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# Oxidative cleavage of C–C double bond in cinnamic acids with hydrogen peroxide catalysed by vanadium(v) oxide†

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We have developed a cheap, green, mild and environmentally friendly method for the selective cleavage of carbon–carbon double bonds with a 30% aqueous solution of hydrogen peroxide as the oxidant and vanadium(v) oxide as the catalyst. The selectivity of the oxidative cleavage of cinnamic acid derivatives **1** depends on the substituents and the solvent used (DME – MeOCH<sub>2</sub>CH<sub>2</sub>OMe, TFE – 2,2,2-trifluoroethanol or MeCN). In DME, *p*-hydroxy derivatives were selectively converted to benzaldehyde derivatives **2**, in TFE, oxidative cleavage led to the formation of benzoquinone derivatives **4**, while in MeCN, cinnamic acid derivatives were selectively converted to benzoic acid derivatives **3**. Ferulic acid **1a** was quantitatively and selectively converted to vanillin **2a** in a 91% isolated yield on a gram scale. Dimeric difurandione **1a'** was isolated as an intermediate, which was confirmed by *in situ* ATR-IR spectroscopy, while the formation of diols or epoxides was not observed. The analogous styrene derivative, 4-vinylguaiacol **1e** was also selectively converted to either vanillin **2a** or 2-methoxyquinone **4a** in a high yield. The green metric for the conversion of ferulic acid to vanillin by different methods was calculated and compared to our method, and showed that our method has better environmental parameters.

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## Introduction

The selective oxidative cleavage of carbon–carbon double bonds is a synthetically important reaction to introduce oxygen functionality into molecules or to degrade complex compounds, especially those from natural sources and biomass, *i.e.* oils, terpenes, or cinnamic acids. It is important to prepare aromatic compounds from lignin, a sustainable alternative to conventional crude oil based methods.<sup>1–3</sup> This is also a fundamental reaction in the industrial organic synthesis and valorisation of biomass *i.e.* oils and terpenes.<sup>4</sup>

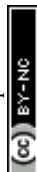
In recent decades, researchers have devoted much attention to this topic, and many protocols have been proposed. The standard method for the oxidative cleavage of olefins into aldehydes, ketones, and carboxylic acids is ozonolysis.<sup>5–7</sup> However, the ozone is a highly reactive, ground-level air pollutant and a dangerous, toxic, corrosive, unstable and very potent oxidation reagent. Alternatively, many other oxidants have been investigated to achieve the selective oxidative cleavage of double bonds, *e.g.* OsO<sub>4</sub>/NaIO<sub>4</sub> (Lemieux–Johnson reaction),<sup>8,9</sup> Oxone,<sup>10,11</sup> *m*-CPBA,<sup>12</sup> *t*-BuOOH,<sup>13–15</sup> KMnO<sub>4</sub>,<sup>16,17</sup> *etc.* These

methods also have some disadvantages, such as toxicity, high price, and the generation of a stoichiometric oxidant as waste. Using biobased molecules as feedstock demands the use of environmentally friendly oxidants such as oxygen and hydrogen peroxide. Oxygen is used because of its lower cost, atom efficiency and environmental friendliness. The aerobic oxidative cleavage of carbon–carbon double bonds is very promising; however, improvements are still needed to compete with conventional oxidants.<sup>18–24</sup> Hydrogen peroxide is similar to oxygen in that water is the only by-product, while the reactions can be carried out in a homogeneous phase.<sup>25–27</sup> The use of H<sub>2</sub>O<sub>2</sub> for the oxidative cleavage of olefins has been described in several articles, however there is a lack of simple and cost-effective methods.<sup>28–34</sup>

Cinnamic and ferulic acid derivatives are readily available and found in many plants, fruits, vegetables, *etc.*<sup>35,36</sup> Ferulic acid, the most abundant natural aromatic compound, is found in the lignocellulosic biomass in the cell walls of plants, grasses, vegetables, flowers, leaves, seeds and nuts.<sup>37–39</sup> Therefore, this class of compounds is interesting feedstock for various aromatic molecules and environmentally friendly processes are being sought for the production of various aromatic molecules. Some methods are known for converting the cinnamic acid model compounds into corresponding benzaldehydes or benzoic acids using H<sub>2</sub>O<sub>2</sub>, but the choice of substrates is extremely limited.<sup>40,41</sup> The conversion of ferulic acid

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to vanillin is one of the best-known examples. Biotechnological processes proceed selectively, but many auxiliary components are required in a process that yields a dilute aqueous solution of vanillin.<sup>42</sup> Synthetic processes with green oxidants are limited to hydrogen peroxide using catalysts, such as a metal-organic framework HKUST-1,<sup>43</sup> metal-organic polyhedron Cu(II),<sup>44</sup> Cu-MOF-74<sup>45</sup> or photocatalytic Cu/TiO<sub>2</sub>.<sup>46</sup> The selectivity of ferulic acid to vanillin conversion poses a serious problem due to further oxidation to vanillic acid.

