RSC Advances

PAPER

Cite this: *RSC Adv.*, 2019, **9**, 19549

Efficient and sustainable laccase-catalyzed iodination of *p*-substituted phenols using KI as iodine source and aerial O_2 as oxidant†

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Received 4th April 2019
Accepted 27th May 2019

DOI: 10.1039/c9ra02541c

rsc.li/rsc-advances

The laccase-catalyzed iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives using KI as iodine source and aerial oxygen as the oxidant delivers the corresponding iodophenols in a highly efficient and sustainable manner with yields up to 93% on a preparative scale under mild reaction conditions.

Introduction

The iodophenol moiety represents an important structural motif for many of the nearly 200 iodine-containing natural products known so far.[1] Typical examples include the cytotoxic tyramine derivative iodocionin (**I**) from the Mediterranean ascidian *Ciona edwardsii*,[2a] the cytotoxic 6′-iodoaureol (**II**) from the sponge *Smenospongia* sp.,[2b] the antibiotic cyclic depsipeptide miuraenamide B (**III**) from the myxobacterial SMH-27-4 [2c] and the thyroid hormones triiodothyronine (**IV**)[2d] and thyroxin (**V**) (Fig. 1).[2d] The most prominent non-natural biologically active iodophenol is amiodarone (**VI**)[3] which is widely used as an antiarrhythmic drug in the treatment of ventricular and supraventricular tachyarrhythmias. Iodoaromatics in general and iodophenols in particular are important substrates for Pd-catalyzed cross couplings,[4] such as the Sonogashira-coupling,[5a] the carbonylative Sonogashira-coupling,[5b] the Negishi-coupling,[5c] the Suzuki–Miyaura-coupling[5d] and related reactions,[5e] Stille-,[5f] Hiyama-[5g] and Heck-couplings.[5h] Iodophenols can also be used as substrates for the preparation of organometallics, such as Grignard reagents, under suitable conditions.[6] This is why the development of selective, efficient and environmentally benign methods for the preparation of iodoaromatics in general and iodophenols in particular is of the greatest importance.

Over the years, a number of methods have been developed for the preparation of iodoaromatics.[7] Without doubt, the most popular is the electrophilic aromatic substitution. Among the classical methods are also the Sandmeyer reaction,[8] the *ortho*-lithiation/halogenation[9] and the Hunsdiecker reaction.[10] Recently, the synthesis of iodoaromatics has been achieved by methods which are based on sp^2 C–H activation.[7b]

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† Electronic supplementary information (ESI) available: Experimental data and copies of the ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c9ra02541c

For the preparation of iodophenols the electrophilic aromatic substitution is also the most widely used method. For this purpose, phenols are reacted (a) with iodination agents like NIS,[11a] PyICl,[11b] TICA,[11c] BMPDCI,[11d] IPy_2BF_4,[11e] BTMA ICl_2,[11f] I_2,[11g] I_2-amine complex,[11h] $I_2/AgNO_3$,[11i] or I_2/KI,[11j] (b) with I_2 in combination with an oxidant, such as $(n\text{-BuPPh}_3)_2S_2O_8$,[12a] HIO_3,[12b] K_2FeO_4/K10,[12c] H_2O_2,[12d] $O_2/NaNO_2$[12e] or TICA/SiO_2,[12f] (c) with an iodide in combination with an oxidant such as NaOCl,[13a] $NaClO_2$,[13b] H_2O_2,[13c] $KClO_3$,[13d] $NaIO_4$,[13e] oxone,[13f] KIO_3,[13g] DMSO,[13h] H_2SO_4[13i] or *tert*-butylhypochlorite.[13j]

Most of these methods have a number of serious disadvantages. Among them are the use of more than equimolar amounts of iodination agents and/or oxidants. Many of the reagents employed are acutely toxic, corrosive, explosive and

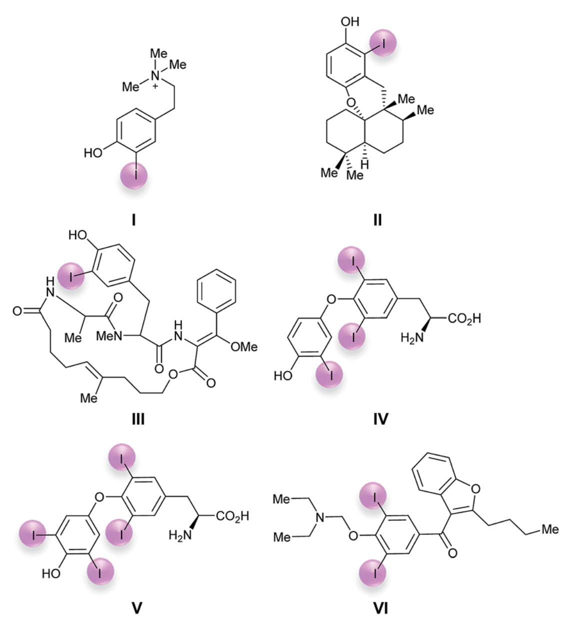


Fig. 1 Important iodinated phenolic compounds.

oxidizing, while others are commercially not available, expensive or difficult to prepare. In addition, many iodinations have to be performed in highly volatile and/or toxic organic solvents. Most electrophilic aromatic substitutions with I_2 or iodide as iodine source can only be run successfully in the presence of heavy metal reagents and/or strong oxidants. All methods which make use of I_2 as iodine source suffer from the fact, that only one iodine atom ends up in the product of the electrophilic aromatic substitution while the other remains unused in the reaction medium. Clearly, this results in lower values of atom economy.[14] Approaches which are based on the combination of I_2 and iodides, respectively, as the iodine source, with sustainable oxidants, such as O_2[12e] or H_2O_2,[12d,13c] are often hampered by their restricted substrate scope[12d,e] or by the fact that they require highly acidic conditions.[12e,13c] As a result, there is great demand for iodination methods which are not only highly selective and efficient but also fulfill the requirements of sustainable chemistry in order to protect the environment.

