Electronic Supplementary Material (ESI) for Green Chemistry.


# Supporting Information

## Aerobic Oxidation of Vanillyl Alcohol to Vanillin Catalyzed by Air-Stable and Recyclable Copper Complex and TEPMO under Base-Free Conditions

Narayan Ch. Jana,[1] Subrat Sethi,[1] Ratnakar Saha,[1] and Bidraha Bagh*[1]

[1]School of Chemical Sciences, National Institute of Science Education and Research (NISER), HBNI, Bhubaneswar, PO Bhimpur-Padanpur, Via Jatni, District Khurda, Odisha, PIN 752050, India

*Corresponding author, E-mail: bidraha@niser.ac.in

Number of pages: 51

Number of figures: 38

Number of tables: 15

## Table of Contents

## General experimental

All experiments were performed in air unless noted otherwise. All solvents (acetonitrile, dichloromethane, diethyl ether, THF, ethyl acetate, acetone, methanol and ethanol) and chemicals (diphenylmethanol, cysteamine hydrochloride, boron trifluoride diethyl ether, copper (II) chloride, copper (II) perchlorate hexahydrate, sodium borohydride, pyridine-2-carboxaldehyde, TEMPO and vanillyl alcohol) were purchased from commercial suppliers and used without further purification. For recording NMR spectra, $CDCl_3$ was purchased from Sigma-Aldrich and used without further purification. $^1H$ and $^{13}C$ NMR spectra were recorded at Bruker AV-400 and JEOL-400 spectrometer ($^1H$ at 400 MHz and $^{13}C$ at 101 MHz). $^1H$ NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethylsilane (δ 0.00 ppm) and $^{13}C\{^1H\}$ NMR chemical shifts are referenced in ppm with respect to $CDCl_3$ (δ 77.16 ppm). The coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: bs = broad signal, s = singlet, d = doublet, t = triplet, q = quadtrate, m = multiplate. High resolution mass spectra were recorded on a Bruker micrOTOF-Q II Spectrometer. Elemental analysis was carried out on a EuroEA Elemental Analyser. Room temperature and low temperature EPR spectra at X-band frequency were obtained with a Bruker EMX (ER 073) system. UV-vis spectral studies were performed on a Perkin Elmer LAMBDA 730 spectrometer.

**Synthesis of 2-(benzhydrylthio)-ethanamine.** 2-(benzhydrylthio)-ethanamine was synthesized by adopting a literature method with slight modification.[S1]

Diphenylmethanol (1.842 g, 10.00 mmol) was dissolved in acetic acid (40 mL) under $N_2$ atmosphere. Cysteamine hydrochloride (1.128 g, 10.00 mmol) and $BF_3.OEt_2$ (1.402 g, 12.00 mmol) were added separately to the above solution under $N_2$ atmosphere. The resultant mixture was then stirred at 95°C for 1 hour on a preheated oil bath under $N_2$ atmosphere. The following

manipulations were done in air. The reaction mixture was cooled down to r.t. and diethyl ether was added which yielded white precipitate. The white solid was filtered, dried and kept over NaOH pellets for three days yielded 2-(benzhydrylthio)-ethanamine hydrochloride (2.744 g, 98%) as white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 4H), 7.25–7.22 (m, 4H), 7.15 (t, *J* = 7.3 Hz, 2H), 5.23 (s, 1H), 2.94 (t, *J* = 6.2 Hz, 2H), 2.53 (t, *J* = 6.2 Hz, 2H).

In the following step, HCl was removed from 2-(benzhydrylthio)-ethanamine hydrochloride. 2-(Benzhydrylthio)-ethanamine hydrochloride (2.798 g) was dissolve in saturated $NaHCO_3$ solution (100 mL) and extracted with chloroform (3 x 20 mL). The organic phase was dried over $Na_2SO_4$. All volatiles were evaporated under high vacuum to yield 2-(benzhydrylthio)-ethanamine (2.381 g, 98%) as light yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.47–7.40 (m, 4H), 7.35–7.27 (m, 4H), 7.26–7.18 (m, 2H), 5.16 (s, 1H), 2.81 (t, *J* = 6.3 Hz, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 1.64 (bs, 2H).

**Synthesis of N-(2-(benzhydrylthio) ethyl)-1-(pyridine-2-yl) methanimine ($L_1$).** A solution of 2-(benzhydrylthio)-ethanamine (0.972 g, 4.00 mmol) in methanol (20 mL) was added to a solution of pyridine-2-carboxaldehyde (0.428 g, 4.00 mmol) in methanol (10 mL) with continuous stirring. The resultant mixture was refluxed for 10 hours in a preheated oil bath. The solution was then cooled down to r.t. and all volatiles were removed under high vacuum to yield **$L_1$** (1.297 g, 98%) as a reddish brown oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.4 Hz, 1H), 8.35 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.75–7.71 (m, 1H), 7.44–7.42 (m, 4H), 7.33–7.27 (m, 5H), 7.24–7.19 (m, 2H), 5.26 (s, 1H), 3.83 (t, *J* = 6.3 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.05, 154.36, 149.59, 141.41, 136.64, 128.63, 128.44, 127.28, 124.91, 121.52, 60.95, 54.48, 32.91. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{21}N_2S$ 333.1425, Found 333.1417. Anal. Calcd. for $C_{21}H_{20}N_2S$ (332.46): C, 75.87; H,

6.06; N, 8.34; S, 9.64. Found: C, 75.71; H, 6.03; N, 8.10; S, 9.53. FTIR $\nu_{max}$ ($cm^{-1}$): 2800–3100 (C–H), 1646 (CH=N), 1410–1600 (C=N, py; C=C, ph), 600–710 (C–S).

**Synthesis of 2-(benzhydrylthio)-N-(pyridine-2-ylmethyl) ethan-1-amine ($L_2$).** A solution of $\mathbf{L_1}$ (1.328 g, 4.00 mmol) in methanol (30 mL) was cooled down to 0 ℃ in an ice-bath. Solid $NaBH_4$ (0.341 g, 9.00 mmol) was then added in small quantity to the solution at 0 ℃ under vigorous stirring. The resultant reaction mixture was stirred at 0 ℃ for another 10 minutes. Then the reaction mixture was warmed up to r.t. and stirred at r.t. for another 6 hours. Water (20 mL) was added to the reaction mixture and the mixture was extracted with dichloromethane (3 x 20 mL). Combined organic phase was dried over $Na_2SO_4$ and dried under high vacuum to get $\mathbf{L_2}$ (1.321 g, 99%) as brown oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.56–8.54 (m, 1H), 7.65–7.61 (m, 1H), 7.43–7.40 (m, 4H), 7.32–7.26 (m, 5H), 7.19–7.23 (m, 2H), 7.18–7.14 (m, 1H), 5.18 (s, 1H), 3.88 (s, 2H), 2.80 (t, $J$ = 6.6 Hz, 2H), 2.61 (t, $J$ = 6.6 Hz, 2H), 2.38 (bs, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.68, 149.38, 141.43, 136.64, 128.66, 128.41, 127.30, 122.34, 122.11, 54.75, 53.96, 47.88, 32.60. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{23}N_2S$ 335.1582, Found 335.1577. Anal. Calcd. for $C_{21}H_{22}N_2S$ (334.48): C, 75.41; H, 6.63; N, 8.38; S, 9.58. Found: C, 75.28; H, 6.63; N, 8.40; S, 9.48. FTIR $\nu_{max}$ ($cm^{-1}$): 3310 (N–H), 2750–3110 (C–H), 1405–1610 (C=N, py; C=C, ph), 600–720 (C–S).

**Synthesis of 1a.** A solution of $Cu(ClO_4)_2.6H_2O$ (0.093 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of $\mathbf{L_1}$ (0.166 g 0.50 mmol) in methanol (10 mL) at r.t. The mixture was stirred at r.t. for 10 min. Then the resulting mixture was refluxed for additional 1 h yielded a green solution. After cooling to r.t, the solution was collected after filtration. Slow evaporation of the solution at ambient conditions for two days gave green crystalline blocks. The crystals were collected after filtration, washed with cold methanol/ether (1:2) mixture and dried under high vacuum to give pure **1a** (0.206 g, 85%) as green solid. Note: Metal precursor

and ligand stoichiometric ratio of 1:1 also gave complex **1a**. HRMS (ESI-TOF) *m/z*: Calcd. for $[C_{42}H_{41}CuN_4S_2]^+$ $[M]^+$ 728.2069, Found 728.2097. Anal. Calcd. for $C_{42}H_{41}Cl_2CuN_4O_{8.5}S_2$ (937.37): C, 53.87; H, 4.41; N, 5.98; S, 6.85. Found: C, 53.58; H, 4.52; N, 6.80; S, 6.71. FTIR $\nu_{max}$ ($cm^{-1}$): 2880–3120 (C–H), 1650 (CH = N), 1405–1610 (C=N, py; C=C, ph), 1080 and 620 ($ClO_4^-$), 680–790 (C–S).