We present a study on the development of a simple and cost-effective method for the oxidative cleavage of the C–C double bond in cinnamic acid derivatives with the use of vanadium(V) oxide and hydrogen peroxide, where the choice of solvent determines the selectivity towards benzaldehydes, benzoic acids, and benzoquinones. The selectivity and efficiency of the process was demonstrated on the ferulic acid to vanillin conversion. The green metric was used to evaluate the conversion of ferulic acid to vanillin with other similar methods.

## Results and discussion

Ferulic acid **1a** was used as a model substrate for the oxidative cleavage of the carbon–carbon double bond with a 30% aqueous solution of hydrogen peroxide. Various simple transition metal salts were tested as catalysts (Fe<sub>2</sub>O<sub>3</sub>, ZrBr<sub>2</sub>, (NH<sub>4</sub>)<sub>2</sub>MoO<sub>4</sub>, RuCl<sub>3</sub>, NiCl<sub>2</sub>, Co<sub>2</sub>(CO)<sub>8</sub>, Na<sub>2</sub>MoO<sub>4</sub>, CuBr, CuBr<sub>2</sub>, Na<sub>3</sub>VO<sub>4</sub>, NH<sub>4</sub>VO<sub>3</sub>, VO(acac)<sub>2</sub>, VOSO<sub>4</sub>·H<sub>2</sub>O, VCl<sub>2</sub> and V<sub>2</sub>O<sub>5</sub>) (Table 1). The reaction was carried out in acetonitrile using 7 equiv. of H<sub>2</sub>O<sub>2</sub> and 0.1 equiv. of catalyst at room temperature for 2 h. In the absence of a catalyst, the reaction did not take place. The same was observed in the presence of Fe<sub>2</sub>O<sub>3</sub>, ZrBr<sub>2</sub> and (NH<sub>4</sub>)<sub>2</sub>MoO<sub>4</sub> (Table 1, entries 1–3). When RuCl<sub>3</sub>, NiCl<sub>2</sub>,

Co<sub>2</sub>(CO)<sub>8</sub> and Na<sub>2</sub>MoO<sub>4</sub> were used, some conversion occurred but the formation of vanillin **2a** was not observed. Instead, a small amount (2–17%) of dimeric product **1a'** (*vide supra*) was formed (Table 1, entries 4–7, Scheme 1). Copper catalysts, CuBr and CuBr<sub>2</sub>, were found to be moderately effective in catalysing the conversion of **1a** to **2a** (Table 1, entries 8 and 9). Vanadium catalysts were the most efficient for the conversion to **2a**, but further oxidation to vanillic acid **3a** and 3-methoxy-1,2-benzoquinone **4a** was also observed. The best result was obtained with V<sub>2</sub>O<sub>5</sub> (68% of **2a**) (Table 1, entry 15). The yield of **2a** did not change when the amount of V<sub>2</sub>O<sub>5</sub> was reduced to 5 mol% and further reactions were carried out with 0.05 equiv. of V<sub>2</sub>O<sub>5</sub>.

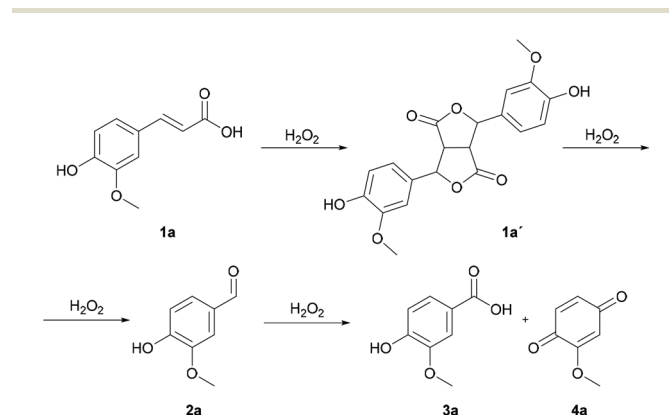
Next, we tested different solvents for the V<sub>2</sub>O<sub>5</sub>-catalysed C–C bond cleavage of **1a** with H<sub>2</sub>O<sub>2</sub>. As can be seen from the results in Table 2, the solvent has an important effect on the transformation.