Over the last few years, a keen interest in oxidative halogenations, which allow for the use of halides as halogen sources instead of the halogens themselves, has emerged.[7d] With respect to sustainability, transition metal- and enzyme-catalyzed transformations using H_2O_2 or O_2 as oxidants are particularly attractive. Enzyme-catalyzed oxidative halogenations with H_2O_2 as oxidant are usually catalyzed by less specific heme- and vanadium-dependent haloperoxidases, while oxidative halogenations with O_2 are mainly catalyzed by more substrate specific flavin-dependent halogenases and non-iron O_2-dependant halogenases.[15] In this context, studies towards the regioselective bromination and chlorination catalyzed by FAD-dependant tryptophan halogenases[16a] deserve to be mentioned since they can be performed on a preparative scale.[16b] In contrast, enzyme-catalyzed iodinations have received only marginal attention so far. It is known that oxidative iodinations can be catalyzed by lactoperoxidases,[17a–c] a chloroperoxidase[17d] and a horseradish peroxidase.[17e] However, as good as nothing is known concerning substrate specificity, substrate scope, selectivity, efficiency, scalability and sustainability of these reactions. First observations concerning the laccase-catalyzed oxidation of iodide to iodine can be traced back to the reports of Xu[17f] and Amachi *et al.*[17g] Later, Ihssen *et al.* have reported on the laccase-catalyzed iodination of phenolic compounds.[17h] However, a closer look at their results reveals that their method does not allow for the chemoselective iodination of phenols on a preparative useful scale. In most cases, the formation of the iodophenols was accompanied by the formation of products resulting from oxidative dimerization. Structure and yields of the iodinated products are difficult to evaluate since they were not isolated in pure form. Moreover, the scope of the method was not studied.

Laccases (benzenediol:oxygen oxidoreductase, EC 1.10.3.3) are enzymes which are produced by animals, plants, fungi and bacteria.[18] Some are commercially available at a reasonable price. Laccases are known to catalyze a number of oxidations under mild reaction conditions in aqueous solvent systems at pH 3–8 using cheap and environmentally benign aerial oxygen as a sustainable oxidant.[19] The substrate oxidation is accompanied by the reduction of O_2 to H_2O, which is the only byproduct of laccase-catalyzed reactions. Laccases with low (0.4–0.5 mV), medium (0.5–0.6 mV) and high (0.7–0.8 mV) redox potentials are known.[20a–c] By using laccase/mediator systems the substrate scope of laccase-catalyzed oxidations can be significantly widened.[19,20d] Among the transformations that can be catalyzed by laccases on a semi preparative or preparative scale are oxidations of several functional groups ($CH_3 \rightarrow CHO$,[21a] $CH_2OH \rightarrow CHO$,[21b] $CH_2OH \rightarrow CO_2H$,[21c] $CH_2NH_2 \rightarrow CHO/CO_2H$[21d]), the transformation of 1,4-dihydropyridines to pyridines[21e] and oxidative couplings of phenols[21f–i] and related substrates[21j] as well as thiophenols.[21k] The oxidation of catechols and hydroquinones is also known. The resulting *o*- and *p*-benzoquinones can be intercepted in different reactions like 1,4-additions and Diels–Alder reactions. This approach provides not only access to simple 1,4-adducts[22] but also to different carbo- and heterocycles.[23]

Here we show for the first time, that the laccase-catalyzed iodination of a wide range of *p*-substituted phenolic substrates delivers the iodinated products in a highly chemoselective manner on a preparative scale; the dimerization could be completely suppressed. Moreover, we will show that the laccase-catalyzed iodination can be developed to a sustainable iodination method.

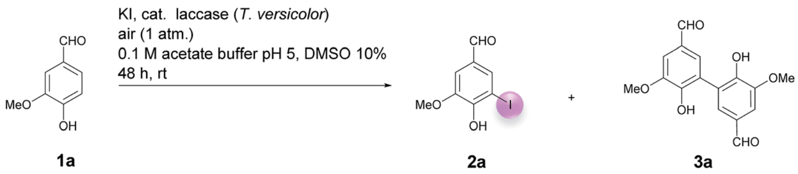
Results and discussion

Reaction condition optimization

Motivated by our interest in using laccases as catalysts in preparative organic chemistry we wondered whether it would be possible to develop a selective, efficient, atom economic and sustainable iodination of aromatics on a preparative useful scale based on the laccase-catalyzed oxidation of alkali iodides to iodine using aerial oxygen as oxidant.

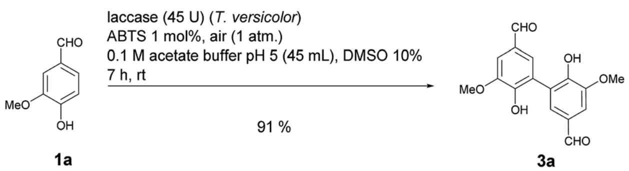
The optimization of the reaction conditions was performed using the iodination of vanillin (**1a**) to 4-hydroxy-3-iodo-5-methoxybenzaldehyde (**2a**) as a model reaction since vanillin is a natural product that is manufactured from biomass by means of an established industrial process on a large scale.[24] Against the background of our experience in the field of laccase-catalyzed transformations, equimolar amounts of **1a** and KI were stirred with catalytic amounts (225 U) of *T. versicolor* laccase in the presence of aerial oxygen in acetate buffer (pH 5) : DMSO = 9 : 1 for 48 h at rt (Table 1, entry 1). Under these conditions, the desired iodination product **2a** was formed in only 7% yield. The main product was the dimer 6,6′-dihydroxy-5,5′-dimethoxy-[1,1′-biphenyl]-3,3′-dicarbaldehyde (divanillin) (**3a**). However, the formation of **3a** was not surprising, since the laccase-catalyzed oxidative dimerization of **1a** is known to deliver **3a**.[21f] Under the conditions presented in Scheme 1, we isolated **3a** in 91% yield (Scheme 1). To increase the yield of **2a**, and to improve the **2a** : **3a** ratio towards the formation of **2a**, the reaction was run with 20 equiv. of KI. This resulted in an increase of the yield of **2a** to 24% and an improvement of the **2a** : **3a** ratio to 20 : 1 (Table 1, entry 2). To further suppress the oxidative dimerization, it was decided to keep the actual concentration of **1a** in the reaction mixture as low as possible.