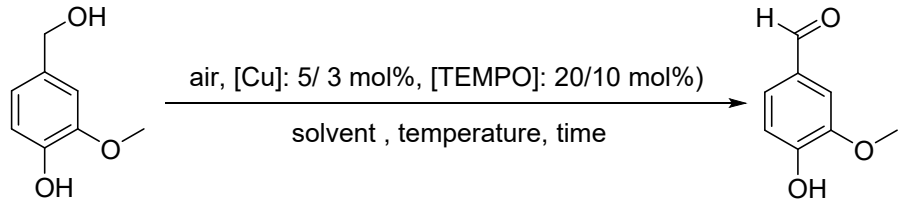
**Synthesis of 1b.** A solution of $Cu(ClO_4)_2.6H_2O$ (0.093 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of $\mathbf{L_2}$ (0.167 g 0.50 mmol) in methanol (10 mL) at r.t. The mixture was stirred at r.t. for 10 min. Then the resulting mixture was refluxed for additional 30 mins. The greenish-blue solution was filtered and cooled down to r.t. The solution was allowed to stand at r.t. for a day and light blue plates were obtained. The crystals were collected after filtration, washed with cold methanol/ether (1:2) and dried under high vacuum to give pure **1b** (0.186 g, 80%) as light blue solid. The light blue plates were suitable for single crystal X-ray analysis. Note: Metal precursor and ligand stoichiometric ratio of 1:1 also gave complex **1b**. HRMS (ESI-TOF) *m/z*: Calcd. for $[C_{42}H_{43}CuN_4S_2]^+$ $[M]^+$ 732.2382, Found 732.2353. Anal. Calcd for $C_{43}H_{48}Cl_2CuN_4O_9S_2$ (963.44): C, 53.61; H, 5.02; N, 5.82; S, 6.66. Found: C, 53.53; H, 5.07; N, 5.82; S, 6.75. FTIR $\nu_{max}$ ($cm^{-1}$): 3182 and 3270 (N–H), 2820–3100 (C–H), 1400–1610 (C=N, py; C=C, ph), 1079 and 620 ($ClO_4^-$), 675–780 (C–S).

**Synthesis of 2a.** A solution of $CuCl_2$ (0.033 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of $\mathbf{L_1}$ (0.083 g 0.25 mmol) in methanol (10 mL) at r.t. The mixture was stirred at r.t. for 10 min. Then the resulting mixture was refluxed for additional 1 h during which the color of the solution changed to apple green and green crystalline precipitate appeared. After cooling to r.t, the solid was collected after filtration and dried under high vacuum. The solid was dissolved in DMF (1.0 mL) and slow diffusion of diethyl ether into the DMF solution gave green crystalline plates. The crystals were collected after filtration, washed

with cold methanol/ether (1:2) mixture and dried under high vacuum to give pure **2a** (0.100 g, 86%) as green solid. The green plates were suitable for single crystal X-ray analysis. HRMS (ESI-TOF) *m/z*: Calcd for $[C_{21}H_{20}CuN_2S]^+$ $[M-2Cl]^+$ 395.0643, Found 395.0617. Anal. Calcd. for $C_{42}H_{40}Cl_4Cu_2N_4S_2$ (933.82): C, 54.02; H, 4.32; N, 6.00; S, 6.87. Found: C, 53.97; H, 4.30; N, 6.03; S, 6.89. FTIR $\nu_{max}$ ($cm^{-1}$): 2885–3110 (C–H), 1638 (CH=N), 1410–1610 (C=N, py; C=C, ph), 680–785 (C–S).

**Synthesis of 2b.** A solution of $CuCl_2$ (0.033 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of $\mathbf{L_2}$ (0.084 g 0.25 mmol) in methanol (10 mL) at r.t. The mixture was stirred at r.t. for 10 min. Then the resulting mixture was refluxed for additional 30 mins. The solution was filtered and cooled down to r.t. The solution was allowed to stand at r.t. for 16 h and bluish-green block-shaped crystals were obtained. The crystals were collected after filtration, washed with cold methanol/ether (1:2) and dried under high vacuum to give pure **2b** (0.096 g, 82%) as bluish-green solid. The bluish-green blocks were suitable for single crystal X-ray analysis. HRMS (ESI-TOF) *m/z*: Calcd. for $[C_{21}H_{22}ClCuN_2S]^+$ $[M-Cl]^+$ 432.0488, Found 432.0493. Anal. Calculated. for $C_{21}H_{22}Cl_2CuN_2S$ (468.93): C, 53.79; H, 4.73; N, 5.97; S, 6.84. Found: C, 53.93; H, 4.85; N, 6.09; S, 6.91. FTIR $\nu_{max}$ ($cm^{-1}$): 3244 (N–H), 2875–3120 (C–H), 1400–1620 (C=N, py; C=C, ph), 675–785 (C–S).

**General conditions for the catalytic oxidation of vanillyl alcohol to vanillin.**




All manipulations were performed in air. Vanillyl alcohol (0.077 g, 0.50 mmol), copper complex **1a**/ **1b**/ **2a**/ **2b** (5/ 3 mol%) and TEMPO radical (20/ 10 mol%) were weighed and

placed in a vial (10 mL). Thereafter, 2 mL pure solvent/ solvent mixture was added. The resultant mixture was heated at appropriate temperature (25/ 40/ 50/ 70/ 100 °C) in a preheated oil bath for appropriate time (3/ 6/ 9/ 12/ 15/ 16/ 18/ 20/ 24/ 30/ 36 h). Thereafter, the mixture was cooled down to r.t. (and occasionally GC was measured from the mixture). The mixture was dried under vacuum (using rotary evaporator). Ethyl acetate (5 mL) was added and the mixture was passed through a short bed of silica gel. The resultant solution was dried under high vacuum and the product was dissolved in $CDCl_3$ (0.5 mL). The solution was transferred in a NMR tube. Required amount of THF (40.6 μL, 0.50 mmol) as external standard was added to the $CDCl_3$ solution and $^1H$ NMR spectrum was recorded. Occasionally the $CDCl_3$ solution was dried under high vacuum and the product vanillin was purified by column chromatography. Note: In case of complete conversion of vanillyl alcohol, further purification using column chromatography was not required.

**Note:** Isolated yield and conversion were calculated as following:

**Isolated yield:**

$$\text{Isolated yield} = \frac{\text{weight of isolated vanillin/molecular weight of vanillin}}{\text{weight of vanillyl alcohol used/molecular weight of vanillyl alcohol}} \times 100\%$$

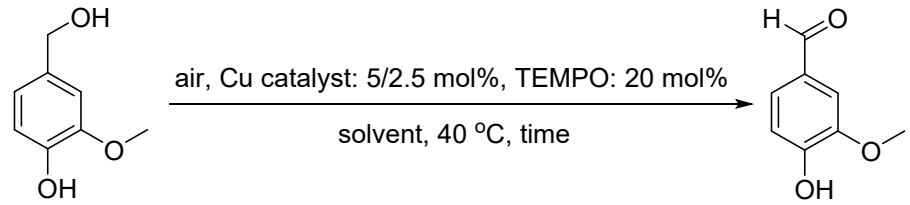
$$= \frac{\text{moles of isolated vanillin}}{\text{moles of used vanillyl alcohol}} \times 100\%$$

$$\text{For example, isolated yield} = \frac{1.520 \text{ g}/152.15 \text{ g/mol}}{1.541 \text{ g}/154.17 \text{ g/mol}} \times 100\% = \frac{10 \text{ mmol}}{10 \text{ mmol}} \times 100\% = 100\%$$

**Conversion:** Besides a few gram scale synthesis, 0.5 mmol vanillin was used for all other catalytic studies. 0.5 mmol THF was used as standard. For conversion calculation, following characteristic resonances of THF, vanillyl alcohol and vanillin was used: THF: $CH_2$ peak (four protons) at 1.58 ppm, vanillyl alcohol: benzyl peak (two protons) at 4.58 ppm and vanillin:

aldehyde peak (one proton) at 9.79 ppm. The integrations were done of the above resonances and ratio of one proton for three peaks of those compounds (THF, vanillyl alcohol and vanillin) were calculated, which was converted into conversion in percentage. The above ratio gives how much vanillyl alcohol is unreacted and how much vanillyl alcohol is converted to vanillin.

**Table 1:** Catalytic performance of **1a**, **1b**, **2a** and **2b** for the aerobic oxidation of vanillyl alcohol to vanillin.[a]




| Ent | Cu (mol%) | TEMPO (mol%) | Temp. (°C) | Time (h) | Solvent (1:1 mixture) | Conv.[b] (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** (5) | 20 | 40 | 6 | MeCN | 6 (6[c]) |
| 2 | **1b** (5) | 20 | 40 | 6 | MeCN | 6 (5[c]) |
| 3 | **2a** (2.5) | 20 | 40 | 6 | MeCN | 24 (21[c]) |
| 4 | **2b** (5) | 20 | 40 | 6 | MeCN | 34 (32[c]) |
| 5 | **1a** (5) | 20 | 40 | 3 | water | 6 |
| 6 | **1b** (5) | 20 | 40 | 3 | water | 8 |
| 7 | **2a** (2.5) | 20 | 40 | 3 | water | 26 (24[c]) |
| 8 | **2b** (5) | 20 | 40 | 3 | water | 34 (33[c]) |
| 9 | **1a** (5) | 20 | 40 | 6 | ethanol | 5 |
| 10 | **1b** (5) | 20 | 40 | 6 | ethanol | 6 |
| 11 | **2a** (2.5) | 20 | 40 | 6 | ethanol | 25 (23[c]) |
| 12 | **2b** (5) | 20 | 40 | 6 | ethanol | 32 (30[c]) |
| 13 | **1a** (5) | 20 | 40 | 6 | acetone | <5 |
| 14 | **1b** (5) | 20 | 40 | 6 | acetone | <5 |
| 15 | **2a** (2.5) | 20 | 40 | 6 | acetone | 13 |
| 16 | **2b** (5) | 20 | 40 | 6 | acetone | 16 |
| 17 | **1a** (5) | 20 | 40 | 6 | THF | 6 |
| 18 | **1b** (5) | 20 | 40 | 6 | THF | 7 |
| 19 | **2a** (2.5) | 20 | 40 | 6 | THF | 26 (23[c]) |
| 20 | **2b** (5) | 20 | 40 | 6 | THF | 31 (30[c]) |

[a]Reactions conducted in a vial (10 ml) with 0.50 mmol of vanillyl alcohol, 5/2.5 mol% of Cu-cat and 20 mol% of TEMPO (16 mg) in 2 mL of solvent at 40 °C. [b]Conversions of vanillyl alcohol to vanillin were determined by $^1$H NMR spectroscopy using THF (0.50 mmol) as external standard. [c]Isolated yields.