No reaction took place in water, TFA or DMSO (Table 2, entries 1–3). Reactions in other solvents were nonselective for **2a**, with the notable exception of DME, where no overoxidation to **3a** and **4a** was observed (Table 2, entry 15), 95% of vanillin **2a** was formed, and 5% of intermediate **1a'** remained. The oxidative cleavage of the C–C double bond occurred quantitatively in DCM, however the reaction was not selective (Table 2, entry 10). An interesting result was observed in THF where the selectivity was good but other products were formed (Table 2, entry 12). The NMR spectra show that THF reacted during the reaction and was oxidized to 2-hydroxytetrahydrofuran and  $\gamma$ -butyrolactone (ESI Scheme S2.1 and Fig. S2.1†). In ethanol and acetonitrile, the reaction was quantitative (Table 2, entries 13 and 14), the selectivity for **2a** was better in acetonitrile than in ethanol, and 8% of ethyl vanillate was also formed in EtOH. The selectivity of the reaction in MeCN was not improved when the reaction was carried out at a lower temperature (0 °C) or when H<sub>2</sub>O<sub>2</sub> was added in four portions. Only when DME was used as a solvent was the further oxidation of vanillin **2a** to vanillic acid **3a** sufficiently slow to allow for the selective formation of vanillin **2a**. Fluorinated alcohols are activating solvents for oxidations,<sup>47,48</sup> and the use of TFE resulted in

**Table 1** The effect of the catalyst structure on the oxidative cleavage of the C–C double bond in ferulic acid **1a** with H<sub>2</sub>O<sub>2</sub>

Entry	Catalyst	<b>1a</b> <sup>a</sup> [%]	<b>1a'</b> <sup>a</sup> [%]	<b>2a</b> <sup>a</sup> [%]	<b>3a</b> <sup>a</sup> [%]	<b>4a</b> <sup>a</sup> [%]
1	Fe <sub>2</sub> O <sub>3</sub>	100	0	0	0	0
2	ZrBr <sub>2</sub>	100	0	0	0	0
3	(NH <sub>4</sub> ) <sub>2</sub> MoO <sub>4</sub>	100	0	0	0	0
4	RuCl <sub>3</sub>	98	2	0	0	0
5	NiCl <sub>2</sub>	97	3	0	0	0
6	Co <sub>2</sub> (CO) <sub>8</sub>	92	8	0	0	0
7	Na <sub>2</sub> MoO <sub>4</sub>	83	17	0	0	0
8	CuBr	79	10	11	0	0
9	CuBr <sub>2</sub>	32	21	39	8	0
10	Na <sub>3</sub> VO <sub>4</sub>	87	9	4	0	0
11	NH <sub>4</sub> VO <sub>3</sub>	75	11	14	0	0
12	VO(acac) <sub>2</sub>	0	6	66	9	19
13	VOSO <sub>4</sub> ·H <sub>2</sub> O	1	15	57	15	12
14	VCl <sub>2</sub>	0	0	57	13	30
15	V <sub>2</sub> O <sub>5</sub>	0	0	68	8	24
16	V <sub>2</sub> O <sub>5</sub> <sup>b</sup>	0	0	68	10	22
17	V <sub>2</sub> O <sub>5</sub> <sup>c</sup>	76	13	11	0	0

Reaction conditions: **1a** (0.1 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (0.7 mmol), catalyst (0.01 mmol), MeCN (1 mL), rt, 2 h. <sup>a</sup> Conversion was determined by <sup>1</sup>H NMR. <sup>b</sup> V<sub>2</sub>O<sub>5</sub> (0.005 mmol). <sup>c</sup> V<sub>2</sub>O<sub>5</sub> (0.001 mmol).



**Scheme 1** Transformation of ferulic acid **1a** to vanillin **2a** via intermediate **1a'**.



**Table 2** The effect of the solvent on the oxidative cleavage of ferulic acid **1a** with H<sub>2</sub>O<sub>2</sub>

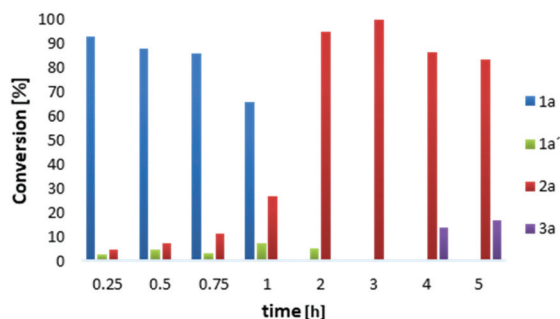
Entry	Solvent	<b>1a</b> <sup>a</sup> [%]	<b>1a'</b> <sup>a</sup> [%]	<b>2a</b> <sup>a</sup> [%]	<b>3a</b> <sup>a</sup> [%]	<b>4a</b> <sup>a</sup> [%]
1	H <sub>2</sub> O	100	0	0	0	0
2	TFA	100	0	0	0	0
3	DMSO	100	0	0	0	0
4	TFE	0	0	0	0	100
5	DMC	64	5	16	0	15
6	Isopropanol	29	10	45	6	10
7	Diethyl ether	80	5	11	0	4
8	EtOAc	59	3	8	0	30
9	Hexane	58	8	24	5	5
10	DCM	0	40	32	24	4
11	MeOH	19	22	28	22	9
12	THF	53	1	39	5	2
13	EtOH	0 <sup>b</sup>	0	59	11	22
14	MeCN	0	0	68	8	24
15	DME	0	5	95	0	0

Reaction conditions: **1a** (0.1 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (0.7 mmol), V<sub>2</sub>O<sub>5</sub> (0.005 mmol), solvent (1 mL), rt, 2 h. <sup>a</sup> Conversion was determined by <sup>1</sup>H NMR. <sup>b</sup> 8% of ethyl vanillate was formed.

the complete conversion of **1a** to benzoquinone **4a**, which was isolated in an 84% yield (Table 2, entry 4).

