Organofluorine compounds have become important building blocks for a broad range of advanced materials, polymers, agrochemicals, and increasingly for pharmaceuticals. Despite tremendous progress within the area of fluorination chemistry, methods for the direct introduction of fluoroalkyl-groups into organic molecules without prefunctionalization are still highly desired. Here we present a concept for the introduction of the trifluoromethyl group into unprotected phenols by employing a biocatalyst (laccase), tBuOOH, and either the Langlois’ reagent or Baran’s zinc sulfinate. The method relies on the recombination of two radical species, namely, the phenol radical cation generated directly by the laccase and the CF₃-radical. Various functional groups such as ketone, ester, aldehyde, ether and nitrile are tolerated. This laccase-catalysed trifluoromethylation proceeds under mild conditions and allows accessing trifluoromethyl-substituted phenols that were not available by classical methods.
The introduction of fluoroalkyl-groups (for example, CF₃, CHF₂, CH₂F, etc.) into organic compounds has become a major subject in various fields of chemical research, in particular medicinal chemistry and drug discovery. This is due to the metabolic stability, increased permeability or enhanced binding properties of the organo-fluorine compounds in comparison to their non-fluorinated counterparts. Among all fluorine-containing moieties, the trifluoromethyl group is privileged, and trifluoromethylated arenes are of interest for agrochemicals, pharmaceuticals and advanced materials. Several excellent methods to provide structurally diverse CF₃-building blocks have been elaborated, common strategies to introduce the CF₃-group into aromatic compounds involve metal-mediated/catalysed functional group interconversions, where halogens, boronic acids, boronates and even amines are replaced by nucleophilic, electrophilic or radical CF₃-sources (Fig. 1a). Other methods rely on directing groups as well as on visible light and photocatalysis (Fig. 1b,c).

While trifluoromethylation of (substituted) mono- and biaryl-systems has been broadly investigated, only few reports deal with the transformation of unprotected phenols (Fig. 1d), and these give non-regioselective transformations and/or unsatisfying conversions. Hence, a general method for attaching the CF₃-moiety to phenols in a practical manner remains elusive. We report an efficient and selective method for trifluoromethylation of unprotected phenols by biocatalytic introduction of a trifluoromethyl group derived from common precursors.

**Results**

**Reaction concept.** The approach for the trifluoromethylation of phenols via C–C bond formation presented in this paper is based on the recombination of two radicals, namely a CF₃-radical and a phenol-derived radical, wherein the two radicals are formed via two different pathways (Fig. 2). The phenol-derived radical is formed by a laccase (E.C. 1.10.3.2), which catalyses in general the one-electron oxidation of phenols and anilines using molecular oxygen as the oxidant. Simultaneously, the electrophilic CF₃-radical is generated in situ from either Langlois’ reagent or Baran’s zinc sulfinate.

![Chemical radical formation](image1)

**Functional group tolerance.** To tap the scope and functional group tolerance of this method, various substituted phenols were transformed under optimized conditions, whereby the ortho- and para-position with respect to the phenolic hydroxyl moiety were blocked for substrate 1a-c (Table 2). In these cases, products were isolated with the CF₃-moiety meta to the OH were isolated with exquisite regio-control (entry 1–3), and for 2b and 2c also verified by X-ray crystallography (Fig. 3). Comparable results were obtained independent of the trifluoromethylation agent employed: thus, the Langlois’ reagent as well as the Baran’s zinc sulfinate led to comparable isolated yields up to 62%. Moreover, the reaction system tolerated ketone-, ester-aldehyde, as well as amine-functionalities, emphasizing the mildness of the reaction. Interestingly, nitrogen-containing substrates like indol or 4-aminoacetophenone were not converted at all under the reaction conditions investigated, while other substrates like