**General conditions for gram scale synthesis of vanillin from vanillyl alcohol.** A mixture of vanillyl alcohol (1.541 g, 10.00 mmol), copper complex **2b** (3/ 5 mol%) and TEMPO radical (10/ 20 mol%) in 1:1 mixture of solvents (40 mL) was heated at 40/ 70 °C in a preheated oil bath for appropriate time. Following reaction conditions were used for six methods: Method A: **2b**, 5 mol%, TEMPO, 20 mol%, acetone/water (1:1), 40 °C, 12 h; Method B: **2b**, 3 mol%, TEMPO, 10 mol%, acetone/water (1:1), 40 °C, 20 h; Method C: **2b**, 5 mol%, TEMPO, 20 mol%, ethanol/water (1:1), 40 °C, 15 h; Method D: **2b**, 3 mol%, TEMPO, 10 mol%, ethanol/water (1:1), 40 °C, 24 h; Method E: **2b**, 3 mol%, TEMPO, 10 mol%, ethanol/water (1:1), 70 °C, 16 h; Method F: **2b**, 5 mol%, TEMPO, 20 mol%, THF/water (1:1), 40 °C, 15 h. The resultant reaction mixture was cooled down to room temperature and dried under high vacuum followed by the addition of water (30 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over $Na_2SO_4$. The solution was dried under high vacuum to give pure vanillin (**A.** 1.518 g, 100%, **B.** 1.520 g, 100%; **C.** 1.521 g, 100%; **D.** 1.516 g, 100%; **E.** 1.518 g, 100% and **F.** 1.515 g, 100%). Pure vanillin was characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.46–7.37 (m, 2H), 7.06–6.99 (m, 1H), 6.49 (s, 1H), 3.93 (s, 3H). $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 191.12, 151.90, 147.32, 129.92, 127.65, 114.56, 108.97, 56.20.

**General conditions for catalyst recycle.** A mixture of vanillyl alcohol (1.541 g, 10.00 mmol), copper complex **2b** (3/ 5 mol%) and TEMPO radical (10/ 20 mol%) in 1:1 mixture of solvents (40 mL) was heated at 40/ 70 °C in a preheated oil bath for appropriate time. Following reaction conditions were used for six methods: Method A: **2b**, 5 mol%, TEMPO, 20 mol%, acetone/water (1:1), 40 °C, 12 h; Method B: **2b**, 3 mol%, TEMPO, 10 mol%, acetone/water (1:1), 40 °C, 20 h; Method C: **2b**, 5 mol%, TEMPO, 20 mol%, ethanol/water (1:1), 40 °C, 15 h; Method D: **2b**, 3 mol%, TEMPO, 10 mol%, ethanol/water (1:1), 40 °C, 24 h; Method E: **2b**, 3 mol%, TEMPO, 10 mol%, ethanol/water (1:1), 70 °C, 16 h; Method F: **2b**, 5 mol%, TEMPO,

20 mol%, THF/water (1:1), 40 °C, 15 h. The resultant reaction mixture was cooled down to room temperature and dried under high vacuum followed by the addition of water (30 mL). The organic product was extracted with ethyl acetate (3 x 10 mL). The catalysts **2b** stays in water phase. The combined organic phase was dried over $Na_2SO_4$. The solution was dried under high vacuum to give pure vanillin. Thereafter, the volume of the aqueous phase was reduced to 20 mL followed by the addition of vanillyl alcohol (1.541 g, 10.00 mmol), TEMPO radical (10/ 20 mol%) and solvent (acetone/ ethanol/ THF: 20 mL). The mixture was heated at 40/ 70 °C in a preheated oil bath for appropriate time. The resultant reaction mixture was cooled down to room temperature and dried under high vacuum followed by the addition of water (30 mL). The organic was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried over $Na_2SO_4$. The solution was dried under high vacuum to give pure vanillin. The entire process was repeated thrice. Thus, complex **2b** was recycled three times and no change in catalytic activity was observed. **Note:** Recycled catalyst **2b** was dried and dissolved in minimum amount of $CHCl_3$. Slow evaporation of the $CHCl_3$ solution gave crystals which were analysed by single crystal X-ray analysis. And it confirmed the unaltered identity of **2b**.

**General conditions for reactions at various concentration of vanillyl alcohol**: A mixture of vanillyl alcohol (0.25/ 0.50/ 0.75/ 1.00/ 1.25/ 1.50/ 2.0 mmol), **2b** (3 mol%) and TEMPO (10 mol%) in 1:1 mixture of acetone/water (2 mL) was heated at 40 °C in a preheated oil bath for 20 h. The resultant reaction mixture was cooled down to r.t. and dried under high vacuum followed by the addition of water (30 mL). The mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic phase was dried under high vacuum. The product was dissolved in $CDCl_3$ (0.5 mL). Required amount of THF as standard was added and $^1H$ NMR spectrum was recorded. Finally, the $CDCl_3$ solution was dried under high vacuum and the product vanillin was purified by column chromatography.

