**Highly efficient oxidation of amines to aldehydes via flow-based biocatalysis**

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**Abstract:** A new mild and efficient process for the preparation of aldehydes in water employed as flavour and fragrance components in food, beverage, cosmetics, as well as in pharmaceuticals was developed using a continuous-flow approach based on an immobilized pure transaminase-packed bed reactor. HEWT, an ω-transaminase from the haloadapted bacterium *Halomonas elongata,* has been selected for its excellent stability and substrate scope. Sixteen different amines were rapidly (3-15 min) oxidized into the corresponding aldehydes (90 to 99 %) with only 1 to 5 equivalents of sodium pyruvate. The process was fully automated allowing for the in-line recovery of the pure aldehydes (chemical purity >99% and isolated yields above 80%), without any further work-up procedure.

**Introduction**

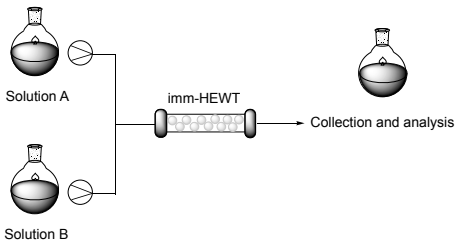
Aromatic aldehydes are important intermediates in a number of synthetic processes and have a prominent role as flavour and fragrance components. Among other synthetic methods,[1] they can be obtained by the corresponding primary aromatic amines, which are readily available substrates. Methods for the oxidation of amines to carbonyl compounds have received notable attention, but these approaches are frequently poorly sustainable, since they deliver wastes and by-products difficult to recycle, require drastic reaction conditions, and often proceed with poor selectivity.[1a,2] Biocatalytic processes are an interesting alternative for amine oxidations under mild and benign conditions. For example, copper amine oxidases (CAOs) have been used to catalyse the oxidation of primary amines to aldehydes (while $O_2$ is simultaneously reduced to $H_2O_2$).[3] Vanillin has been prepared by oxidation of vanillylamine using an amine oxidase (AO) from *Aspergillus niger*.[4] Recently, selective oxidation of amines to aldehydes has been obtained using a laccase and TEMPO as mediator and $O_2$ as oxidant.[5] Aromatic aldehydes can also be enzymatically prepared using other approaches, such as oxidation of primary alcohols[6] and reduction of carboxylic acids.[7]

In this context, we developed an efficient bio-preparation of nature-identical flavours and fragrances exploiting the immobilized amine transaminase from the moderate halophilic bacterium *Halomonas elongata* (HEWT),[8] able to tolerate a range of temperature, pH, salts and co-solvents in a continuous flow reactor. The combination of biocatalysis and flow reactor technology can be considered as an enabling methodology intrinsically compatible with the principles of green chemistry.[9] Flow-based biocatalysis was recently applied for peptide condensation,[10] hydrolysis and formation of esters and sugars,[11] stereoselective carbonyl reduction,[12] formation of C-C bond,[13] production of nucleosides,[14] monosaccharides,[15] and oligosaccharides,[16] and finally interconversion of carbonyls and amines using transaminases.[17]

We recently reported on the application of HEWT in flow for the bio-synthesis of amines[18] and we describe here an eco-friendly and scalable process which enhances the oxidizing capability of this covalently immobilized enzyme for the production of aldehydes. The products are aromatic aldehydes used as flavours and fragrances in food, beverage, cosmetics and pharmaceuticals. They have been obtained in excellent yields, with unprecedented reaction times when compared to traditional batch methods. The use of pyruvate as amino acceptor is extremely favourable and the generated by-product, alanine, is completely benign and can be easily recovered. Furthermore, this approach circumvents potential issues often encountered with whole cells biotransformations such as generation of debris, swelling and permeability.

**Results and Discussion**

The immobilization of pure HEWT (imm-HEWT) on an epoxy-resin was performed as reported by Planchestainer *et al.*[18] and the supported biocatalyst (5 mg/gram$_{resin}$) was then used in packed-bed flow reactor. The system was firstly tuned by optimizing the preparation of benzaldehyde starting from the corresponding benzylamine (Scheme 1).