![Biocatalytic radical formation](image2)
after addition of the CF3-radical to the phenol radical cation (Fig. 6). The energies of the substituted intermediate cations would be favoured over meta-position by 3 kcal mol−1 upon combination with the neutral phenoxy radical. Therefore, in the proposed mechanism the laccase oxidizes the phenol 1d via a single electron transfer to the phenol radical cation (Fig. 5). The latter reacts with the CF3-radical to give the cationic intermediate, which rearranges to the final product. As shown in the initial experiments, trifluoromethylation only occurred in the presence of laccase and TFMS/iBuOOH (Table 1, entry 1); the phenol

| Table 1 | Laccase-mediated trifluoromethylation of unprotected phenols in combination with TFMS. |
|---|---|
| Entry | Catalysts / reagents | Conv. (%) | 2a (%) |
| 1 | Laccase + 1a + TFMS + iBuOOH | 99.4 ± 0.2 | 58.0 ± 1.7 |
| 2 | TFMS + iBuOOH + 1a | n.c. | — |
| 3 | Laccase + 1a | 77.1 ± 0.3 | < 0.1 |
| 4 | Laccase + 1a + TFMS | 23.6 ± 0.8 | < 0.1 |
| 5 | Laccase + 1a + TFMS + H2O2 | n.c. | — |

| Table 2 | Scope and functional group tolerance of the biocatalytic trifluoromethylation of unprotected phenols employing Baran’s zinc sulfinate or Langlois’ reagent in combination with a laccase. |
|---|---|
| Entry | Product | Zn(SO2CF3)2 Iso. yield (%) | NaSO2CF3 Iso. yield (%) |
| 1 | 2a | 61.6 | 52.5 |
| 2 | 2b [x-ray] | 42.2* | 40.5* |
| 3 | 2c [x-ray] | 57.8 | 57.3 |
| 4 | 2d [x-ray] | 41.5† (C2:C3:C6 = 10:1:1) | 29.2† (C2:C3 = 4:1) |
| 5 | 2e | 37.2†† (C2:C3 = 4:1) | 31.3†† (C2:C3 = 4:1) |
| 6 | 2f | 31.7 | 30.5 |
| 7 | 2g | 56.7 | n.p. |
| 8 | 2h | 33.1 | n.p. |

Mechanism. The computational calculations also showed that the CF3-radical has to react preferentially with the phenol radical cation and not with the corresponding already deprotonated phenoxy radical, since the latter would lead, for example, for 1d, to substitution in ortho-position to the hydroxy group and not at the mainly observed meta-position. Substitution in ortho-position would be favoured over meta-position by 3 kcal mol−1 upon combination with the neutral phenoxy radical. Therefore, in the proposed mechanism the laccase oxidizes the phenol 1d via a single electron transfer to the phenol radical cation (Fig. 5). The latter reacts with the CF3-radical to give the cationic intermediate, which rearranges to the final product. As shown in the initial experiments, trifluoromethylation only occurred in the presence of laccase and TFMS/iBuOOH (Table 1, entry 1); the phenol

Regioselectivity. The transformation of phenols 1d and 1e, bearing only a single substituent ortho to the phenolic hydroxy group, led to a mixture of regio-isomers, albeit with significant preference for the meta-isomers (C2:C3 = 4:1 up to 10:1, entry 4 and 5). The preferred meta-substitution for 2d was confirmed via a crystal structure (Fig. 3). It is worth noting that substrate 1f, being devoid of ortho-methoxy substituents, afforded only the isomer bearing the CF3 moity ortho to the alcohol group with 31% isolated yield (entry 6). In a similar fashion, substrate 1g possessing in para position a nitrile group instead of the acetyl group, led to a mixture of regio-isomers, albeit with significant preference for the meta-isomers (C2:C3:C6 = 4:1). The transformation of phenols 1d–f, 1h to di-trifluoromethylated product, 2h, having a CF3-group in ortho as well as meta position with respect to the phenolic OH (entry 8).

The observed regioselectivity for 2d-f can be explained by the transition state energies of the addition of the CF3-radical to the phenol radical cations. For instance, the corresponding transition state leading to 2d with substitution at C2 is energetically preferred over substitution at C3 (2.1 kcal mol−1, M06-2X/6-311 + + G(d,p)) (Fig. 4, Supplementary Fig. 5). The same is true for the analogous transition state leading to 2e (Supplementary Fig. 6). The energies of the substituted intermediate cations after addition of the CF3-radical to the phenol radical cation also reflect the observed regioselectivity. In the case of substrate 1f, the energies of the transition states support the expected and observed substitution in ortho-position to the phenolic OH leading to product 2f (Supplementary Fig. 6). Since the energies of the transition states reflect the observed regioselectivity, the bio-trifluoromethylation is mainly not active site-directed. sesamol, 5,6,7,8-tetrahydro-2-naphthol, 2-naphthol or meta-dimethylamino acetophenone resulted in complex product mixtures.

| Laccase, Agaricus bisporus; n.c., no conversion; TFMS = Zn(SO2CF3)2 = ((trifluoromethyl)sulfinyl)oxy)zinc salt. | Based on recovered starting material. |
| 1a-f | Determined by GC. |
starting material did not react with TFMS/tBuOOH (entry 2), nor did the phenol radical cation (formed by laccase and O2 present) react with TFMS (entry 4).