Table 1 Initial experiments of the laccase-catalyzed iodination of vanillin (**1a**)[a]



Entry	KI (equiv.)	Enzyme (U)	Mediator (mol%)	Buffer (mL)	**2a : 3a**	Yield **2a** (%)
1	1	225	—	45	1 : 2	7
2	20	225	—	45	20 : 1	24
3[b]	20	225	—	45	65 : 1	18
4[c]	20	225	—	45	18 : 1	34
5	20	225	ABTS (1)	45	198 : 1	46
6	20	225	—	90	18 : 1	75
7[b,c]	20	225	ABTS (1)	90	198 : 1	65
8	20	—	ABTS (1)	90	—	—

[a] 2 mmol **1a** were reacted. The yields of **2a** refer to isolated yields, the ratio **2a : 3a** was determined by ^{1}H NMR analysis of the crude product. [b] **1a** in 3 mL DMSO was added during 24 h by syringe pump. [c] Initially, 45 U enzyme were added, additional enzyme (180 U) in 3 mL acetate buffer was added during 24 h by syringe pump.



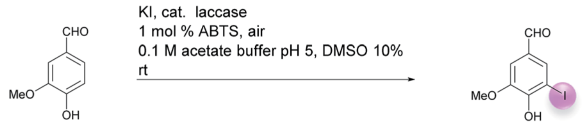
Scheme 1 Laccase-catalyzed oxidative dimerization of vanillin (**1a**) to divanillin (**3a**).

This was achieved by continuous addition of **1a** as a solution in DMSO (2 mmol **1a** in 3 mL DMSO) over 24 h by using a syringe pump. As expected, the amount of dimer **3a** in the crude product could be decreased considerably (**2a : 3a** = 65 : 1); however, the isolated yield of **2a** amounted to only 18% (Table 1, entry 3). Since it is assumed that the laccase undergoes partial iodination, which results in partial deactivation, parts of the laccase were added continuously during the reaction. Consequently, only 45 U laccase were added initially and the remaining laccase (180 U) was added dropwise *via* syringe pump during 24 h. This measure resulted in an increase of the yield of **2a** to 34%; unfortunately, the ratio of **2a : 3a** decreased to 18 : 1 (Table 1, entry 4). It is well known that many laccase-catalyzed reactions give the products in much higher yields in the presence of a mediator.[19,20d] In earlier studies we have established that ABTS is a particularly suitable mediator for *T. versicolor*-catalyzed reactions.[21e,k] When the laccase-catalyzed iodination of **1a** was run in the presence of 1 mol% ABTS, the yield of **2a** increased to 46% and the **2a : 3a** ratio improved to 198 : 1 (Table 1, entry 5). Furthermore, it was found that the reaction volume has a decisive influence on the yield of **2a**. When the buffer volume was doubled to 90 mL and the reaction was run in the absence of ABTS, the isolated yield of **2a** could be improved to 75%. Unfortunately, this was accompanied by an increase of **3a** in the crude product (**2a : 3a** = 18 : 1) (Table 1, entry 6). However, when the transformation was performed in the presence of 1 mol% ABTS in 90 mL buffer, and the laccase as well as the substrate were added gradually, **2a** could be isolated in 65% and the formation of **3a** could be almost completely suppressed (**2a : 3a** = 198 : 1) (Table 1, entry 7). Despite the fact that under these conditions the yield of **2a** was 10% lower than in the absence of ABTS, all further experiments were performed in the presence of 1 mol% ABTS, since this measure guaranteed the effective suppression of **3a**. A control experiment established that in the absence of laccase and in presence of 1 mol% ABTS neither **2a** nor **3a** were formed (Table 1, entry 8). The use of other cosolvents than DMSO (ethanol, acetone, ethyl acetate) and a phase transfer catalyst (Aliquat 336) had no positive impact on the yield of **2a**.

Table 2 summarizes the experiments performed to decrease the amounts of KI and laccase and to shorten the reaction time. Particularly gratifying was the observation that the yield of **2a** can be increased by decreasing the amount of KI (Table 2, entries 1–4). With 3 equiv. of KI, the yield reaches its maximum (85%) (Table 2, entry 3). Even with only 1.5 equiv. KI, **2a** was formed in 77% (Table 2, entry 4). With equimolar amounts of KI, however, the yield of **2a** is only 11% (Table 2, entry 5). Further experiments proved that the amount of laccase can be reduced significantly from 225 U to 90 U without any loss of yield (Table 2, entry 6). Finally, it was revealed that the reaction time (48 h) can be shortened by a more effective air supply. When air was bubbled through the reaction solution at a rate of 20 mL min^{-1}, the transformation was already finished after 15 h. Under these conditions, the yield of **2a** amounted to 77% with 90 U laccase, and to 85% with a total amount of 135 U (Table 2, entries 7 and 8).

As part of the optimization, the influence of the iodide source and the mediator was studied. It was established that the

Table 2 Optimization of amount of KI, air supply, amount of enzyme and reaction time[a]



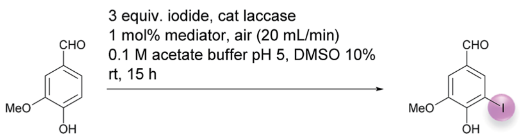
1a **2a**

Entry	Equiv. KI	Air	*t* [h]	Add. enzyme [U], [h]	Yield **2a** (%)
1	20	1 atm	48	180 (44)	65
2	5	1 atm	48	180 (44)	72
3	3	1 atm	48	180 (44)	85
4	1.5	1 atm	48	180 (44)	77
5	1	1 atm	48	180 (44)	11
6	3	1 atm	48	45 (44)	86
7	3	20 mL min^{-1}	15	45 (5)	77
8	3	20 mL min^{-1}	15	90 (5)	85[b]

[a] 2 mmol **1a** were reacted in 90 mL buffer. The yields of **2a** refer to isolated yields. Initially, 45 U laccase were added; additional laccase in 3 mL acetate buffer was added during the time given by syringe pump. Substrate in 3 mL DMSO was added by syringe pump during the same time the enzyme was added. [b] The ratio **2a** : **3a** was determined by ^{1}H NMR analysis of the crude product (198 : 1).