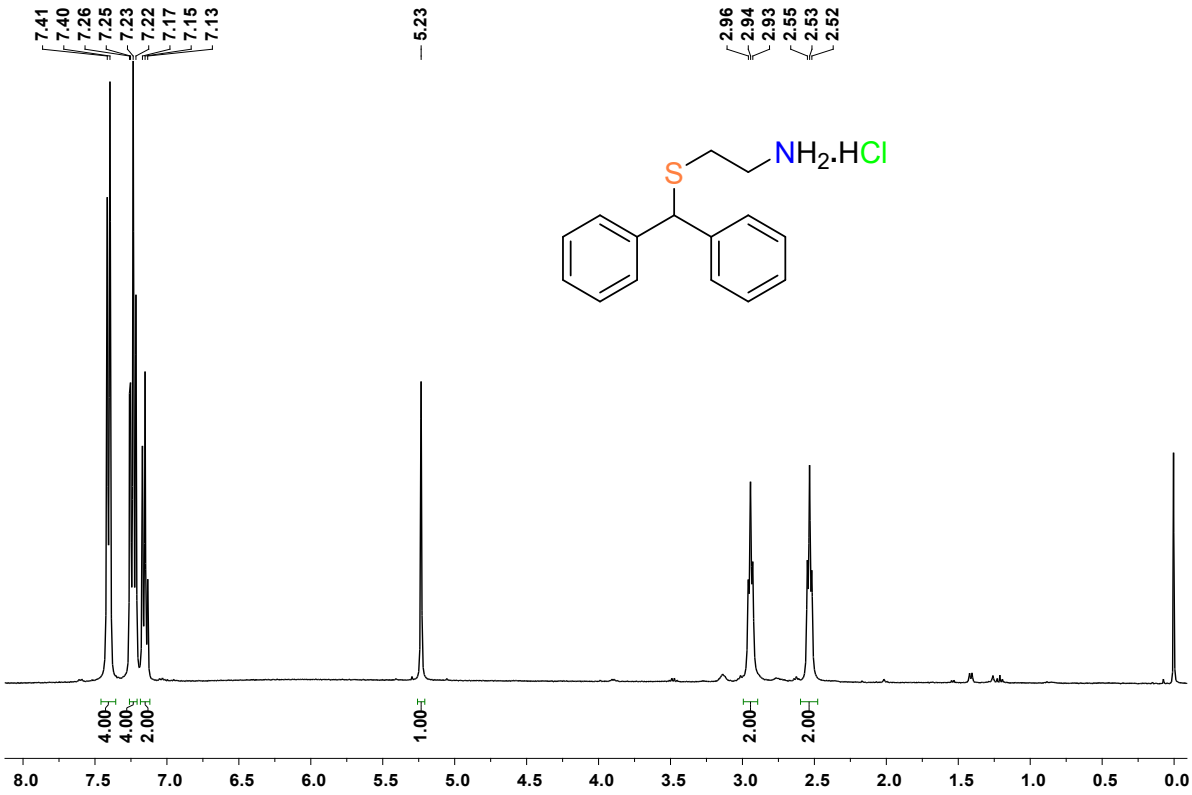



**Figure S1.** $^{1}$H NMR of 2-(benzhydrylthio)-ethanamine hydrochloride in $CDCl_3$ at r.t.

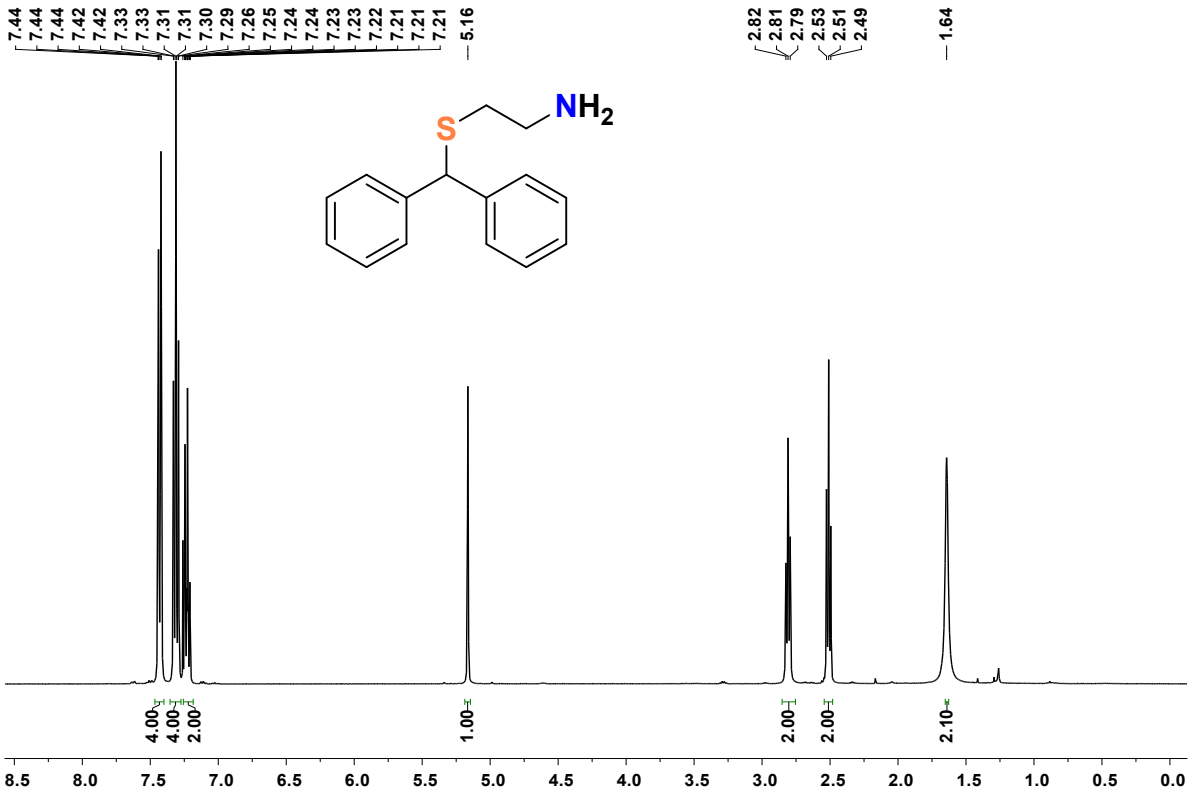



**Figure S2:** $^{1}$H NMR of 2-(benzhydrylthio)-ethanamine in $CDCl_3$ at r.t.

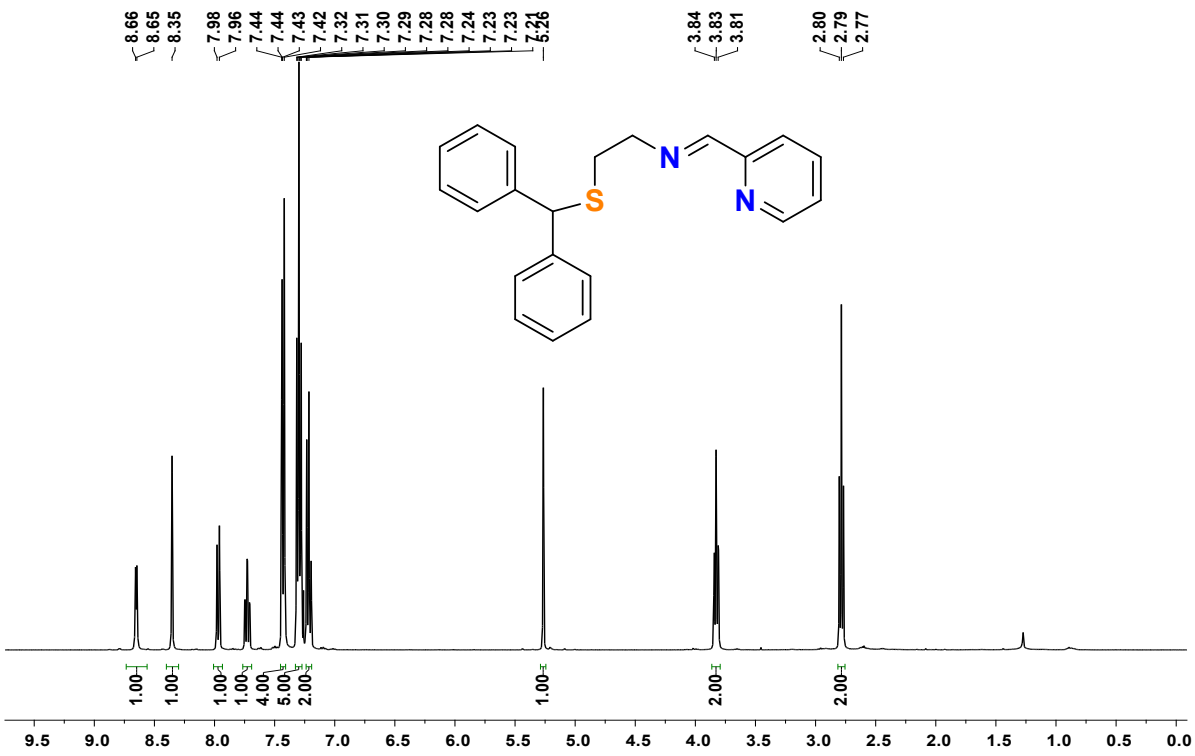



**Figure S3:** $^{1}$H NMR of N-(2-(benzhydrlthio) ethyl)-1-(pyridine-2-yl) methanimine (**$L_1$**) in $CDCl_3$ at r.t.

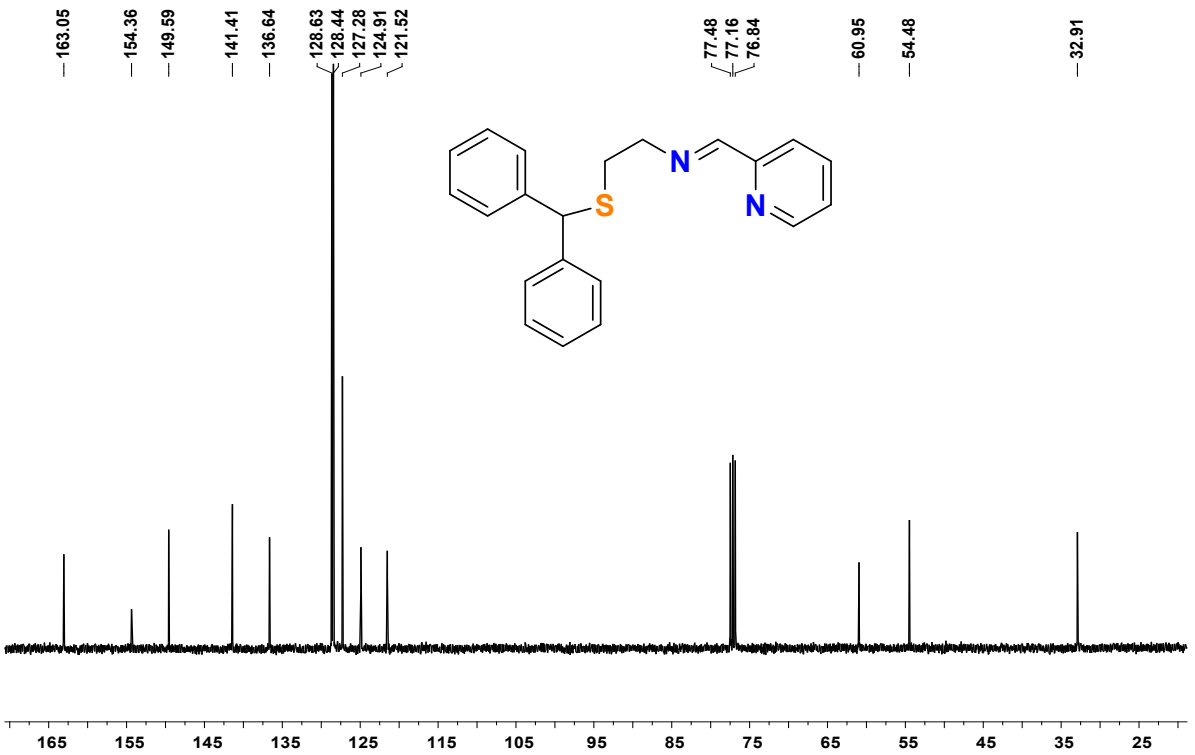



**Figure S4**: $^{13}$C NMR of N-(2-(benzhydrlthio) ethyl)-1-(pyridine-2-yl) methanimine (**$L_1$**) in $CDCl_3$ at r.t.

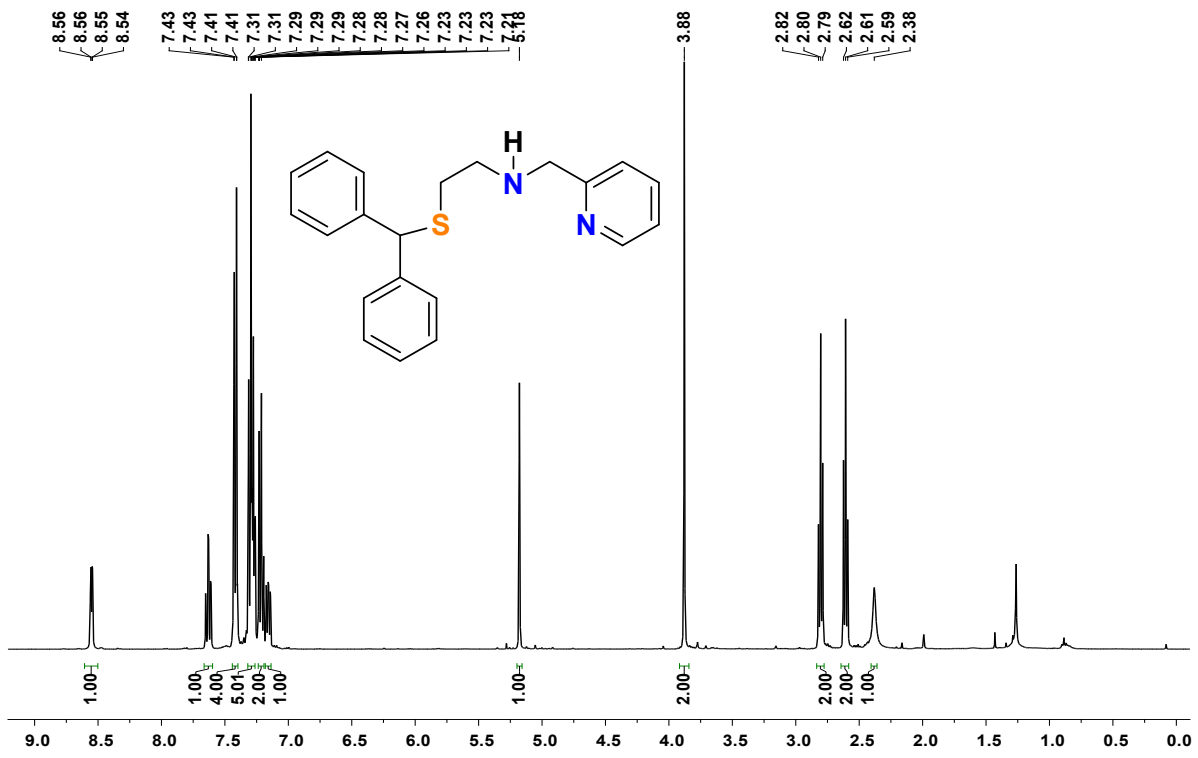



**Figure S5:** $^{1}$H NMR of 2-(benzhydrylthio)-N-(pyridine-2-ylmethyl) ethan-1-amine (**$L_2$**) in $CDCl_3$ at r.t.

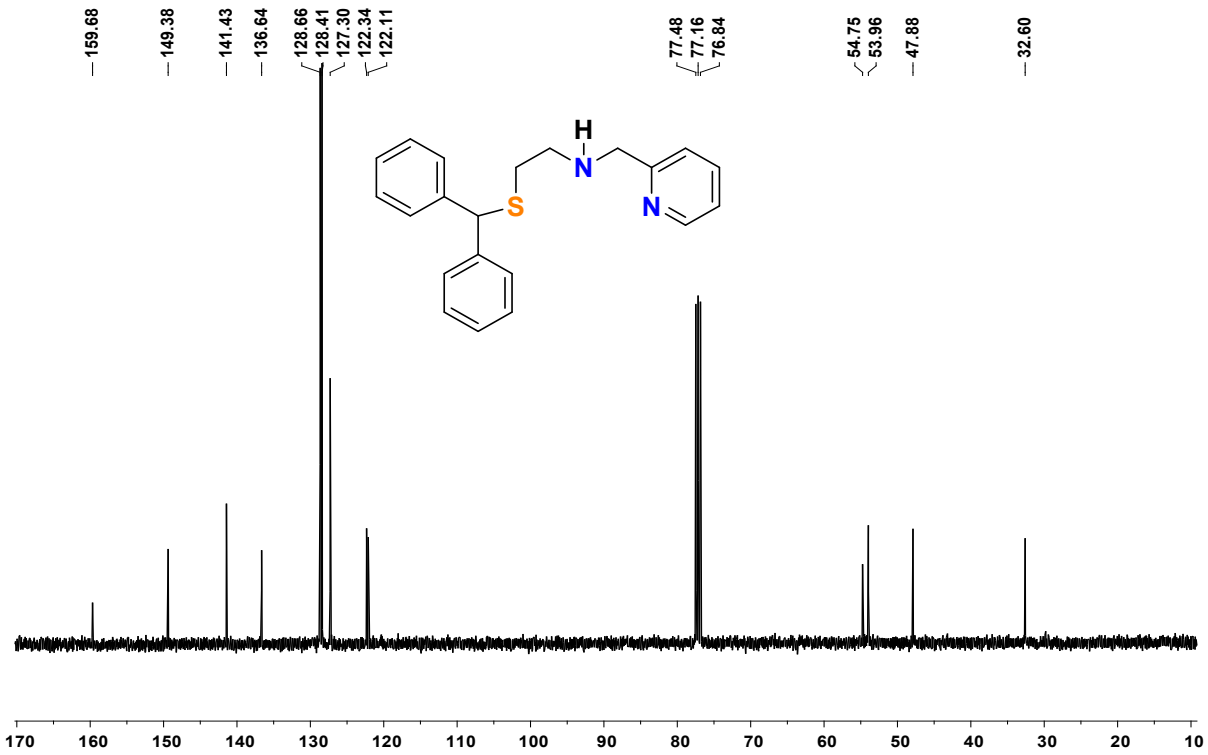