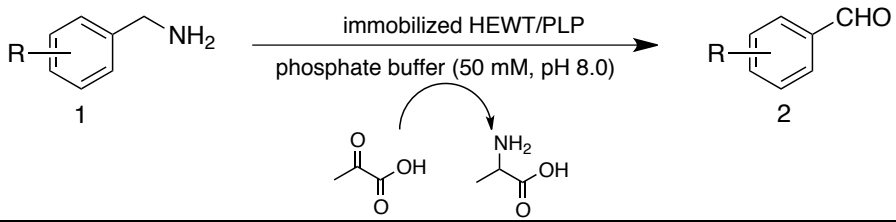


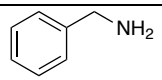
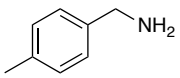
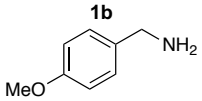
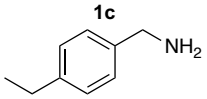
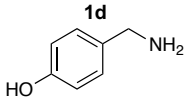
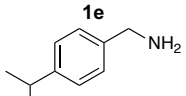

Scheme 1. Solution A: 20 mM solution of benzylamine in phosphate buffer (50 mM, pH 8.0) containing 10% DMSO. Solution B: 20 mM solution of pyruvate containing 0.1 mM PLP. T = 37 °C, P = atm.

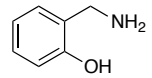
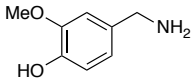
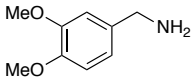
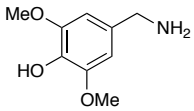
To maximise the solubility of the amine, 10% of DMSO was used as co-solvent in the phosphate buffer (50 mM, pH 8.0). The reaction was performed under optimized conditions at 37 °C, and atmospheric pressure with just one equivalent of pyruvate as the equilibrium for this reaction is extremely favourable; complete substrate oxidation (m.c. > 99%) was obtained with only 3 minutes of residence time (flow rate 0.3 mL/min).

Notably, the use of the same immobilized enzyme in batch gave a full oxidation in about 2 hours. The optimized conditions were applied to the bioconversion of different benzylamines into the corresponding flavour aldehydes (Table 1).

Table 1. Preparation of aromatic benzaldehyde derivatives from the corresponding amines. Reactions were performed in the presence of 10 mM substrates and pyruvate, 0.1 mM PLP, 10% DMSO was used as co-solvent at 37 °C. Isolated yields are reported in the Experimental Section. [a] Conversion rates are normalised to the amount of enzyme used in the reaction and calculated as reported in reference 11a. [b] Liquid-liquid-phase flow stream (see procedure summarized in Scheme 3), in this case DMSO was not added to the buffer.



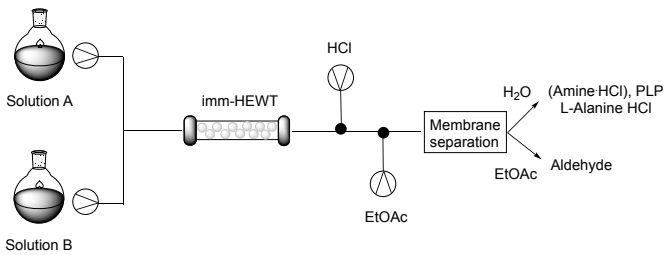

| Entry | Substrate | Reaction time (min) | M. c. (%) | Conv. Rate[a] (µmol/min g) | Residence time (min) | M. c. (%) | Conv. Rate[a] (µmol/min g) |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** | 120 | > 99 | 0.83 | 3 | > 99 | 4.24 |
| 2 |  **1b** | 120 | > 99 | 0.83 | 3 | > 99 | 4.24 |
| 3 |  **1c** | 120 | > 99 | 0.83 | 3 | > 99 | 4.24 |
| 4 |  **1d** | 120 | > 99 | 0.83 | 3 | > 99 | 4.24 |
| 5 |  **1e** | 120 | > 99 | 0.33 | 10 | > 99 | 1.41 |
| 6 |  **1f** | 300 | > 99 | 0.33 | 10 | 90 | 1.29 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 7 |  **1g** | 300 | > 99 | 0.33 | 10 | 90 | 1.29 |
| 8 |  **1h** | 120 | > 99 | 0.83 | 3 | 95 | 4.07 |
| 9 |  **1i** | 300 | > 99 | 0.33 | 10 | > 99[b] | 1.41[b] |
| 10 |  **1j** | 300 | > 99 | 0.33 | 10 | > 99[b] | 1.41[b] |

Specific reaction rates in the batch and continuous-flow systems were calculated using the equations reported in the Experimental Section; the time taken (conversion rate) for the reaction to reach maximum conversion, whether in batch or continuous-flow, were calculate and normalised to the amount of catalyst used for both set-ups.[11a]

Benzylamine-derivatives (entries 1-8) were oxidized into the corresponding aroma-compounds with high molar conversion; in all cases, a greater than 4-fold increase in rates was observed when reactions were carried out under flow conditions, since conversions ≥ 90% were reached within a residence time between 3 and 10 minutes (flow rate 0.3 mL/min and 0.1 mL/min respectively), at 37 °C and atmospheric pressure.