The reaction was further optimized by changing the amount of hydrogen peroxide (Table 3). Decreasing the amount of hydrogen peroxide to 5 equiv. resulted in a lower conversion, while a higher temperature only slightly improved the conversion. The quantitative conversion of **1a** to **2a** occurred with 7 equiv. of H<sub>2</sub>O<sub>2</sub> for 3 h or 30 min at 60 °C (Table 3, entries 5 and 6). Further increasing H<sub>2</sub>O<sub>2</sub> to 10 equiv. resulted in a partial overoxidation to **3a**. The concentration of hydrogen peroxide (3% vs. 60% aq. solution) is also important. A higher concentration leads to the formation of **3a** in a shorter time, while more dilute H<sub>2</sub>O<sub>2</sub> is not strong enough.

We followed the conversion of **1a** to **2a** with 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (7 equiv.) and 5 mol% of V<sub>2</sub>O<sub>5</sub> by NMR spectroscopy (Fig. 1). After 2 h of reaction, the conversion of **1a** was 100% complete, but a small amount of the intermediate **1a'** was still present (5%). The latter was completely converted to product **2a** after

**Fig. 1** Reaction profile for vanillin **2a** formation in DME. Reaction conditions: **1a** (0.1 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (0.7 mmol), V<sub>2</sub>O<sub>5</sub> (0.005 mmol), DME (1 mL), rt.

3 h, while further conversion to vanillic acid **3a** started after 4 h of reaction. Despite the longer reaction time, no quinone **4a** was detected in DME.

The reaction in DME was followed by *in situ* ATR-IR spectroscopy, but we had to use 100% H<sub>2</sub>O<sub>2</sub> to avoid the peak of water in the IR spectrum (Fig. 2). Consequently, some acid **3a** was also formed. The ATR-IR experiment confirmed that the product **1a'** with a characteristic peak at 1704 cm<sup>-1</sup> is an intermediate product. When 100% H<sub>2</sub>O<sub>2</sub> was used, the selectivity was lost and **3a** (1521 cm<sup>-1</sup>) started to form after 2 hours, which slowly increased in the last phase of the reaction (Fig. 2 and ESI Fig. S2.2†). The same reaction course was observed when this reaction was followed by NMR spectroscopy (ESI Fig. S2.3†). Similarly, an *in situ* ATR-IR experiment was also performed for the reaction in TFE. The reaction proceeded too quickly to observe the formation of **1a'** and the signals of benzoquinone **4a** predominated (ESI Fig. S2.4†).

To investigate the mechanism of the reaction, the experiments were performed with the addition of TEMPO, which is used as a radical quencher, and AIBN as a radical initiator. Upon the addition of TEMPO, the reaction was inhibited, indicating that the reaction proceeds *via* a radical pathway. On the other hand, the addition of the initiator AIBN resulted in the faster formation of vanillin **2a** (Table 4).

Based on the experimental results, the oxidative cleavage of the C–C double bond occurs *via* a radical mechanism. The formation of the intermediate **1a'** indicates an initial reaction at the double bond, in which the OH group at the *para* position could play an important role in stabilizing the intermediate. The formation of epoxides and diols was not observed using NMR spectroscopy.

We tested this procedure on other derivatives containing an aromatic ring from the lignin core (Table 5). Ferulic acid **1a**, its ethyl ester **1b**, and *p*-coumaric acid **1c** were converted to their corresponding aldehydes in excellent yields, however caffeic acid **1d** was very reactive and benzoquinone **4d** was always the major product, regardless of the reaction conditions, amount of oxidant, and time. The best yield of an aldehyde was only 15%. The reaction was also effective with a styrene derivative **1e**.

Under the same reaction conditions, but replacing DME with a more activating solvent 2,2,2-trifluoroethanol (TFE),

**Table 3** The effect of H<sub>2</sub>O<sub>2</sub> on the oxidative cleavage of the C–C double bond in **1a**

Entry	Equiv. of H <sub>2</sub> O <sub>2</sub>	<b>1a</b> [%]	<b>1a'</b> [%]	<b>2a</b> [%]	<b>3a</b> [%]
1	2	70	8	22	0
2	3	69	8	23	0
3	5	37	9	54	0
4	5 <sup>a</sup>	36	2	62	0
5	7	0	0	100	0
6	7 <sup>b</sup>	0	0	100	0
7	7 <sup>c</sup>	91	4	5	0
8	7 <sup>d</sup>	86	4	10	0
9	7 <sup>e</sup>	0	0	85	15
10	10	0	0	86	14

Reaction conditions: ferulic acid **1a** (0.1 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (0.2–1.0 mmol), V<sub>2</sub>O<sub>5</sub> (0.005 mmol), DME (1 mL), rt, 3 h. Conversion was determined by <sup>1</sup>H NMR. <sup>a</sup> 2 h, 60 °C. <sup>b</sup> 0.5 h, 60 °C. <sup>c</sup> 3%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub>. <sup>d</sup> 3%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub>, 24 h. <sup>e</sup> 60%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub>.