**Figure S6:** $^{13}$C NMR of 2-(benzhydrylthio)-N-(pyridine-2-ylmethyl) ethan-1-amine (**$L_2$**) in $CDCl_3$.

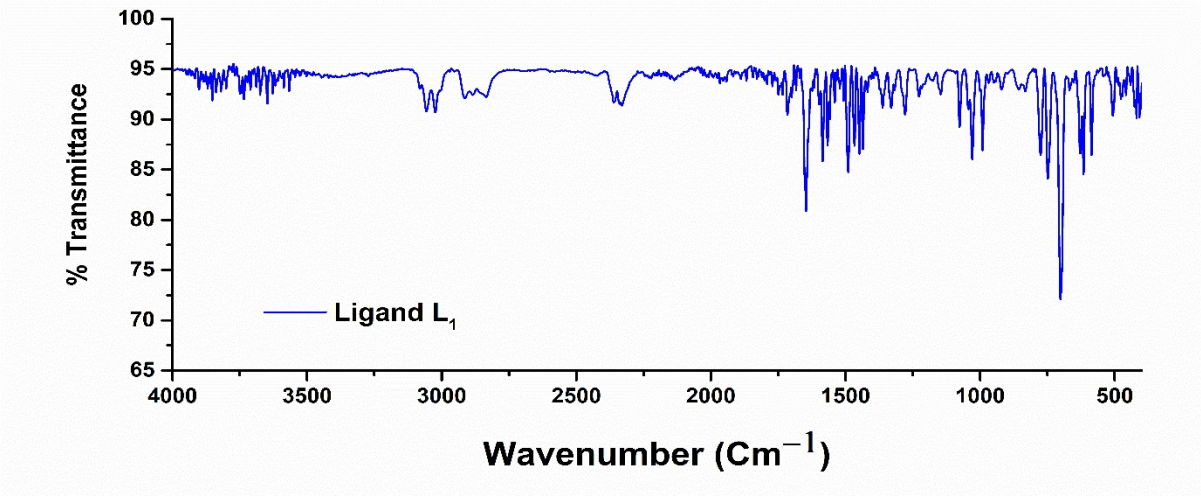



**Figure S7**: FTIR Spectrum of Ligand $\mathbf{L_1}$.

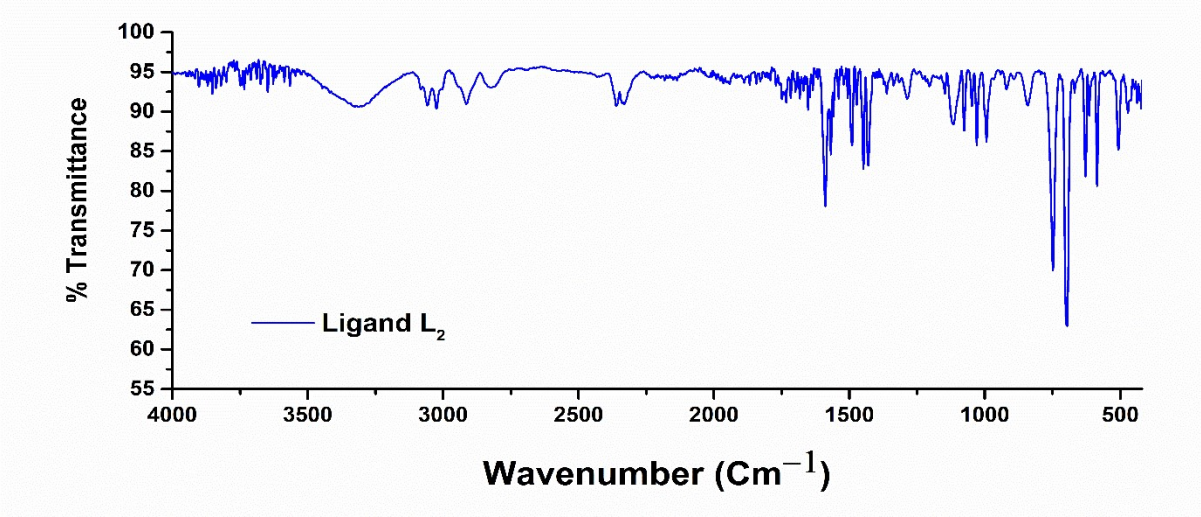



**Figure S8**: FTIR Spectrum of Ligand $\mathbf{L_2}$.

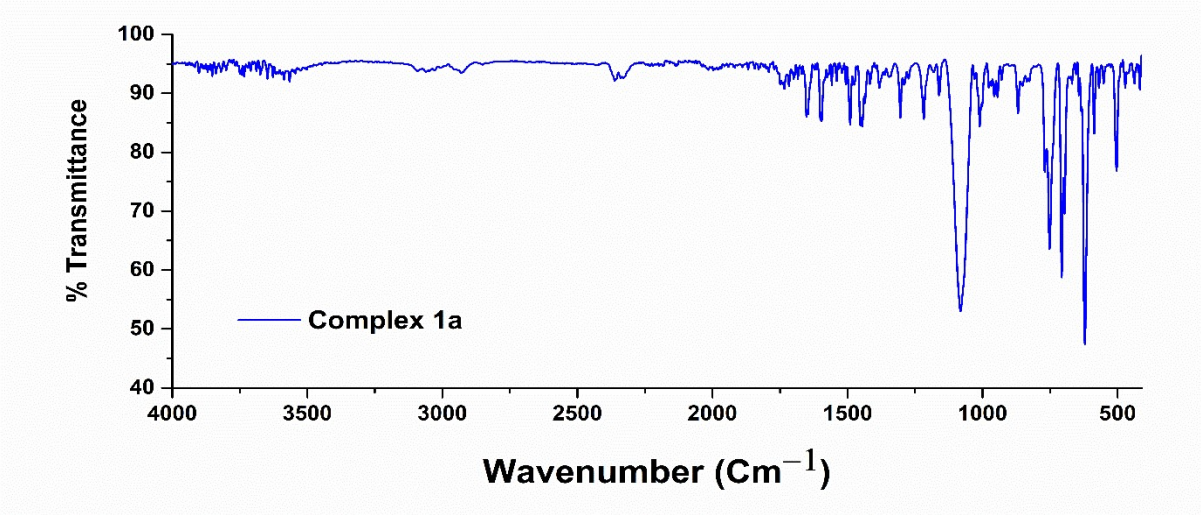



**Figure S9**: FTIR Spectrum of Complex **1a**.

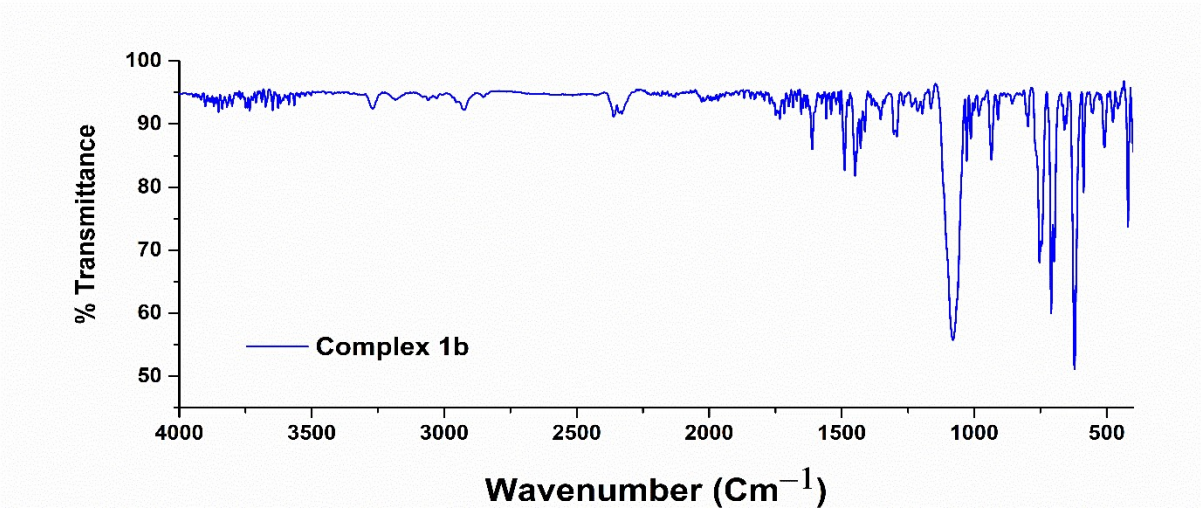



**Figure S10**: FTIR Spectrum of Complex **1b**.

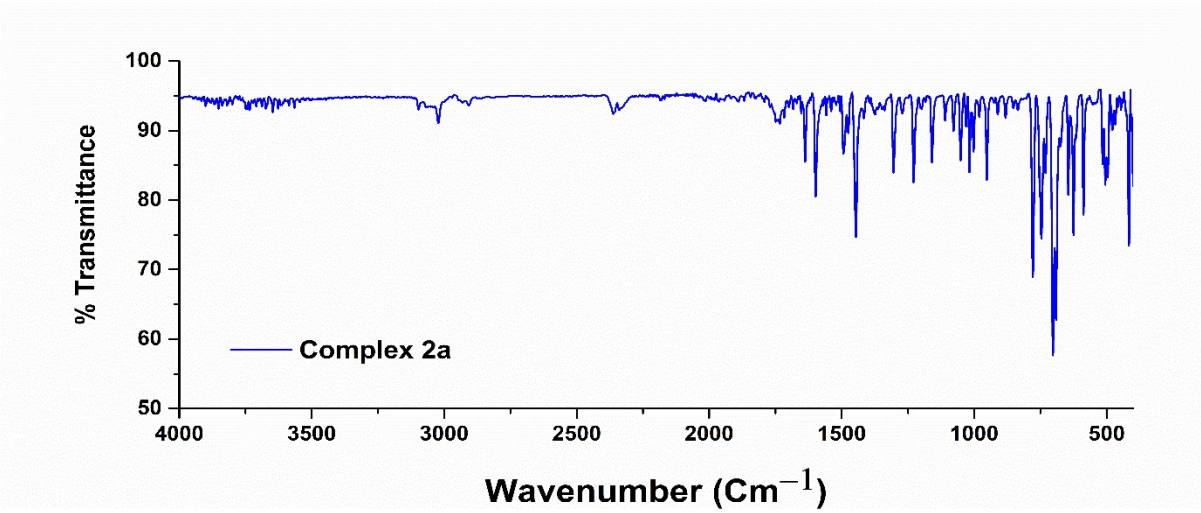



**Figure S11**: FTIR Spectrum of Complex **2a**.

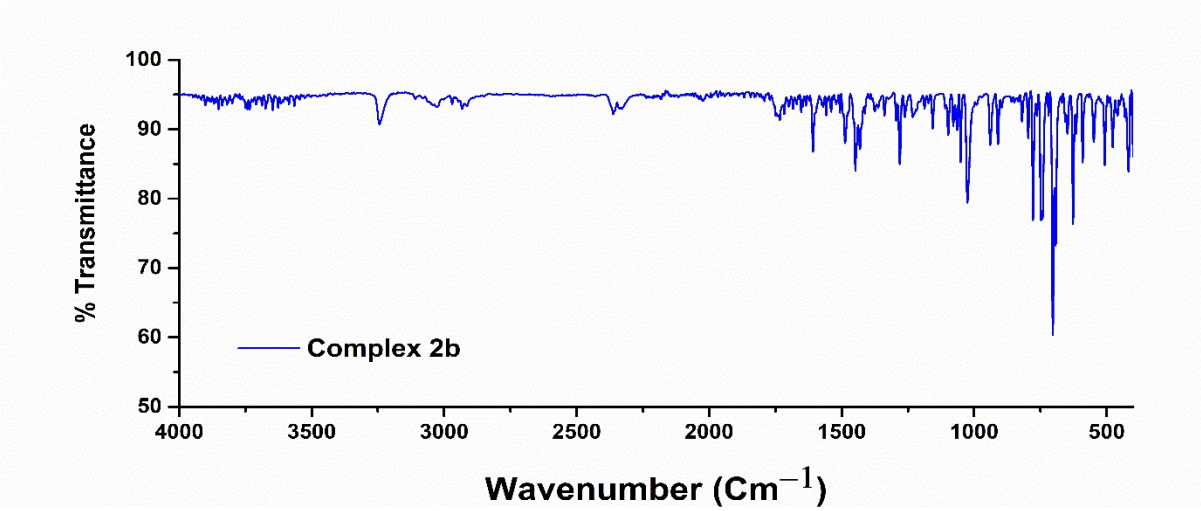



**Figure S12**: FTIR Spectrum of Complex **2b**.

## Molecular structure determination by single crystal X-ray crystallography

A crystal of complex **1a**, **1b**, **2a**, **2b** and **2b** (recycled) with accession code CCDC 2088325, 2088326, 2088327, 2088328 and 2088330 were mounted in air at ambient conditions. All measurements were made on an *Oxford Diffraction SuperNova* area-detector diffractometer[S2] using an INCOATEC micro source (Cu-Kα radiation, λ = 1.54 Å, multilayer optics) and Al filtered.[S3] The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of reflections in the range $2.1 < \theta < 26.4°$. A total of 1090 frames were collected using ω scans, with 30+30 seconds exposure time, a rotation angle of 1.0° per frame, a crystal-detector distance of 65.0 mm.