iodination cannot only be achieved with KI, but also with LiI, NaI, CsI and NH_4I in comparable yields (81–87%) of **2a** (Table 3, entries 1–5). In no case, the formation of **3a** could be observed. The small yield differences suggest that the influence of the cation of the iodide source is negligible. In contrast, the mediator has a decisive influence on yield and selectivity. With

Table 3 Optimization of the iodide source and the mediator[a]



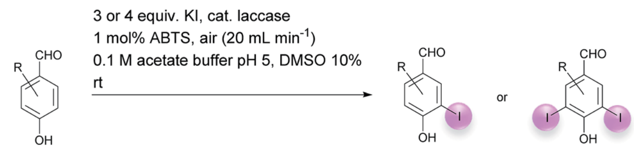
1a **2a**

Entry	Iodide source	Mediator	Yield **2a** (%)
1	KI	ABTS	85
2	LiI	ABTS	81
3	NaI	ABTS	82
4	CsI	ABTS	87
5	NH_4I	ABTS	81
6	KI	Violuric acid	22
7	KI	4-Acetamido-TEMPO	33
8	KI	4-Methoxy-TEMPO	29
9	KI	HOBt	21[b]
10	KI	Methyl syringate	37

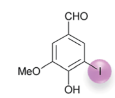
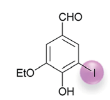
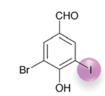
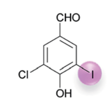
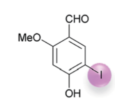
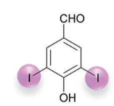
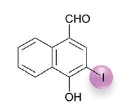
[a] 2 mmol **1a** were reacted in 90 mL buffer. The yields of **2a** refer to isolated yields. Initially, 45 U enzyme were added, additional laccase (90 U) in 3 mL acetate buffer was added during 5 h. Substrate in 3 mL DMSO was added by a second syringe pump during the same time the enzyme was added. [b] In addition to **2a**, dimer **3a** was detected (TLC). **2a** and **3a** were formed in a ratio of 2.3 : 1 as revealed by ^{1}H NMR analysis of the crude product after filtration.

none of the other mediators tested (violuric acid, 4-acetamido-TEMPO, 4-methoxy-TEMPO, HOBt, methyl syringate) comparable yields of **2a** could be realized (Table 3, entries 6–10). In addition, it was found (TLC) that the formation of iodovanillin (**2a**) was accompanied by considerable amounts of the dimer **3a**. Using 1 mol% HOBt as a mediator, this phenomenon was studied in some detail. The crude product analysis by ^{1}H NMR showed that the **2a** : **3a** ratio amounted to 2.3 : 1 (Table 3, entry 9). Finally, it was demonstrated that at 50 °C, which is close to the temperature optimum of many laccases,[25] only traces of **2a**

Table 4 Laccase-catalyzed iodination of 4-hydroxybenzaldehydes and related compounds **1a–g**[a]



1 **2** **4**

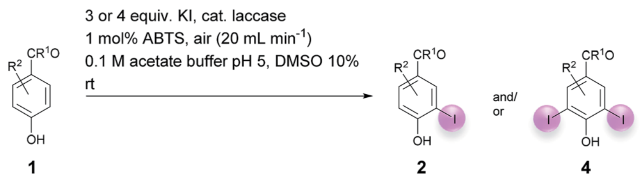
Entry	1	Laccase (U)	Time (h)	Yield product (%)
1	**a**	45 + 90	15	 **2a** (85)
2	**b**	45 + 90	15	 **2b** (81)
3	**c**	45 + 90	15	 **2c** (66)
4	**d**	45 + 90	48	 **2d** (50)
5	**e**	45 + 90	15	 **2e** (83)
6[b]	**f**	45 + 300	144	 **4f** (70)
7	**g**	45 + 90	15	 **2g** (50)

[a] 2 mmol **1** were reacted in 90 mL buffer. The yields of **2** and **4** refer to isolated yields. Initially, 45 U enzyme were added, additionally laccase in buffer was added during 5 h by syringe pump. Substrate in 3 mL DMSO was added by a second syringe pump during the same time the enzyme was added. Substrates with one iodination site were reacted with 3 equiv. KI, substrates with 2 iodination sites were reacted with 4 equiv. KI. [b] Additional enzyme and substrate were added during 15 h.

were found. Experiments with laccases from other organisms, such as *Agaricus bisporus* and *Pleurotus ostreatus*, were also not effective.

To summarize, the optimization studies showed that best results were obtained when **1a** was reacted with 3 equiv. KI, catalytic amounts of laccase of *T. versicolor* (45 U + 90 U) and 1 mol% ABTS in acetate buffer (pH 5) : DMSO = 9 : 1 at rt for 15 h while bubbling air through the reaction solution. In this way, **2a** was isolated in 85% yield; the corresponding dimer **3a** could not be detected (Table 3, entry 1). It should be mentioned that the model reaction can easily be upscaled from the 2 mmol to the 15 mmol scale. In doing so, **2a** can easily be synthesized in gram amounts.