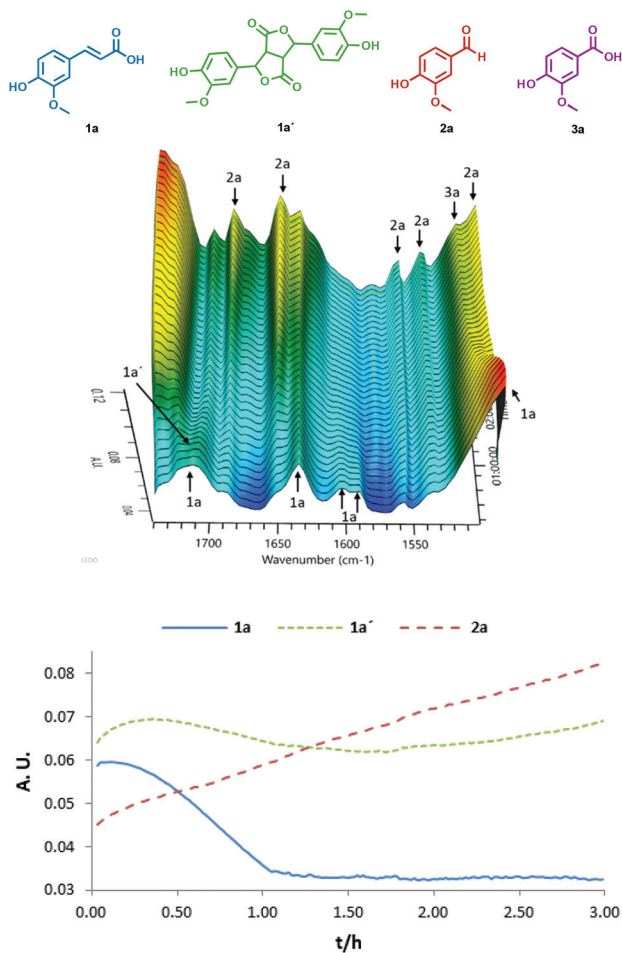


Fig. 2 ATR-IR of the reaction of ferulic acid **1a** ( $1517\text{ cm}^{-1}$ ) with 100%  $\text{H}_2\text{O}_2$ . Reaction conditions: **1a** (6.2 mmol), 100%  $\text{H}_2\text{O}_2$  (30.0 mmol),  $\text{V}_2\text{O}_5$  (0.3 mmol), DME (25 mL), rt.

benzoquinones **4** were selectively prepared in good yields (79–91%), while the reaction proceeded at room temperature for 2 h (Table 6).

The reaction was also tested on various substrates without the presence of the *p*-hydroxy substituent. In all of the cases, the conversion of the starting substrates **1** did not occur in the presence of the solvent DME. In acetonitrile, the reaction was unselective for vanillin **2a**, while the conversion to vanillic acid

Table 4 Oxidative cleavage of the C–C double bond of ferulic acid **1a** in the presence of TEMPO and AIBN

Entry		Time	Conversion <sup>a</sup> [%]
1	—	3 h	100
2	TEMPO	3 h	0
3	AIBN	20 min	16
4	AIBN	40 min	100
5	AIBN	2 h	100

Reaction conditions: ferulic acid **1a** (0.1 mmol), 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (0.7 mmol),  $\text{V}_2\text{O}_5$  (0.005 mmol), TEMPO (0.2 mmol) or AIBN (0.1 mmol), DME (1 mL), rt, time. <sup>a</sup> Conversion was determined by  $^1\text{H}$  NMR.

Table 5 The scope for the synthesis of benzaldehydes **2**

$\text{R}_1\text{-C}_6\text{H}_3(\text{R}_2)\text{-CH=CH-COOH} \xrightarrow[\text{DME, rt, t}]{30\% \text{H}_2\text{O}_2, \text{V}_2\text{O}_5 (5 \text{ mol}\%)} \text{R}_1\text{-C}_6\text{H}_3(\text{R}_2)\text{-CHO}$			
Substrate	Product	Time	Yield <sup>a</sup>
		3 h	94%
		4 h	91%
		24 h	92%
		1 h	15% <sup>b</sup>
		2 h	85%

Reaction conditions: substrate **1** (0.5 mmol), 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (3.5 mmol),  $\text{V}_2\text{O}_5$  (0.025 mmol), DME (5 mL), rt, t. <sup>a</sup> Isolated yield. <sup>b</sup> NMR yield, the main product is **4d**.