Data reduction was performed using the *CrysAlisPro*[S2] program. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method using SCALE3 ABSPACK in *CrysAlisPro*[S2] was applied. Data collection and refinement parameters are given in Table 1.

The structure was solved by direct methods using *SHELXT*[S4], which revealed the positions of all non-hydrogen atoms of the title compound. The non-hydrogen atoms were refined anisotropically. All H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2Ueq of its parent atom.

Refinement of the structure was carried out on *F*[S3] using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)$ [S3]. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. All calculations were performed using the *SHELXL-2016/6*[S5] program.

**Table S2.** Crystallographic Data and Refinement Parameters for **1a**, **1b**, **2a**, **2b** and **2b** (recycled).

| | **1a** | **1b** | **2a** | **2b** | **2b** (recycled) |
|---|---|---|---|---|---|
| Empirical formula | $C_{42}H_{40}Cl_2CuN_4O_{8.5}S_2$ | $C_{43}H_{48}Cl_2CuN_4O_9S_2$ | $C_{42}H_{40}Cl_4Cu_2N_4S_2$ | $C_{21}H_{22}Cl_2CuN_2S$ | $C_{22}H_{23}Cl_5CuN_2S$ |
| CCDC | 2088325 | 2088326 | 2088327 | 2088328 | 2088330 |
| Formula weight (g $mol^{-1}$) | 935.34 | 963.41 | 933.78 | 468.90 | 588.27 |
| Temperature | 297(2) | 293(2) | 100.00(10) | 293(2) | 100(10) |
| Wavelength | 1.54184 | 1.54184 | 1.54184 | 1.54184 | 1.54184 |
| Crystal system | Monoclinic | Monoclinic | Triclinic | Monoclinic | Orthorhombic |
| Space group | *I*2/a | $P2_1/c$ | $P\bar{1}$ | $P2_1/c$ | *P*bca |
| *a* (Å) | 21.1362(6) | 15.46340(11) | 8.7543(2) | 17.0171(3) | 19.10688(11) |
| *b* (Å) | 11.2833(2) | 16.54964(10) | 8.91433(17) | 9.22230(10) | 9.75754(6) |
| *c* (Å) | 38.192(2) | 18.85843(14) | 14.2328(6) | 13.3042(2) | 26.37158(16) |
| $\alpha$ (deg) | 90 | 90 | 92.973(3) | 90 | 90 |
| $\beta$ (deg) | 104.463(4) | 111.1946(8) | 97.234(3) | 96.124(2) | 90 |
| $\gamma$ (deg) | 90 | 90 | 113.730(2) | 90 | 90 |
| volume ($Å^3$) | 8819.7(6) | 4499.68(6) | 1002.26(6) | 2076.00(5) | 4916.61(5) |
| Z | 1 | 4 | 2 | 4 | 8 |
| $D_{calc}$ (g $cm^{-3}$) | 1.407 | 1.422 | 1.547 | 1.500 | 1.589 |
| $\mu$ ($mm^{-1}$) | 3.172 | 3.130 | 5.022 | 4.849 | 7.156 |
| *F*(000) | 3856 | 2004 | 478 | 964 | 2392 |
| Crystal Size | 0.3 × 0.2 × 0.1 $mm^3$ | 0.4 × 0.3 × 0.2 $mm^3$ | 0.12 × 0.11 × 0.1 $mm^3$ | 0.3 × 0.2 × 0.1 $mm^3$ | 0.2 × 0.1 × 0.1 $mm^3$ |
| $\theta$ Range (deg) | 4.096−68.248 | 3.668−68.247 | 5.456−68.249 | 5.228−68.232 | 3.352−68.250 |
| Index Ranges | -24 ≤ h ≤ 25, -12 ≤ k ≤ 13, -45 ≤ l ≤ 46 | -18 ≤ h ≤ 15, -19 ≤ k ≤ 19, -21 ≤ l ≤ 22 | -10 ≤ h ≤ 10, -10 ≤ k ≤ 8, -17 ≤ l ≤ 17 | -20 ≤ h ≤ 19, -11 ≤ k ≤ 11, -16 ≤ l ≤ 16 | -23 ≤ h ≤ 23, -10 ≤ k ≤ 11, -31 ≤ l ≤ 28 |
| Reflections collected | 60471 | 66480 | 14701 | 29160 | 83189 |
| Independent reflections ($R_{int}$) | 8076 (0.1078) | 8238 (0.0439) | 3667(0.0485) | 3790(0.0828) | 4495(0.1195) |
| Completeness to theta = $66.97^0$ | 99.94 | 99.96 | 99.93 | 99.95 | 99.96 |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| Data/Restraints/parameters | 8076/0/575 | 8238/2/557 | 3667/0/244 | 3790/0/244 | 4495/0/280 |
| Goodness-of-fit on *F*2 | 1.058 | 1.083 | 1.194 | 1.042 | 1.098 |
| Final *R* indices [I>2σ(I)] | $R_1$ =0.1106, w$R_2$=0.2839 | $R_1$ =0.0734, w$R_2$=0.2103 | $R_1$ =0.0853, w$R_2$=0.2628 | $R_1$ =0.0406, w$R_2$=0.1082 | $R_1$ =0.0513, w$R_2$=0.0988 |
| *R* indices (all data) | $R_1$ =0.1247, w$R_2$=0.2952 | $R_1$ =0.0764, w$R_2$=0.2132 | $R_1$ =0.0873, w$R_2$=0.2633 | $R_1$ =0.0423, w$R_2$=0.1098 | $R_1$ =0.0539, w$R_2$=0.1001 |
| Largest diff. peak/hole (e $Å^{-3}$) | 0.877/−0.549 | 2.00/−2.44 | 2.45/−0.79 | 0.97/-0.84 | 1.05/-0.67 |

**Response to alert B in 1a:**

PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) ..... O9 Check

Author Response: Crystals diffracted extremely weakly and the isolated oxygen atom is the solvated water molecule. This water molecule is in highly disorder. It's increasing the shift value upon addition of hydrogen atom. However, this structure is reported in order to support the geometry of the metal complex.

PLAT341_ALERT_3_B Low Bond Precision on C-C Bonds ..... 0.01505 Ang.

Author Response: Crystals diffracted extremely weakly. Apart from that all results were consistent with the model in this report (from the Cu data collection). However, this structure is reported in order to support the geometry of the metal complex.

**Response to alert B in 2a:**

PLAT341_ALERT_3_B Low Bond Precision on C-C Bonds ..... 0.01595 Ang.

Author Response: Crystals diffracted extremely weakly. Apart from that all results were consistent with the model in this report (from the Cu data collection). However, this structure is reported in order to support the geometry of the metal complex.

PLAT930_ALERT_2_B FCF-based Twin Law ( 0 0 1) Est.d BASF 0.26 Check

Author Response: This parameter arises due to twin character of the crystal. However, this structure is reported in order to support the geometry of the metal complex.

**Table S3.** Bond lengths (Å) around the metal centre in copper complexes.

| Bonds | **1a** | **1b** | **2a** | **2b** | **2b·$CHCl_3$** |
|---|---|---|---|---|---|
| Cu–N (pyridine) | 2.078(6)<br>2.257(8) | 2.016(3)<br>2.012(3) | 2.035(8) | 2.0166(19) | 2.023(3) |
| Cu–N (imine) | 1.941(7)<br>2.004(7) | – | 2.025(8) | – | |
| Cu–N (secondary amine) | – | 2.059(3)<br>2.040(3) | – | 2.0345(18) | 2.040(2) |
| Cu–S (thioether) | 2.410(8)<br>2.943(8) | 2.8099(8) | – | 2.7991(6) | 2.829(8) |
| Cu–Cl (bridge) | – | – | 2.590(3)<br>2.288(3) | – | |
| Cu–Cl (terminal) | – | – | 2.251(3) | 2.2567(6)<br>2.2622(6) | 2.2818(8)<br>2.2637(8) |

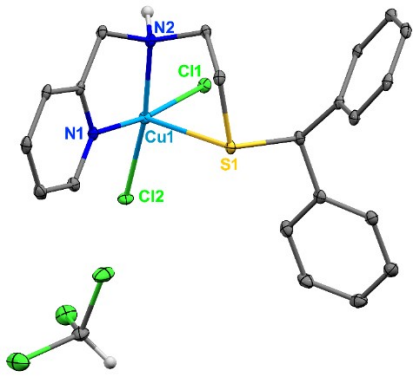



**Figure S13.** Molecular structure of **2b** (recycled) showing 30% thermal ellipsoid. Hydrogen atoms are removed for clarity except the chloroform and amine protons.