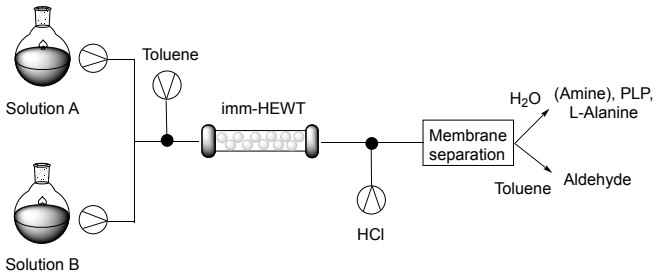
The process was implemented with the addition of an in-line acidification step followed by extraction with EtOAc. The two phases were continuously separated using a Zaiput liquid/liquid separator and the desired aldehydes were recovered in the organic phase, significantly accelerating the overall work up which did not require further purification (Scheme 2).




Scheme 2. Solution A: 20 mM solution of amines (entries 1-8) in phosphate buffer (50 mM, pH 8.0) with 10% DMSO. Solution B: 20 mM, solution of pyruvate containing 0.1 mM PLP. T = 37 °C, P = atm.

This protocol was successful applied to substrates **1a**-**1h**. Aldehydes obtained from substrates **1i** and **1j** (entries 9 and 10) proved initially difficult to recover as they were retained by the packing material, despite different and extensive washing steps.

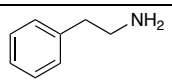
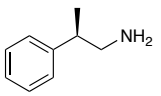
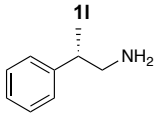
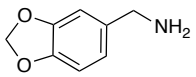
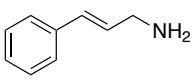
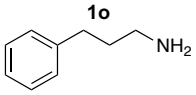
A liquid-liquid-phase reaction system was therefore set up, where toluene was flown into the system upstream of the packed column (Scheme 3). Upon acidification, downstream of the process, the products **2i** and **2j** were extracted in-line and recovered by membrane separation as pure compounds. Remarkably, the presence of toluene had no effect on the catalytic efficiency of the immobilized enzyme which was extensively utilized over several weeks.




Scheme 3. Solution A: 20 mM solution of amines (entries 9, 10 Table 1 or 14-16 Table 2) in phosphate buffer (50 mM, pH 8.0). Solution B: 20 mM, 40 mM or 100 mM solution of pyruvate containing 0.1 mM PLP. T = 37 or 45 °C, P = atm. Toluene is added at the same flow rate to form a 50:50 biphasic stream.

A second set of amines (**1k**-**1p**) was investigated with the same methodologies (either in a monophasic environment or the biphasic one) to prove the versatility of the system with different aromatic substrates. (Table 2).

Table 2. Preparation of aryl-alkyl aldehydes from the corresponding amines. Reactions were performed in the presence of 10 mM substrates and pyruvate, 0.1 mM PLP, 10% DMSO was used as co-solvent at 37 °C. Isolated yields are reported in the Experimental Section [a] Conversion rates are normalised to the amount of enzyme used in the reaction and calculated as reported in reference 11a. [b] Liquid-liquid-phase flow stream (see procedure summarized in Scheme 3), in this case DMSO was not added to the buffer. [c] Reactions performed at 45 °C. [d] 20 mM Pyruvate. [e] 50 mM pyruvate. [f] Calculated at a similar degree of conversion of the batch reaction

| Entry | Substrate | Reaction time (min) | M. c. (%) | Conv. Rate[a] (μmol/min g) | Residence time (min) | M. c. (%) | Conv. Rate[a] (μmol/min g) |
|---|---|---|---|---|---|---|---|
| **11** |  **1k** | 120 | > 99 | 0.83 | 3 | > 99 | 4.24 |
| **12** |  **1l** | 180 | > 99 | 0.55 | 3 | > 99 | 4.24 |
| **13** |  **1m** | 180 | > 99 | 0.55 | 3 | > 99 | 4.24 |
| **14[c]** |  **1n** | 1440 | > 99 | 0.07 | 15 | > 99[b] | 0.95[b] |
| **15[c]** |  **1o** | 1440 | 50 | 0.04 | 15 | > 99[b,d] | 1.02[b,d,f] |
| **16[c]** |  **1p** | 300 | 24 | 0.04 | 15 | 90[b,e] | 0.86[b,e,f] |