In the recently proposed mechanism39, traces of redox metals are proposed to initiate the reaction for the first transformation of tBuOOH to tBuO• and OH•. tBuO• enables the formation of the CF3• species. In the reported catalytic cycle the activation of tBuOOH was triggered by the heteroaromatic radical intermediates.

Since in the laccase-catalysed trifluoromethylation of phenol, the laccase provides already one reactive radical species for the C–C bond forming reaction, namely the phenol radical cation, stoichiometric amounts of redox metal (for example, Fe, Co, Cu mentioned in previous work) would be required to obtain the amount of tBuO• needed. Since the trifluoromethylation went to high conversion without addition of any metals or other redox reagents, it was deduced that the copper Cu(I) present in the laccase also reacts with tBuOOH to give tBuO• and Cu(II) as already proposed in previous papers using only Cu (ref. 31). This was also supported by photometric assays in laccase-catalysed oxidative dimerization of 2,6-dimethoxy phenol showing that the presence of tBuOOH led to a faster reaction (Supplementary Methods, Photometric Enzymatic Activity Assay). Thus, the Cu(I) of the laccase can be oxidized by tBuOOH, which leads to tBuO• as previously reported31; the latter reacts with the CF3SO2• to set free the CF3-radical, as proven elsewhere39.

Comparison to literature methods. To compare the here-presented laccase/tBuOOH protocol with published methods for the chemical trifluoromethylation of (electron-rich) arenes and hetero-arenes29,30, phenols 1a (R = Me) and 1b (R = H) were treated with Ruppert-Prakash reagent44 TMSCF3 in the presence of catalytic silver (AgF) and PhI(OAc)2 as oxidant (Fig. 6a).

For both substrates 1a and 1b only minor amounts of 2a and 2b were found in a complex product mixture; the major product components were the trifluoromethyl-aryl-ethers 3a and 3b (13–17% isolated yield). A related CF3-ether formation was reported recently45.

As a second literature method a metal-free alternative for the trifluoromethylation of arenes and biaryls was investigated30, whereby the CF3-radical is generated by the oxidation of the Langlois’ reagent NaSO2CF3 with phenyl-iodine bis(trifluoroacetate) (Fig. 6b). In this case the transformation of 1a and 1b led to the corresponding trifluoromethanesulfonates 4a and 4b as the main products (18–89% isolated yield), while 2a and 2b (R = H) were found only in negligible quantities.

As a third method the Togni reagent32,46 was employed for substrate 1a (Fig. 6c); although the substrate was completely converted, product 2a was only a minor product (8%), while two non-identified main products were detected, which did not contain any CF3-group.
The laccase from *A. brasilensis* (7.5 U, 5.0 mg mL\(^{-1}\) final conc.) was dissolved in a sodium acetate buffer (695 μL, 250 mM, pH 5.5) prior to addition of Zn(SO\(_4\))\(_2\) (2 eq., 33.2 mg dissolved in DMSO). Afterwards ketone 1 (50 mM final concentration, dissolved in DMSO) was added followed by aqueous rBuOOH solution (8.0 eq., 55 μL, 70% aqueous solution) to reach a total volume of 1.0 mL (25 vol% DMSO). The reactions were shaken in an orbital shaker at 30 °C (Zn(SO\(_4\))\(_2\)) or 40 °C in case of NaSO\(_2\)CF\(_3\) for 24 h at 900 r.p.m. (horizontal position). Then, each 1 ml reaction was extracted four times with EtOAc (500 μL) and combined organic fractions were dried over NaSO\(_3\). The solutions were filtered, concentrated under reduced pressure and the residue was purified by various solvent mixtures to afford the trifluoromethylated phenol derivative 2.