Table 5 Laccase-catalyzed iodination of 4-hydroxyarylketones and related compounds **1h–p**[a]



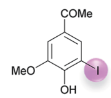
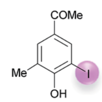
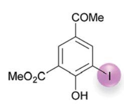
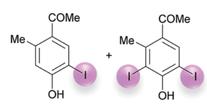
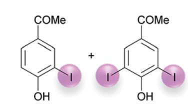
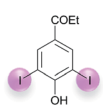
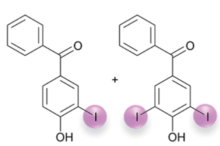
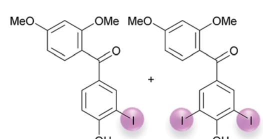
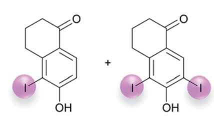
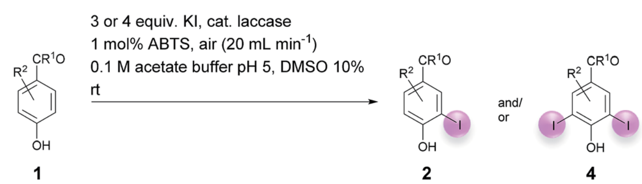
Entry	1	Laccase (U)	Time (h)	Yield products (%)
1	**h**	45 + 90	15	 **2h** (73)
2	**i**	45 + 90	15	 **2i** (87)
3	**j**	45 + 180	168	 **2j** (11)
4	**k**	45 + 180	15	 **2k** (73) (78)[b] + **4k** (13) (4)[b]
5	**l**	45 + 225	24	 **2l** (23) (-)[c] + **4l** (64) (84)[c]
6[d]	**m**	45 + 360	168	 **4m** (75)
7	**n**	45 + 180	60	 **2n** (70) + **4n**(6)
8[e]	**o**	45 + 360	120	 **2o** (35) + **4o** (53)
9	**p**	45 + 90	24	 **2p** (49) + **4p** (41)

Table 5 (*Contd.*)

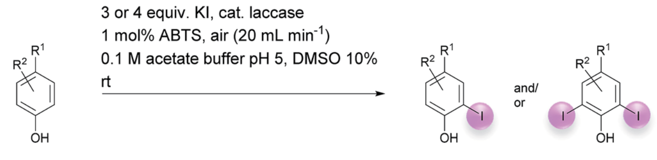


[a] 2 mmol **1** were reacted in 90 mL buffer. The yields of **2** and **4** refer to isolated yields. Initially, 45 U enzyme were added, additionally laccase in buffer was added during 5 h by syringe pump. Substrate in 3 mL DMSO was added by a second syringe pump during the same time the enzyme was added. Substrates with one iodination site were reacted with 3 equiv. KI, substrates with 2 iodination sites were reacted with 4 equiv. KI. [b] Initially, 1.1 equiv. KI and the substrate were added as solids. No DMSO was used. 180 U enzyme were added during 12 h. [c] 180 mL buffer and 6 equiv. KI were used. 300 U additional enzyme and substrate were added during 5 h. [d] Additional enzyme and substrate were added during 30 h. [e] Additional enzyme and substrate were added during 20 h.

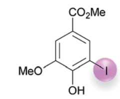
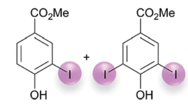
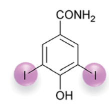
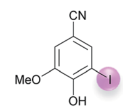
Substrate scope

Against this background, scope and limitations of the laccase-catalyzed iodination of phenolics were studied in greater detail (Tables 4–6). Initial experiments had revealed that 4-carbonyl- and 4-carboxyl-substituted phenols are the most suitable substrates. The reactions were performed under the conditions of Table 3, entry 1. If necessary, the reaction time and/or the amount of laccase was increased, and the addition rates of substrate and enzyme were adapted. Substrates with 2 potential iodination sites were reacted with 4 equiv. KI. Taking the successful iodination of **1a** as a starting point, we set out to test a number of different 4-hydroxybenzaldehydes as substrates (Table 4). It was found that the 3-OMe group in **1a** could be replaced easily with an OEt group (Table 4, entry 2) as well as different halogen atoms (Br, Cl) (Table 4, entries 3 and 4). The experiment with **1e** demonstrates that substrates with an OMe group at C-2 can be iodinated in high yields, too (Table 4, entry 5). It is remarkable that with the unsubstituted 4-hydroxybenzaldehyde **1f** the formation of the monoiodinated product could not be detected at all. Instead, the 3,5-diiodo derivative **4f** was isolated in 70% (Table 4, entry 6). The laccase-catalyzed iodination is not restricted to benzene derivatives as the reaction with 4-hydroxy-1-naphthaldehyde (**1g**) clearly proves. The comparative low yield of **2g** might be due to the tendency of the substrate for polymerization (Table 4, entry 7). Polymerization was also dominant in reactions with phenols carrying no aldehyde group in *p*-position, such as 4-bromo-2-methoxyphenol, 4-chloro-2-methoxyphenol, 2-methoxy-4-methylphenol, 4-methylphenol and 2,3-dihydroxybenzaldehyde. When the aldehyde group in *p*-position was replaced with an allyl group and an alkylidene group,[21g] resp., the exclusive formation of dimers was observed. Benzaldehydes carrying no hydroxyl group in *p*-position, such as 3,4-dimethoxybenzaldehyde and the *o*-hydroxyl substituted benzaldehydes 2-hydroxy-1-naphthaldehyde, 2-hydroxy-3-methoxybenzaldehyde, 2-hydroxybenzaldehyde, 5-bromo-2-hydroxybenzaldehyde and 5-chloro-2-hydroxybenzaldehyde, either didn't react at all or the iodinated product was only formed in traces. Next, a selection of *p*-hydroxyarylketones was employed as substrates (Table 5). The vanillin derivative 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one, *i.e.*, acetovanillon (**1h**) could be transformed into the monoiodinated compound 1-(4-hydroxy-3-iodo-5-methoxy-phenyl)ethan-1-one (**2h**) in 73% without any problems (Table 5, entry 1). When the methoxy group in **1h** was replaced with a methyl group, *i.e.* **1i**, the yield of the monoiodo product **2i** was even higher (87%) (Table 5, entry 2). However, when the methoxy group was replaced with an electron withdrawing methoxycarbonyl group, *i.e.* **1j**, the yield of **2j** dropped dramatically to only 11% (Table 5, entry 3). C-2 substituted *p*-hydroxyarylmethylketones, such as **1k**, could be iodinated easily as well. However, due to two free *o*-positions adjacent to the hydroxyl group, the formation of both the monoiodinated and the diiodinated products **2k** and **4k** took place. Fortunately, the ratio of the products **2** and **4** can be influenced by the reaction conditions. With 4 equiv. KI, the transformation of **1k** delivered **2k** and **4k** with 73% and 13%, resp. When **1k** was reacted with 1.1 equiv. KI, the yield of the monoiodinated **2k** could be raised to 78% while the diiodo compound **4k** was formed in only 4% (Table 5, entry 4). Using the transformation of **1l** as an example, it was demonstrated that the **2** : **4** ratio can also be shifted in direction towards the diiodo product **4**. With 4 equiv. of KI, **2l** and **4l** were isolated with 23% and 64%, respectively. However, when the amount of KI was raised to 6 equiv., the formation of the monoiodinated product **2l** could be suppressed completely. Under these conditions, **4l** was isolated in 84% (Table 5, entry 5). In analogy to 4-hydroxybenzaldehyde **4f**, the transformation of 1-(4-hydroxyphenol)-propan-1-one (**1m**) exclusively delivered the diiodo compound in 75% (Table 5, entry 6). Other substrates with 2 potential iodination sites (**1n–p**) produced mixtures of mono- and diiodo products **2** and **4** when reacted with 4 equiv. KI (Table 5, entries 7–9). Finally, it was studied whether the laccase-catalyzed iodination can also be applied to *p*-hydroxy-benzoic acid derivatives (Table 6). For this purpose, iodination reactions were performed with benzoic acid esters **1q** and **1r**, the benzoic acid amide **1s** and the benzonitrile **1t** as substrates. In all cases, the expected products, *i.e.* **2q**, **2r** and **4r**, **4s** and **2t**, were obtained (Table 6, entries 1–4). It came as a surprise that in contrast to the methylbenzoate **1r** the corresponding benzyl 4-hydroxybenzoate and phenyl 4-hydroxybenzoate did not undergo the laccase-catalyzed iodination. The method presented here allows the iodination of a wide range of *p*-hydroxycarbonyl and *p*-hydroxyarylcarboxyl compounds under mild reaction conditions. By developing suitable reaction conditions, the oxidative coupling could be suppressed completely. Substrates with one iodination site produced the monoiodo products with yields up to 87%. When substrates with two potential iodination sites were used, in some cases the disubstituted products (**1f**, **1m**, **1s**) were formed selectively. In other cases (**1k**, **1l**, **1n–p**, **1r**) mixtures of mono- and diiodo products were observed. By variation of the reaction conditions (amount of enzyme and KI, buffer volume, reaction time, addition rate of enzyme and substrate) the ratio of monoiodo and diiodo products could decisively be influenced.