**3a** was very high. Hence, a synthesis of aromatic benzoic acids **3** by the oxidative cleavage of cinnamic acid derivatives **1** was investigated.

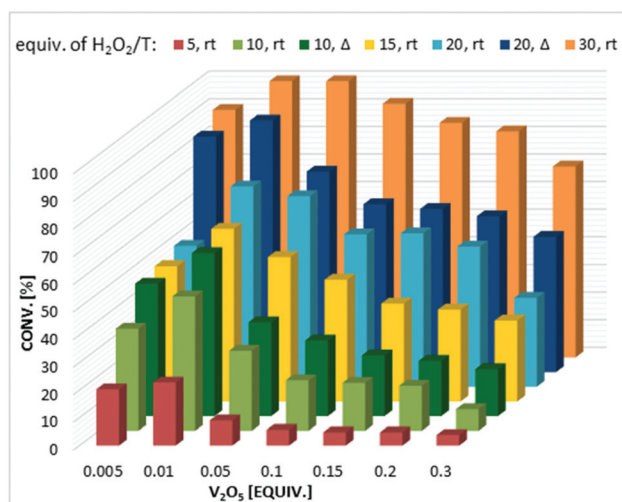
Numerous reaction conditions were carried out to find the optimum reaction conditions for the selective synthesis of benzoic acid **3f** from cinnamic acid **1f** (Fig. 3). Decreasing the amount of catalyst from 1 mol% to 0.5 mol% decreased the yield by 3–22%, depending on the amount of hydrogen peroxide. In contrast, the reaction yield was not improved when the amount of catalyst was increased to 0.3 equiv. The results show that 1 mol% of the vanadium catalyst gave the best result. Screening the amount of hydrogen peroxide showed that it had a very large effect on the reaction. Increasing the amount of oxidant led to more oxidative cleavage of the C–C double bond in **1f**, resulting in the synthesis of benzaldehyde **2f** and benzoic acid **3f**. The complete conversion was only achieved with 30 equiv. of hydrogen peroxide. In these reac-



**Table 6** The scope for the synthesis of benzoquinones **4**

Substrate	Product	Yield <sup>a</sup>
		84%
		88%
		91%
		79%

Reaction conditions: substrate **1** (0.2 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (1.4 mmol), V<sub>2</sub>O<sub>5</sub> (0.01 mmol), TFE (2 mL), rt, 2 h. <sup>a</sup> Isolated yield.



**Fig. 3** Oxidative cleavage of the C–C double bond of cinnamic acid **1f** under different reaction conditions: cinnamic acid **1f** (0.1 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (5–30 equiv.), catalyst (0.005–0.3 equiv.), MeCN (1 mL), rt/Δ (60 °C), 24 h.

tions, temperature did not have much of an influence. Comparing the results at room and reflux temperature (green columns and blue columns, respectively, in Fig. 3) with the same equivalence of catalyst and oxidant, the difference in conversion is only 3–24%.

Having found the optimal reaction conditions, we tested the general validity of the protocol for the oxidative cleavage of the carbon–carbon double bond in the cinnamic acid derivatives to the corresponding benzoic acid derivatives with 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> catalyzed by V<sub>2</sub>O<sub>5</sub> in acetonitrile (Table 7). All of the reactions resulted in a complete substrate conversion. The C–C double bond of the cinnamic acid derivatives **1** was effectively cleaved under optimized reaction conditions to afford benzoic acids **3** in excellent yields (84–94%). The presented protocol

**Table 7** The scope for the synthesis of benzoic acids **3**

		solvent	equiv. of H <sub>2</sub> O <sub>2</sub>
Conditions A		MeCN	28
Conditions B		MeCN, TFA (1:1)	40
Substrate	Product	Cond.	Yield <sup>a</sup>
		A	94%
		A	88%
		A	91%
		A	86%
		A	90%
		B	87%
		B	93%
		B	85%



Table 7 (Contd.)

		solvent	equiv. of H <sub>2</sub> O <sub>2</sub>
Conditions A		MeCN	28
Conditions B		MeCN, TFA (1:1)	40

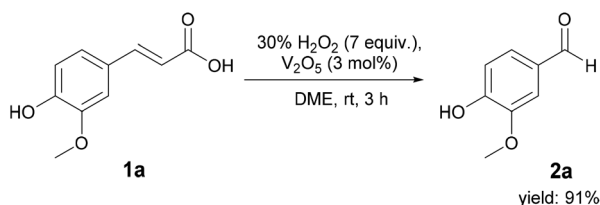
Substrate	Product	Cond.	Yield <sup>a</sup>
		A	91%
		B	84%
		A	90%
		A	89%

Reaction conditions A: substrate **1** (0.5 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (14.0 mmol), V<sub>2</sub>O<sub>5</sub> (1 mol%), MeCN (5 mL), rt. Reaction conditions B: substrate **1** (0.5 mmol), 30%<sub>aq</sub> H<sub>2</sub>O<sub>2</sub> (20.0 mmol), V<sub>2</sub>O<sub>5</sub> (0.005 mmol), MeCN/TFA (1/1, 5 mL), rt. <sup>a</sup> Isolated yield.

tolerates the presence of several functional groups on the aromatic ring. Compounds **1k**, **1l**, **1m** and **1o** were not sufficiently soluble, and a combination of acetonitrile and TFA (1 : 1) had to be used to achieve quantitative conversion.

