyme, as neither the excipients used for enzyme lyophilisation nor generic small molecule bases gave any significant product formation. It is therefore apparent that the enzyme showed superior catalysis compared to the small molecule catalysts. Likewise the enzyme did not catalyse disiloxane formation. The enzyme did catalyse silyl transfer reactions, but with low conversions, possibly due to their unfavourable thermodynamic equilibrium when compared to the analogous reactions employing the silanol.

Going forward, further investigations can be conducted such as expanding the scope of substrates suitable for Sil $\alpha$  condensation reactions, enzyme engineering to enhance activity or selectivity, as well as reaction stoichiometry optimisation. The biocatalytic formation of chiral silyl ethers may also be a worthwhile future avenue of research.<sup>17</sup>

## Experimental

### Materials and equipment

All solvents and reagents were purchased from either Sigma-Aldrich (now Merck), VWR, Fluorochem or Fisher Scientific.



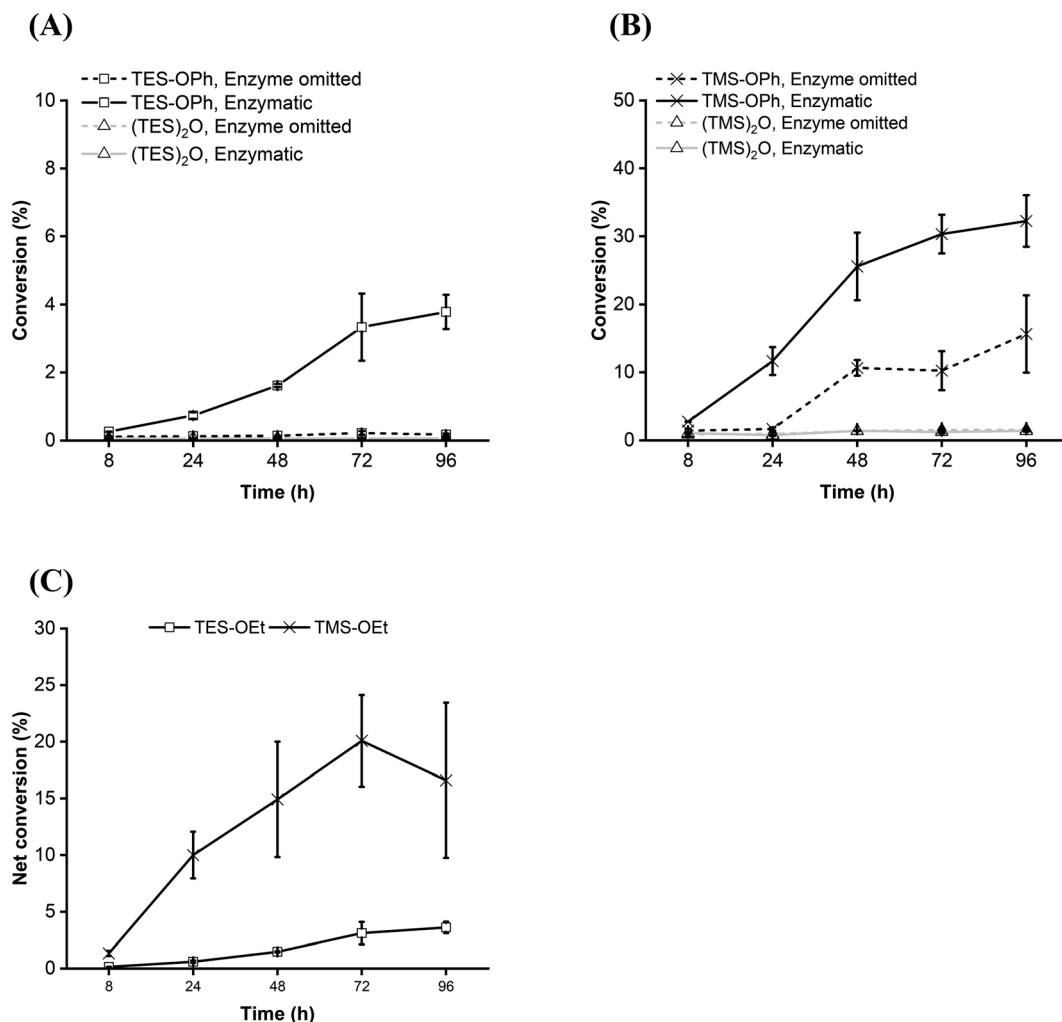


Fig. 4 Graphs of product conversions against time for reactions of silanol with (A) TES-OEt and (B) TMS-OEt, respectively. (C) Net product conversions of the respective TES-OPh (from the TES-OEt reaction) and TMS-OPh (from the TMS-OEt reaction) formed. The reactions were carried out with the ethyl silyl ether and phenol in *n*-octane at 75 °C. TMS-OPh = trimethylphenoxysilane. The error bars shown indicate the standard error of the mean.