Table 6 Laccase-catalyzed iodination of 4-hydroxybenzoic acid derivatives and related compounds **1q–t**[a]



1 **2** **4**

Entry	1	Laccase (U)	Time(h)	Yield products (%)
1	q	45 + 90	36	 **2q** (82)
2[b]	r	45 + 180	120	 **2r** (35) **4r** (54)
3[c]	s	45 + 500	48	 **4s** (62)
4	t	45 + 270	24	 **2t** (78)

[a] 2 mmol **1** were reacted in 90 mL buffer. The yields of **2** and **4** refer to isolated yields. Initially, 45 U enzyme were added, additionally laccase in buffer was added during 5 h by syringe pump. Substrate in 3 mL DMSO was added by a second syringe pump during the same time the enzyme was added. Substrates with one iodination site were reacted with 3 equiv. KI, substrates with 2 iodination sites were reacted with 4 equiv. KI. [b] Additional enzyme and substrate were added during 10 h. [c] Additional enzyme and substrate were added during 30 h.

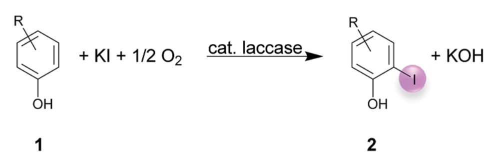
Reaction mechanism

A plausible equation for the laccase-catalyzed iodination of phenolics with KI as the iodine source and oxygen as the terminal oxidant is presented in Scheme 2. From the equation it is clear that only 1 equiv. of KI is required for the iodination and that 1 equiv. KOH is formed during the course of the reaction which results in a pH rise of the reaction solution. It is assumed that the method can be regarded as an electrophilic aromatic substitution of the *p*-hydroxyarylcarbonyls and *p*-hydroxyarylcarboxyls with elemental iodine as the electrophile (Scheme 3). For simplicity, it is assumed that I_2 acts as iodination agent. However, it cannot be excluded that I_3^- is the actual active iodine species, because I_3^- is formed rapidly in aqueous solutions containing iodide and iodine.[26] The mechanism is supported by the observation that the regioselectivity of the iodination is governed by the well-known substituent effects of the electrophilic aromatic substitution. The molecular iodine required as electrophile is generated *in situ* by the laccase-catalyzed oxidation of KI using oxygen as oxidant. Xu has demonstrated that the laccase-catalyzed oxidation of iodide can be enhanced by ABTS.[17f] Consequently, it is assumed that in the first step 2 molecules ABTS undergo oxidation to their corresponding radical cations. The two electrons released from ABTS reduce one oxygen atom to H_2O. The ABTS radical cations on the other hand oxidize two iodides to I_2. The molecular iodine formed in turn reacts with the phenolic substrate Ar–H to produce the iodinated product Ar–I as well as HI. It should be highlighted that in contrast to typical electrophilic substitutions with I_2 as reagent, the HI generated during the electrophilic aromatic substitution is not wasted, but undergoes a laccase-catalyzed reoxidation to I_2. This allows a significant reduction of the amount of the iodine source and an improvement of the atom economy from 72 to 85% (Scheme 4). The atom economy of the laccase-catalyzed reaction can be further improved by replacing KI with NaI, LiI or NH_4I (Table 3, entries 2, 3 and 5).