To confirm the synthetic value of this method, the oxidation of ferulic acid to the important molecule vanillin was performed on a scale of 6.2 mmol (1.2 g) and after 3 h at 22 °C, 91% pure fragrant vanillin was isolated (Scheme 2).

We evaluated the green metrics for the conversion of ferulic acid **1a** to vanillin **2a**, focusing on the use of the green oxidants—H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub>—using a template proposed by Andraos.<sup>49</sup> There is no research reporting on the aerobic oxidation of ferulic acid with useful data for calculating the green metrics. We chose a biotechnological method using the immobilized enzymes *decarboxylase Fdc* and *oxygenase CsO<sub>2</sub>*.<sup>50</sup>

Scheme 2 The gram-scale synthesis of vanillin **2a** from ferulic acid **1a**.Table 8 A comparison of the green metrics for the conversion of **1a** to **2a**

	This article	HKUST-1 <sup>43</sup>	Cu(II)-MOP <sup>44</sup>	Cu-MOF-74 <sup>45</sup>	Biotech. <sup>50</sup>
Yield	91%	95%	60%	71%	17%
AE	58%	58%	58%	58%	78%
1/SF	0.623	0.307	0.294	0.193	1.00
MRP	0.107	0.0052	0.049	0.081	0.005
RME	3.5%	0.2%	0.5%	0.6%	0.1%
<i>E</i> -Factor	28	430	198	154	1542

AE (atom economy), SF (stoichiometric factor), MRP (materials recovery parameter), RME (reaction mass efficiency), *E*-factor (mass of waste/mass of **2a**).

The authors reported obtaining 2.5 mg of vanillin per 1 mL after ten reaction cycles, however, no isolation was reported. Three suitable methods were found with H<sub>2</sub>O<sub>2</sub> using the catalysts HKUST-1,<sup>43</sup> Cu(II)-MOP<sup>44</sup> and Cu-MOF-74.<sup>45</sup> Unfortunately, all of the data needed to calculate the green metrics are not available (the amount of solvent and additives in the work-up and the amount of silica gel and solvents in the isolation step). Furthermore, the isolation of vanillin **2a** from the reaction mixture on an industrial scale would be quite different and the method used on a smaller scale is not as relevant. Hence, we made a three-level comparison – synthesis with workup, synthesis with workup and isolation and the synthesis with potential reuse of components. Where data in the original procedure was missing, we assumed that they used the same amounts of materials for the workup and isolation as we did since the reactions were similar. The parameters of the green metrics for the first level comparison are listed in Table 8 and on a pentagram in Fig. S2–5,† while the analysis of the whole process can be found in the ESI (xls file†). The atom economy was based on the reaction equation and is the same for all of the studied processes with hydrogen peroxide, while the biotechnological process has a better one. A major drawback is in the MRP and RME parameters, where the V<sub>2</sub>O<sub>5</sub> method performs much better, but there is still room for improvement, especially in solvent recovery (ESI†). The *E*-factor defines the amount of waste produced per mass of product. It is obvious that there are significant differences in the *E*-factor (Table 8). The biotechnological process has a higher *E*-factor due to the highly diluted reaction media and additives. On the other hand, the catalytic processes have significant differences in the *E*-factor due to the differences in the amount of solvent and selectivity of the reaction as well as an excess of reagents. Again, the V<sub>2</sub>O<sub>5</sub> catalytic process produces the least amount of waste.

## Experimental

### Materials and methods

All of the chemicals and reagents were obtained from commercial suppliers (Sigma-Aldrich, Fluorochem) and were used as



received without further purification. The TLC was performed on Merck-60-F254 plates using mixtures of EtOAc/heptane (2/1). The crude products were purified by column chromatography on a silica gel (63–200  $\mu\text{m}$ , 70–230 mesh ASTM; Fluka). The products were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, IR spectroscopy and HRMS. The  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded on Bruker Avance III 500 instruments using TMS as the internal standard. The IR spectra were measured on a PerkinElmer 2000 Fourier transform infrared spectroscope. The HRMS data were recorded with an Agilent 6224 Accurate Mass TOF LC/MS System.

FTIR: The spectra were recorded with a ReactIR<sup>TM</sup> 45 instrument with a resolution of  $4\text{ cm}^{-1}$ , averaging 128 scans. An EasyMax 102 controller was used to control the reaction conditions during the reaction. The instruments were controlled by iControl EasyMax 4.2 and iC IR 4.2 software.