All solvents used were supplied as anhydrous and used without further purification. Authentic samples of TES-OPh and TES-OOC were prepared by conventional synthetic silylations of the *n*-octanol and phenol with chlorotriethylsilane under basic conditions,<sup>10,11,15</sup> and the purity and identity of the synthesised compounds confirmed by NMR and MS (data in ESI† Fig. S7–S10). The TMS-OPh standard was commercially sourced from Sigma-Aldrich. The recombinant TF-Sil $\alpha$ -Strep enzyme was heterologously produced in *E. coli* containing a synthetic vector coding for the mature wild-type Sil $\alpha$  from *Suberites domuncula* fused with the TF and strep II tag, as previously described.<sup>13</sup> Lyophilisation was carried out with a Thermo Fisher Heto Lyolab 3000. The condensation reactions were carried out in crimp-sealable vials and analysed by GC-MS, as previously described.<sup>11</sup>

#### Preparation of the lyophilised enzyme and matrix

The isolated enzyme was buffer exchanged into the lyophilising buffer (100 mM KH<sub>2</sub>PO<sub>4</sub>, 100 mM K<sub>2</sub>HPO<sub>4</sub>, 20

mM KCl, pH 7.0) using a PD-10 desalting column. 2.5 mL batches of the enzyme were loaded on to the column after column washing with the lyophilising buffer, and the enzyme was subsequently eluted by adding 3.5 mL of the buffer. The eluted fractions were concentrated by centrifugal ultrafiltration (filter volume 30 mL and 30 000 MWCO at 5600  $\times g$ ) and the final protein concentration adjusted to 5 mg mL<sup>-1</sup> (67  $\mu$ M) with the same buffer. 18-Crown-6 was then added to a 40  $\mu$ M concentration in the final solution. Aliquots of 100  $\mu$ L of this mixture were placed in glass vials, flash frozen by plunging them into liquid nitrogen, and then lyophilised.

For the negative control where the enzyme was omitted, 100  $\mu$ L aliquots containing only the lyophilising buffer with 18-crown-6 were flash frozen and lyophilised. The same procedure was also used for the lyophilisation of the potassium salts and 18-crown-6 separately.

For the reactions involving the small molecule catalysts, the reactions were conducted by utilising the same reaction



conditions as in the previous experiment but with equivalent molar quantities (*i.e.* 67  $\mu\text{M}$  concentration in each reaction) of the catalysts investigated.

### Enzymatic condensation reactions

A stock solution of the substrates was first prepared by mixing the desired alcohol (1.26 mmol) and triethylsilanol (6.33 mmol) in the *n*-octane (3 mL). 100  $\mu\text{L}$  of this mixture was added into each vial containing the lyophilised enzyme and the vial crimp sealed. The vials were then heated at the desired temperature while shaking at 650 rpm. At the desired time point, the vial was removed from heating, hexane (1 mL) was added, and the mixture centrifuged (16000g, 10 min) to separate the solid matter. 800  $\mu\text{L}$  of the supernatant was transferred to a clean vial and analysed by GC-MS. For the quantification of conversion rates, a GC-MS was first calibrated using authentic samples of the relevant compounds (ESI† Fig. S11 and S12).

Each reaction was performed in triplicate, and the error bars presented in the figures refer to the standard error of the mean of the three independent reaction vials (see the ESI† for details of the calculations), whereby each reaction used the enzyme produced from the different batches of cell culture that were separately cultured and induced; and the protein isolated and lyophilized separately.

For the competition experiment, the reactions of phenol and *n*-octanol with silanol were carried out with equivalent molar quantities of the alcohols (*i.e.* 420 mM each in the final reaction mixture) under the same reaction conditions utilised for the individual reactions.

### Data availability

The numerical data used to produce the results herein are available on Figshare at <https://doi.org/10.48420/26556775>.

### Author contributions

Conceptualization, L. S. W.; methodology, C. S. E.; validation, C. S. E.; formal analysis, C. S. E. and L. S. W.; investigation, C. S. E.; resources and data curation, C. S. E.; writing – original draft preparation, C. S. E.; writing – review & editing, C. S. E., P. G. T. and L. S. W.; visualization, C. S. E.; supervision, L. S. W.; project administration, L. S. W.; funding acquisition, P. G. T. and L. S. W.

### Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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