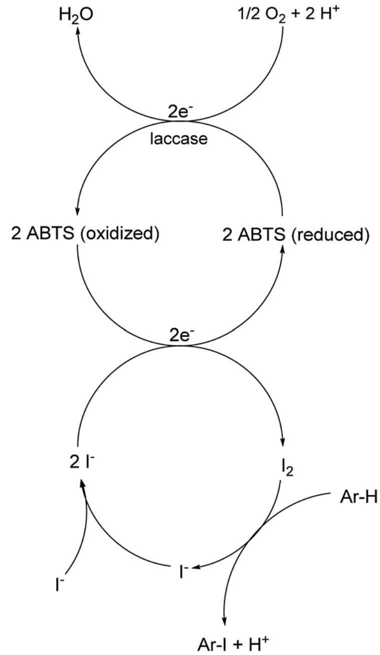
Even if most of the iodinations were run with a considerable excess of KI (3 equiv.) (Tables 4–6) we have demonstrated that the monoiodination can also be performed successfully, when the amount of KI is reduced from 3 to 1.5 equiv. (Table 2). In one case, the monoiodination could be achieved with as little as 1.1 equiv. KI (Table 5, entry 4). Further benefits of this method are as follows: it is based on using (a) a biocatalyst which can be obtained from renewable materials, (b) KI as an easy to handle iodine source and (c) aerial oxygen as the oxidant to generate I_2 from KI. Furthermore, the reactions can be performed under extremely mild reaction conditions, *i.e.* in an aqueous solvent system (pH 5) at room temperature.

Towards sustainable laccase-catalyzed iodinations

The next goal was the development of the laccase-catalyzed iodination towards a truly sustainable synthetic method. Despite of numerous advantages, the laccase-catalyzed

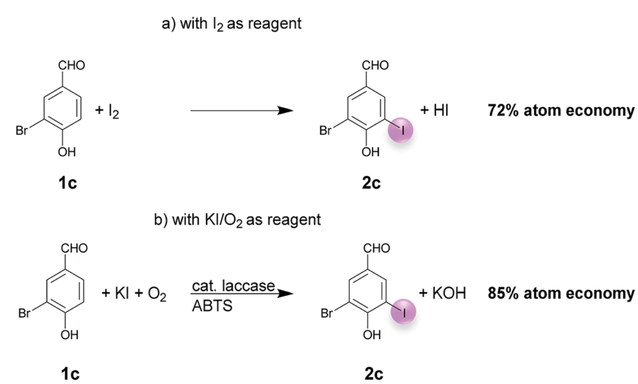


Scheme 2 Chemical equation of the laccase-catalyzed iodination.



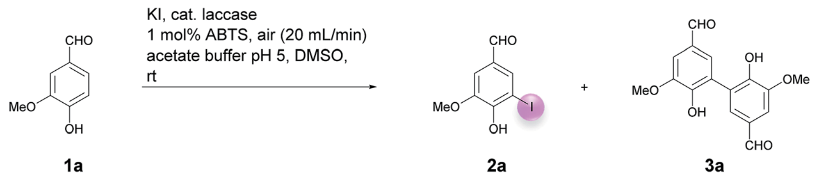
Scheme 3 Proposed mechanism of the laccase-catalyzed iodination.

iodinations presented in Tables 4–6 cannot be regarded as truly sustainable since the amount of waste produced is still too high. For example, the *E*-factor[27] of the transformation of **1a** to **2a** amounts to 31.9 kg kg^{-1} (Table 7, entry 1). The unfavorable *E*-factors are due to (a) the use of an excess of KI (3 equiv. KI for substrates with one iodination site and 4 equiv. for substrates with two iodination sites) and (b) the use of large volumes of solvent. This is why we embarked on further development towards a synthetic method, which fulfills all relevant requirements for a green reaction. To reduce the *E*-factor, a number of options were available. Among them were the reduction of (a) the amount of laccase, (b) the excess of KI, (c) the DMSO concentration, (d) the molarity of the buffer and (e) the chemoselectivity (iodination *versus* oxidative coupling) and on buffer volume itself. However, the focus of our optimizations, was not only the improvement of the *E*-factor, but also on high



Scheme 4 Atom economy of the laccase-catalyzed iodination of **1c** with (a) I_2 and (b) KI/O_2.

Table 7 Experiments towards the optimization of chemical yield, selectivity and *E*-factor of the model reaction[a]



Entry	Laccase (U)	Substrate + enzyme addition *t* (h)	KI (equiv.)	Time (h)	DMSO (vol%)	Buffer (mol L^{-1})	Buffer vol. (mL)	Isolated yield **2a** (%)	**2a** : **3a**	ΔpH	*E*-factor
1	45 + 90	5	3	15	10	0.1	90	85	198 : 1		31.9
2	45 + 90	5	3	15	10	0.1	45	62	38 : 1		19.5
3	45 + 135	5	3	20	10	0.1	45	85	48 : 1		13.9
4	45 + 225	5	3	20	2.5	0.1	45	59	20 : 1		9.6
5	45 + 225	10	3	20	2.5	0.1	45	63	65 : 1		8.9
6	45 + 225	10	2	20	2.5	0.1	45	70	31 : 1		6.6
7	45 + 90	5	3	20	10	0.05	45	64	20 : 1	+2.3	18.5
8	45 + 90	5	3	20	10	0.1	45	66	26 : 1	+2.2	18.3
9	45 + 90	5	3	20	10	0.2	45	58	98 : 1	+1.2	21.9
10	45 + 90	5	3	20	10	0.5	45	43	198 : 1	+0.5	33.8
11	45 + 225	10	2	20	2.5	0.2	45	77	48 : 1		6.6
12	45 + 225	10	1.5	20	2.5	0.2	45	68	65 : 1		7.0
13	45 + 225	15	1.5	20	2.5	0.2	45	67	198 : 1		7.2
14	45 + 225	15	1.5	24	1.25	0.2	45	77[b]	198 : 1		4.6
15	45 + 225	10[c]	1.5	24	0	0.2	45	83[b]	31 : 1		2.9
16[d]	0	15	—	24	1.25	0.2	45	47[d]	198 : 1		6.7

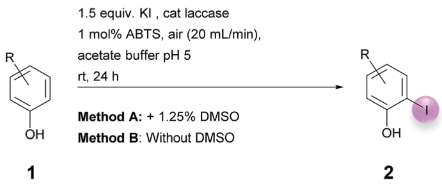
[a] 2 mmol substrate were reacted. 45 U laccase were added initially, additional laccase and substrate were added separately and simultaneously during the time given *via* syringe pump. The ratio of **2a** and **3a** was determined after filtration and drying of the crude product *via* ^{1}H NMR. [b] Isolated yield after filtration. [c] Enzyme was added during 15 h *via* syringe pump and substrate was added manually as a solid. [d] 0.75 equiv. I_2, no laccase and ABTS was used.