#### General procedure for aldehyde synthesis

In a 10 mL volumetric flask, substrate **1** (0.5 mmol) and the  $\text{V}_2\text{O}_5$  catalyst (0.05 equiv.) were added to a 5 mL solution of the solvent DME. The 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (0.36 mL, 7 equiv.) was first purged with argon and slowly added to the reaction mixture in three portions. The mixture was stirred at room temperature and monitored with TLC. After completion of the reaction, the reaction mixture was extracted with EtOAc ( $2 \times 5\text{ mL}$ ). The organic layer was evaporated under vacuum. The crude reaction was subjected to column chromatography with the mobile phase EtOAc/heptane (2/1). The solvent was evaporated *in vacuo* to provide the product.

#### General procedure for benzoquinone synthesis

In a 5 mL volumetric flask, substrate **1** (0.2 mmol) and the  $\text{V}_2\text{O}_5$  catalyst (0.05 equiv.) were added to a 2 mL solution of the solvent TFE (2,2,2-trifluoroethanol). The 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (0.144 mL, 7 equiv.) was first purged with argon and slowly added to the reaction mixture. The mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was extracted with EtOAc ( $2 \times 3\text{ mL}$ ). The organic layer was evaporated under vacuum. The crude reaction was subjected to column chromatography with the mobile phase EtOAc/heptane (2/1). The solvent was evaporated *in vacuo* to provide the product.

#### General procedure for aromatic benzoic acid synthesis (conditions A)

In a 10 mL volumetric flask, substrate **1** (0.5 mmol) and the  $\text{V}_2\text{O}_5$  catalyst (0.01 equiv.) were added to a 5 mL solution of the solvent MeCN. The 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (1.4 mL, 28 equiv., 14.0 mmol) was first purged with argon and slowly added to the reaction mixture in three portions. The mixture was stirred for 24 h at room temperature. After completion of the reaction, the reaction mixture was extracted with EtOAc ( $2 \times 5\text{ mL}$ ). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum. The crude reaction was subjected to column chromatography with the mobile phase EtOAc/heptane (2/1). The solvent was evaporated *in vacuo* to provide the product.

#### General procedure for acid synthesis (conditions B)

In a 10 mL volumetric flask, substrate **1** (0.5 mmol) and the  $\text{V}_2\text{O}_5$  catalyst (0.01 equiv.) were added to a 5 mL solution of the solvent mixture MeCN/TFA (1/1). The 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (2 mL, 40 equiv., 20.0 mmol) was first purged with argon and slowly added to the reaction mixture in three portions. The mixture was stirred for 24 h at room temperature. After completion of the reaction, the reaction mixture was extracted with EtOAc ( $2 \times 5\text{ mL}$ ). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum. The crude reaction was subjected to column chromatography with the mobile phase EtOAc/heptane (2/1). The solvent was evaporated *in vacuo* to provide the product.

#### Scale-up procedure for the preparation of vanillin from ferulic acid

In a 50 mL volumetric flask, ferulic acid (6.2 mmol, 1.2 g) and the  $\text{V}_2\text{O}_5$  catalyst (0.03 equiv., 0.2 mmol, 37.5 mg) were added to a 25 mL solution of the solvent DME. The 30%<sub>aq</sub>  $\text{H}_2\text{O}_2$  (7 equiv., 4.2 mL) was first purged with argon and slowly added to the reaction mixture at  $22\text{ }^\circ\text{C}$ . The mixture was stirred at  $24\text{ }^\circ\text{C}$  and monitored with TLC. After completion of the reaction (3 h), the reaction mixture was extracted with EtOAc ( $2 \times 20\text{ mL}$ ). The organic layer was evaporated under vacuum. The product vanillin (858 mg, 91%) was obtained after column chromatography purification (EtOAc/heptane (2/1)) as a white solid.

## Conclusions

We have developed a method for the oxidative cleavage of the carbon–carbon double bond in cinnamic acid and related compounds under mild reaction conditions using the green and environmentally friendly oxidant hydrogen peroxide and the cheap catalyst vanadium(v) oxide. The choice of solvent (DME, TFE, MeCN) determines the selectivity, and benzaldehydes, aromatic carboxylic acids or benzoquinones were selectively prepared in DME, MeCN or TFE, respectively. The hydroxy substituent in the *para* position of the aromatic ring is necessary for the selective synthesis of the benzaldehyde derivatives. The process also provides a simple and cost-effective alternative for the conversion of ferulic acid to vanillin in a high yield. Calculation of the green metrics for similar processes showed that the  $\text{V}_2\text{O}_5$  catalysed process has much better green parameters than other methods.

## Author contributions

Conceptualization: J. I.; formal analysis: M. H.; funding acquisition: J. I.; investigation: M. H.; methodology: M. H., J. I.; project administration: J. I.; supervision: J. I.; visualization: M. H., J. I.; writing – original draft: M. H., J. I.; writing – review & editing: M. H., J. I.



## Conflicts of interest

Patent pending (LU102332).

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