The batch oxidation of the tested (aryl)alkyl amines with methyl/ethyl side chain (entries 11-14) allowed for the preparation of flavour aldehydes **2k** (hyacinth note), **2j** (floral note), **2m** (floral note), and **2n** (violet note) with excellent conversion (>99%), however the reactions required several hours to go to completion. In line with what observed for the benzylamine derivatives, the same molar conversion was obtained within 3 to 15 minutes of residence time in flow, thus strongly increasing the overall productivity. In particular, piperonylamine (**1n**) was successfully converted into the corresponding aldehyde (piperonal **2n**, the violet fragrance, also known as heliotropin) in only 15 minutes (14-fold faster reaction rate) with >99% of conversion at 45 °C, demonstrating the good

stability and adaptability of this enzyme also at higher temperatures. Both (*S*) and (*R*)-2-pheny-1-propylamine (**1l** and **1m**, respectively) were accepted as substrates of HEWT. The enzyme equally converted both enantiomers and did not show any stereopreference for this particular molecule (entries 12 and 13).
However, the oxidation of cinnamylamine (**1o**, entry 15) to cinnamaldehyde (**2o**, cinnamon aroma) and hydrocinnamylamine (**1p**, entry 16) to hydrocinnamaldehyde (**2p**, honey aroma), appeared more challenging. The batch reaction, with an equimolar concentration of amino donor underwent poor conversion after 24 hours (50 and 52%) without any significant increase over a longer incubation time, likely due to an unfavourable equilibrium. Under flow conditions, with one equivalent of pyruvate, the conversions achieved were 50% and 25% respectively, despite lengthening the residence time to 30 min. To displace the equilibrium, the concentration of pyruvate was increased to 2 and 5 equivalents with respect to the aldehydes **1o** and **1p**, yielding 95% of cinnamaldehyde and 90% of the saturated aldehyde with 15 minutes of residence time at 45 °C. This result underlines that process control strategies (in our case optimization of stoichiometric ratio of the substrates) help to maximize the productivity of HEWT, by accelerating the reaction, while favouring the shift of the equilibrium to the side of product.

## Conclusions

A new biocatalytic method for the synthesis of aldehydes with extensive applications as components of flavours and fragrances was developed. This is the first example of a transaminase exploited in a flow chemistry reactor under highly favourable oxidizing conditions for the preparation of aromatic aldehydes, showing excellent adaptability and stability during the processes. The use of a flow-based approach allowed for dramatic accelerations of the reactions, with all the reaction tested occurring with isolated yields above 80% and very short residence times (3-15 min) of the substrates. This system required in the majority of cases only one equivalent of pyruvate as the amino acceptor, generating alanine as by-product. A successful implementation was achieved with an in-line extraction step, which permitted the recovery of the desired pure aldehydes in the organic stream and alanine in the aqueous one, with an extremely simplified work-up procedure and almost no manipulation. Due to the high local concentration of the (bio)catalyst and to the enhanced heat and mass transfer,[19] the combination between biocatalysis and flow chemistry reactors not only leads to significant reductions of reaction times and increased productivity, but it can be also considered a sustainable technology for the production of aldehydes commonly used in food, cosmetic, and pharmaceutical industry.

## Experimental Section

### Expression, purification, and immobilization of HEWT in *E. coli*

Protein expression and purification was performed following previously reported protocols in Cerioli *et al*.;[8] immobilization was carried out according to the procedure reported by Planchestainer *et al.*. [18]

### Batch reactions with immobilized HEWT

Batch reactions using the imm-HEWT were performed in 1.5 mL micro centrifuge tubes; 500 µL reaction mixture in 50 mM phosphate buffer pH 8.0, containing 10 mM pyruvate, 10 mM amino donor substrate, 0.1 mM PLP, and 50 mg of imm-HEWT (5 mg/g) was left under gentile shaking at 37 °C. 10 µL aliquots were quenched with trifluoroacetic acid (TFA) 0.2% every hour and then analyzed by HPLC equipped with a Supelcosil LC-18-T column (250 mm x 4.6 mm, 5 µm particle size; Supelco, Sigma-Aldrich, Germany). The compounds were detected using an UV detector at 210 nm, 250 nm or 280 nm after an isocratic run with 25% acetonitrile/75% water with TFA 0.1% v/v at 25