chemical yield. A number of observations proved to be decisive for the optimization process which is summarized in Table 7. It was found that (a) the amount of KI can be reduced from 3 to 2 and 1.5 equiv., resp., (Table 7, entries 5, 6 and 11–15), (b) the concentration of DMSO can be reduced from 10 vol% to 1.25 vol% (Table 7, entries 3, 4, 13 and 14) (in some cases the cosolvent could be completely omitted) and (c) the buffer volume can be reduced by 50% (Table 7, entries 1–3). Furthermore, it was found that the dimer formation can be reduced to a minimum by increasing the molarity of the acetate buffer (Table 7, entries 7–10). In this context, the relationship between pH and the proportion of dimer should be mentioned. It was found that an increase of the pH of the reaction mixture during the course of the reaction resulted in an increase of the proportion of the dimer **3a** in the crude product (Table 7, entries 7–10). To keep the proportion of the dimer as low as possible it is necessary to adjust the pH value around pH = 5. Furthermore, it had to be taken into account that the reduction of (a) the amount of KI to 1.5 equiv., (b) DMSO to 1.25 vol% and (c) the buffer volume to half of its initial volume (45 mL) could only be achieved when the amount of laccase was increased to 270 U and the addition rate of enzyme as well as substrate was increased to 15 h. Considering all of the above aspects, the *E*-factor for the transformation of **1a** to **2a** can be reduced from 31.9 kg kg^{-1} (Table 7, entry 1) to 4.6 kg kg^{-1} (Table 7, entry 14). Under these conditions, **2a** was isolated in 77% and the **2a**/**3a** ratio amounted to 198 : 1. A further improvement of the *E*-factor to 2.9 kg kg^{-1} was possible when the reaction was performed in the complete absence of DMSO (Table 7, entry 15). Under these conditions, the yield did increase to 83%; however, the **2a**/**3a** ratio worsened to 31 : 1. Further measures to increase sustainability but not necessarily the *E*-factor of the model reaction related to the reaction mixture workup included the complete renunciation of organic solvents during workup, a substantial renunciation of purification by column chromatography and the replacement of $Na_2S_2O_7$ – which was used to remove residual I_2 from the reaction mixture – with ascorbic acid (Table 7, entries 14, 15 and Table 8). Additional information and calculations concerning the greenness and efficiency (TON, TOF, STY) of selected reactions are presented in the ESI.† A control experiment in absence of the laccase with I_2 clearly revealed that under these conditions the yield is considerable lower than under the conditions of the laccase-catalyzed reaction with KI as iodination agent (Table 7, entry 16).

To prove the usefulness of the conditions developed, a number of substrates were iodinated according to the conditions given in Table 7, entries 14 and 15 (Table 8).

Substrates with a tendency for polymerization (**1a**, **1b**) were reacted according to Table 7, entry 14 (Method A). Under these conditions, the iodination of **1b** produced **2b** with high selectivity and 80% yield (Table 8, entry 2). The *E*-factor for this transformation was 4.14 kg kg^{-1}. A number of substrates with

Table 8 Sustainable iodination of selected substrates[a]



Entry	1	Method	Yield product (%)	2a : 3a	E-factor
1	**a**	A	77 (**2a**)	198 : 1	4.63
2	**b**	A	80 (**2b**)	98 : 1	4.14
3[b]	**c**	B	90 (**2c**)	198 : 1	2.22
4[c]	**e**	B	90 (**2e**)	198 : 1	2.55
5[d]	**i**	B	92 (**2i**)	198 : 1	2.49
6	**k**	B	93 (**2k**)	198 : 1	2.44

[a] 2 mmol substrate were reacted in 45 mL buffer. Initially, 45 U enzyme were added, additionally laccase (225 U) in buffer (562 μL) was added during 15 h by syringe pump. Method A: substrate in 562 μL DMSO was added by a second syringe pump during the same time the enzyme was added. Method B: substrate was added during 10 h as a solid. The yields refer to yields after filtration and washing of the crude product with water. Ratio of **2a : 3a** was analyzed *via* ^{1}H NMR after filtration and drying of the crude product. [b] 72 h reaction time. [c] 255 U laccase were added during 36 h. [d] 48 h reaction time.

no tendency to dimerization (**1c**, **1e**, **1i**, **1k**) were reacted under the conditions of Table 7, entry 15 (Method B) to deliver the monoiodinated products **2c**, **2e**, **2i** and **2k** in remarkably high yields, with outstanding selectivities and remarkably low *E*-factors (Table 8, entries 3–6).

Conclusions

In summary, a simple-to-perform and sustainable enzyme-catalyzed method for the selective and efficient iodination of *p*-hydroxyarylcarbonyl- and *p*-hydroxyarylcarboxylic acid derivatives on a preparative scale has been developed. It relies on the use of easy to handle KI as iodine source which undergoes laccase-catalyzed oxidation to iodine by using safe and cheap aerial oxygen as oxidant. The reactions can be performed in an aqueous solvent system under mild reaction conditions. The iodinated products which arise from electrophilic aromatic substitutions could be isolated with yields up to 93%. Depending on the substitution pattern of the substrates either monoiodinated or diiodinated products are formed. The use of KI instead of I_2 as iodination agent allows the increase of the atom economy from 72 to 85%. By proper choice of the reaction conditions the competing oxidative phenolic coupling can be completely suppressed. Further optimization measures such as decreasing the amounts of KI and laccase, optimizing the buffer system, completely dispensing with organic solvents during workup, using ascorbic acid to destroy residual iodine and avoiding chromatographic purification enabled us to develop the laccase-catalyzed reaction towards a sustainable iodination method.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Mr Mario Wolf (University of Hohenheim) for recording NMR spectra and Dr Alevtina Mikhael, Dr Claudia Oellig (University of Hohenheim), and Mr Joachim Trinkner (University of Stuttgart) for recording mass spectra.

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