**QM calculations.** Full geometry optimizations, transition structure searches and single-point computations were carried out with the Gaussian 09 package.\(^7\) All geometry optimizations were carried out with the unrestricted version of the hybrid B3LYP functional.\(^6\) For C, O, N and H, the double-zeta basis set 6–31G(d) was employed to obtain the geometries, and the larger 6–311 + G(d,p) basis set was used to calculate single-point energies. Additional single-point energy calculations using functionals able to account for dispersion forces such as M06-2X (ref. 49) in conjunction with the 6–311 + G(d,p) basis set were performed (Supplementary Table 5). Thermal and entropic corrections to energy were calculated from vibrational frequencies. The nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix from the frequency calculations. Frequencies were not scaled.

**Data availability.** Crystal structures that support the findings of this study have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 1480621 (2b), 1480623 (2c) and CCDC 1480622 (2d). All other data supporting the findings of this study are available within the article and its Supplementary Information file or from the author upon reasonable request.

**Discussion**

With this study, we have achieved radical C-CF\(_3\) bond formation by the recombination of two radical species—one generated biocatalytically and the other in a chemical reaction. This method represents the first biocatalyst-dependent trifluoromethylation of organic compounds, especially unprotected phenols, giving access to building blocks that were not accessible as major products by any other method described before. Moreover, the methods display a high functional group tolerance, allowing the conversion of aldehydes, esters and ketones without decomposition, which makes this method suitable for late-stage trifluoromethylation. The method proceeds under mild reaction conditions with high regioselectivity.

**Methods**

**Representative trifluoromethylation procedure (1 mL).** The laccase from *A. brasilensis* (7.5 U, 5.0 mg mL\(^{-1}\) final conc.) was dissolved in a sodium acetate buffer (695 μL, 250 mM, pH 5.5) prior to addition of Zn(SO\(_4\))\(_2\) (2 eq., 33.2 mg dissolved in DMSO). Afterwards ketone 1 (50 mM final concentration, dissolved in DMSO) was added followed by aqueous rBuOOH solution (8.0 eq., 55 μL, 70% aqueous solution) to reach a total volume of 1.0 mL (25 vol% DMSO). The reactions were shaken in an orbital shaker at 30 °C (Zn(SO\(_4\))\(_2\)) or 40 °C in case of NaSO\(_2\)CF\(_3\) for 24 h at 900 r.p.m. (horizontal position). Then, each 1 ml reaction was extracted four times with EtOAc (500 μL) and combined organic fractions were dried over NaSO\(_3\). The solutions were filtered, concentrated under reduced pressure and the residue was purified by various solvent mixtures to afford the trifluoromethylated phenol derivative 2.

**Determination of aldehydes, esters and ketones**

For reasons of clarity the scheme displays only the productive pathway for the here-presented laccase/Trifluoromethylation methods for electron-rich arenes for comparison with the methods described before. The main products (58% + 34%) are formed in excess shown.

![Figure 5 | Proposed mechanism for laccase-catalysed trifluoromethylation of phenols. Proposed mechanism for the laccase-mediated trifluoromethylation of unprotected phenols exemplified for substrate 1d. For reasons of clarity the scheme displays only the productive pathway relevant for the formation of 2b; other reactions, for example, like HCF\(_3\) formation, dimerization of the CF\(_3\)-radical or the radical cation, the decay of rBuOOH and the oxidation of SO\(_2\) are omitted, as well as the formation of minor regio-isomers.](image)

**Figure 6 | Methods from literature tested for comparison.** Trifluoromethylation methods for electron-rich arenes with comparison to the here-presented laccase/rBuOOH concept. (a) Method involving silver as metal; metal-free trifluoromethylations using phenyl-iodine bis(trifluoroacetate) (b) or Togni-reagent (c).

Thus, the laccase trifluoromethylation reported here is clearly complementary to literature methods tested.

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Author contributions
R.C.S. and W.K. conceived, designed and supervised the project. E.B. performed chemical control reactions, V.R. photometric assays, R.C.S. and N.R. analytical optimization studies. Preparative scale experiments and interpretation: R.C.S. and V.R. W.K. performed computational experiments. R.C.S., K.N.H. and W.K. wrote and edited the manuscript. All authors discussed the results and commented on the manuscript.

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