°C with a flow rate of 1 mL/min. The retention times in minutes are: benzylamine (4.1 min), benzaldehyde (9.4 min), *p*-methylbenzylmine (5.2 min), *p*-tolualdehyde (16.4 min), *p*-methoxylbenzylmine (4.4 min), *p*-anisaldehyde (10.3 min), *p*-ethylbenzylamine (5.0 min), *p*-ethylbenzaldehyde (16.5 min), *p*-hydroxybenzykamine (3.8 min), *p*-hydroxybenzaldehyde (10.5 min), *p*-isopropylbenzylmine (10.0 min), cuminaldehyde (35.0 min), 2-(aminomethyl)-phenol (3.7 min), salicilaldehyde (10.3 min), vanillylamine (3.7 min), vanillin (5.7 min), veratrylamine (4.1 min), veratraldehyde (8.0 min), 4-(aminomethyl)-2,6-dimethoxyphenol (3.5 min), syringaldehyde (5.4 min), 2-phenethylamine (3.9 min), phenylacetaldehyde (9.8 min), (*R*)-2-pheny-1-propylamine (4.3 min), (*S*)-2-phenyl-1-propylamine (4.3 min), 2-phenylpropanaldehyde (10.9 min), piperonylamine (4.2 min), piperonal (9.9 min), cinnamylamine (6.6 min), cinnamaldehyde (15.6 min), hydrocinnamylamine (5.1 min), hydrocinnamaldehyde (13.6 min), confirmed by comparison with commercially available compounds.

**Flow reactions with immobilized HEWT**

Continuous flow biotransformations were performed using a R2+/R4 Vapourtec® flow reactor equipped with an Omnifit® glass column (0.3421 mm i.d × 100 mm length) filled with 0.7 g of imm-HEWT (5 mg/g). A 20 mM sodium pyruvate in phosphate buffer (50 mM, pH 8.0) containing 0.1 mM PLP, and 20 mM amino donor solution with 10% of DMSO were prepared. The two solutions were mixed in a T-piece and the resulting flow stream was directed into the column packed with the biocatalyst (packed bed reactor volume: 1.0 mL). The flow rate was varied and optimized. An in-line acidification was performed by using an inlet of 1N HCl aqueous solution (flow rate: 0.1 mL/min) that was mixed to the exiting reaction flow stream using a T-junction. The resulting aqueous phase was extracted in-line using a stream of EtOAc (flow rate: 0.2 mL/min) and a Zaiput liquid/liquid separator. Both the organic and aqueous phase were analyzed by HPLC using the above reported conditions. The amount of substrate and product was evaluated by exploiting a previously prepared calibration curve. For the optimization procedure, the reactions have been performed by injecting 250 µL of each starting solutions (volume of EtOAc used for the in-line extraction: 1 mL). To isolate the product, 10 mL of each starting solutions have been used (volume of EtOAc used for the in-line extraction: 40 mL). The organic phase, containing the aldehyde, was evaporated to yield the desired product.

Specific reaction rates in batch and continuous-flow systems were calculated using the following equations:

$$r_{batch} = \frac{\eta_p}{t \, x \, m_B} \ (\mu mol / min \, g)$$

Where $[n_p]$ is the amount of product (expressed as µmol), *t* is the reaction time (expressed as min), and $m_B$ [g] is the amount of biocatalyst employed.

$$r_{flow} = \frac{[P] \, x \, f}{m_B} \ (\mu mol / min \, g)$$

Where [P] is the product concentration flowing out of the reactor (expressed as µmol $mL^{-1}$), f is the flow rate (expressed as mL $min^{-1}$), and $m_B$ [g] is the amount of biocatalyst loaded in the column.

Comparison of the rates of the same reaction in a batch or flow-mode was made at similar degrees of conversion.

**Flow reactions in liquid-liquid-phase systems with immobilized HEWT**

A 20, 40 or 100 mM pyruvate in phosphate buffer (50 mM, pH 8.0) containing 0.1 mM PLP, and 20 mM amino donor solution were prepared. The two solution were mixed in a T-piece. A second junction for additional supplement of toluene at the same flow rate was installed before the packed enzyme column. The resulting segmented flow stream was directed to the imm-HEWT. The flow rate was varied and optimized. After an in-line acidification step, as previously reported, the exiting flow stream was separated by a Zaiput liquid/liquid separator, the organic and aqueous phases analyzed by HPLC exploiting a calibration curve (see conditions above) and the toluene, containing the desired product, was evaporated to yield the aldehydes.

**Characterization of the products**

The purity of aldehydes was assessed by HPLC and $^1$H NMR. $^1$H NMR spectra were recorded with a Varian Mercury 300 (300 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm, and coupling constants (J) are expressed in Hz.

**Benzaldehyde (2a)**: colourless oil; yield 95%; $^1$H NMR ($CDCl_3$) δ 10.00 (s, 1H), 8.15-8.12 (m, 2H), 7.67-7.51 (m, 3H) ppm.

***p*-Tolualdehyde (2b)**: yellow oil; yield 96%; $^1$H NMR ($CDCl_3$) δ 9.95 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 2.40 (s, 3H) ppm.

***p*-Anisaldehyde (2c)**: colourless oil; yield 94%; $^1$H NMR ($CDCl_3$) δ 9.85 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H) ppm.

***p*-Ethyl benzaldhyde (2d)**: yellow oil; yield 94%; $^1$H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H) ppm.

***p*-Hydroxybenzaldehyde (2e)**: yellow solid; yield 92%; $^1$H NMR ($CDCl_3$): δ 9.61 (s, 1 H), 7.60 (d, *J* = 8.3 Hz, 2 H), 6.73 (d, *J* = 8.3 Hz, 2 H) ppm.

**Cuminaldehyde (2f)**: colourless oil; yield 84%; $^1$H NMR ($CDCl_3$) δ 9.98 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 3.00 (septet, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H) ppm.

**Salicilaldehyde (2g):** yellow oil; yield 82%; $^1$H NMR ($CDCl_3$) δ 11.00 (bs, 1H, OH), 9.85 (s, 1H), 7.46-7.54 (m, 2H), 6.94-7.00 (m, 2H) ppm.

**Vanillin (2h)**: white solid; yield 90%; $^1$H NMR ($CDCl_3$) *δ* 9.78 (s, 1H), 7.37–7.40 (m, 2H), 7.02 (d*, J* = 8.5 Hz, 1H), 6.72 (bs, 1H, OH), 3.90 (s, 3H) ppm.

**Veratrylaldehyde (2i)**: yellow solid; yield 96%; $^1$H NMR ($CDCl_3$) δ 9.85 (s, 1H), 6.70-7.65 (m, 3H), 3.98 (s, 3H), 3.95 (s, 3H) ppm.

**Syringaldehyde (2j)**: yellow solid; yield 94%; $^1$H NMR ($CDCl_3$) *δ* 9.83 (s, 1H), 7.15 (s, 2H), 6.10 (s, 1H), 3.98 (s, 6H) ppm.

**Phenylacetaldehyde (2k)**: pale yellol oil; yield 97%; $^1$H NMR ($CDCl_3$) δ 9.70 (t, *J* = 2.0 Hz, 1H), 7.30–7.10 (m, 5H), 3.56 (d, *J* = 2.0 Hz, 2H) ppm.

**2-Phenylpropanaldehyde (2l/2m)**: coulourless oil; yield 90%; $^1$H NMR ($CDCl_3$) *δ* 9.62 (s, 1H), 7.30-7.40 (m, 2H), 7.20-7.28 (m, 3H), 3.60 (q, *J* = 7.0, 1H), 1.45 (d, *J* = 7.0, 3H) ppm.

**Piperonal (2n)**: white solid; yield 87%; $^1$H NMR ($CDCl_3$) *δ* 9.80 (s, 1H), 7.40 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.32 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.07 (s, 2H) ppm.

***Trans*-Cinnamaldehyde (2o)**: yellow oil; yield 89% $^1$H NMR ($CDCl_3$) *δ* 9.70 (d, *J* = 7.7 Hz 1H), 7.55 (dd, *J* = 5.2, 2.0 Hz, 2H), 7.50 (d, *J* = 15.9 Hz, 1H), 7.42–7.46 (m, 3H), 6.73 (dd, *J* = 15.9, 7.7 Hz, 1H) ppm.

**Hydrocinnamaldehyde (2p)**: pale yellow oil: yield 86% $^1$H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.35 (q, *J* = 7.4 Hz, 2H), 7.25-7.30 (m, 3H), 3.00 (t, *J* = 15.1 Hz, 2H), 2.82-2.85 (m, 2H) ppm.

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