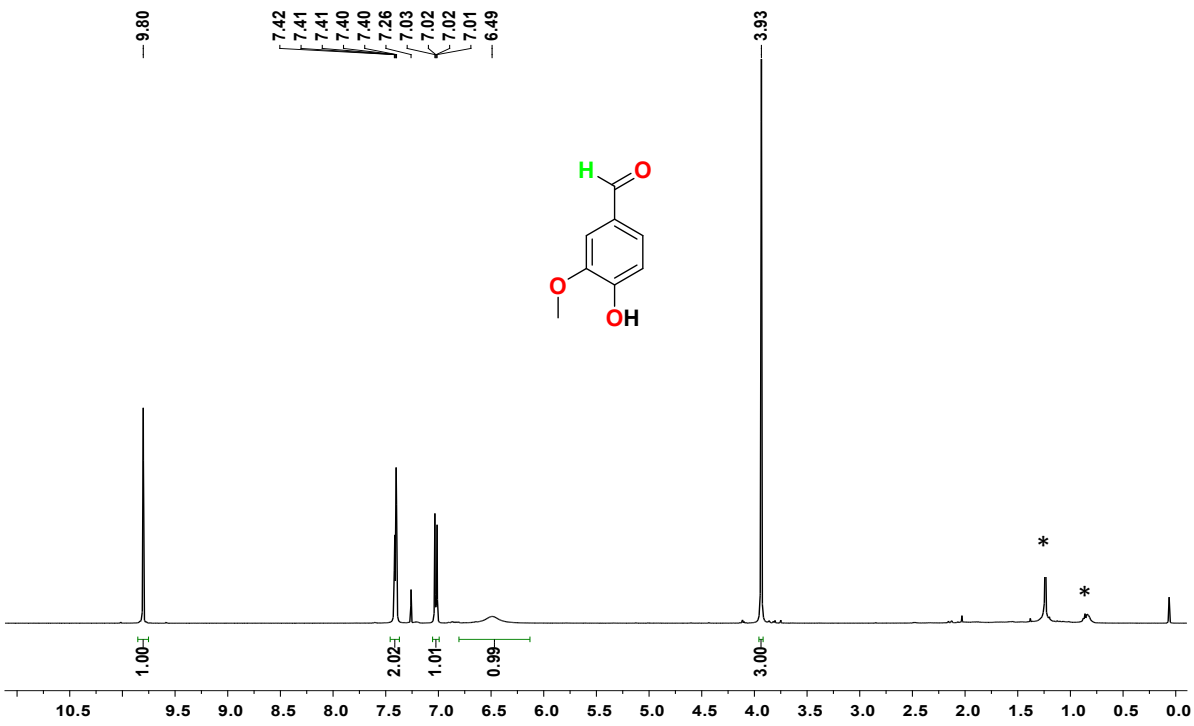



**Figure S14.** [1]H NMR (400 MHz) spectrum of vanillin obtained from the aerobic oxidation of vanillyl alcohol at 50 °C for 20 h with 10 mol% of TEMPO and 3 mol% of **2b** in acetone/water (1:1) mixture (* indicates grease peak).

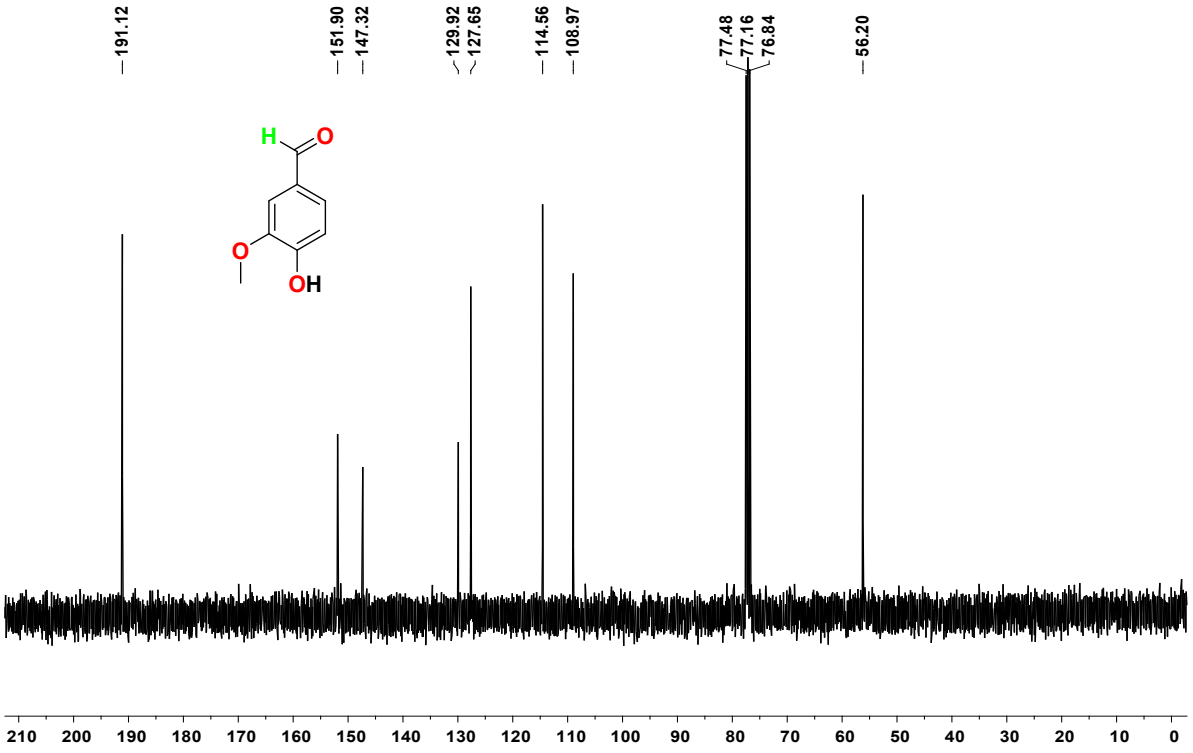



**Figure S15.** [13]C NMR (101 MHz) spectrum of vanillin obtained from the aerobic oxidation of vanillyl alcohol at 50 °C for 20 h with 10 mol% of TEMPO and 3 mol% of **2b** in acetone/water (1:1) mixture.

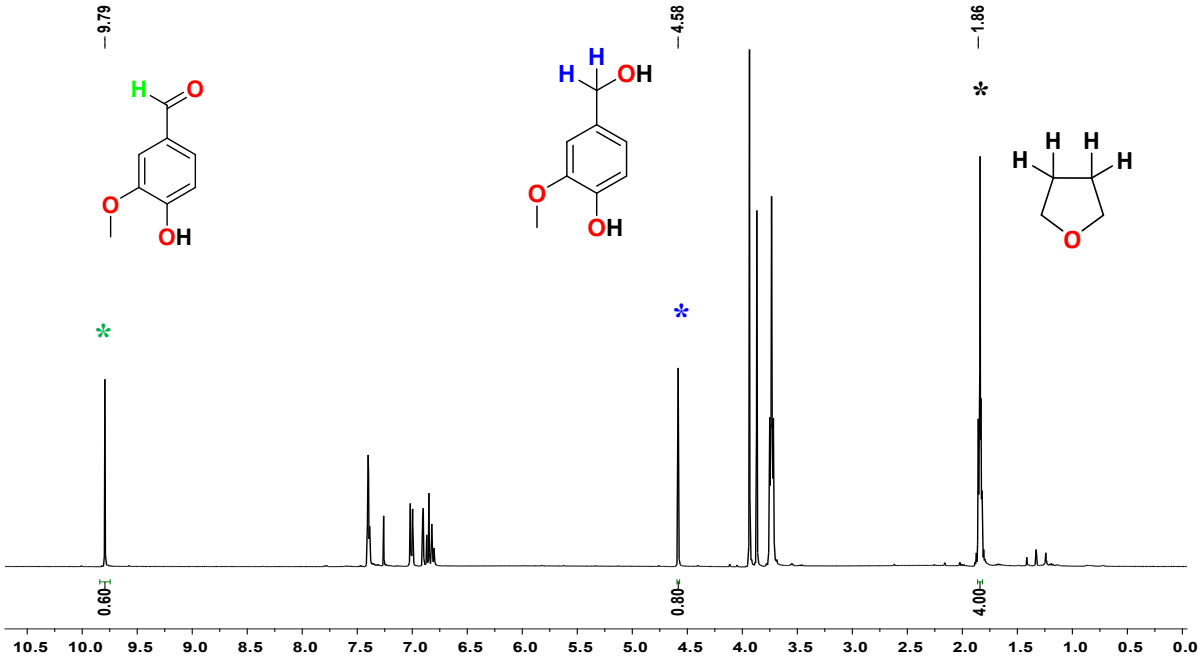



**Figure S16.** $^{1}$H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 20 mol% of TEMPO and 5 mol% of **2b** in ethanol/water (1:4) mixture. Conversion of vanillyl alcohol to vanillin was determined by $^{1}$H NMR spectroscopy using THF (0.50 mmol) as external standard.

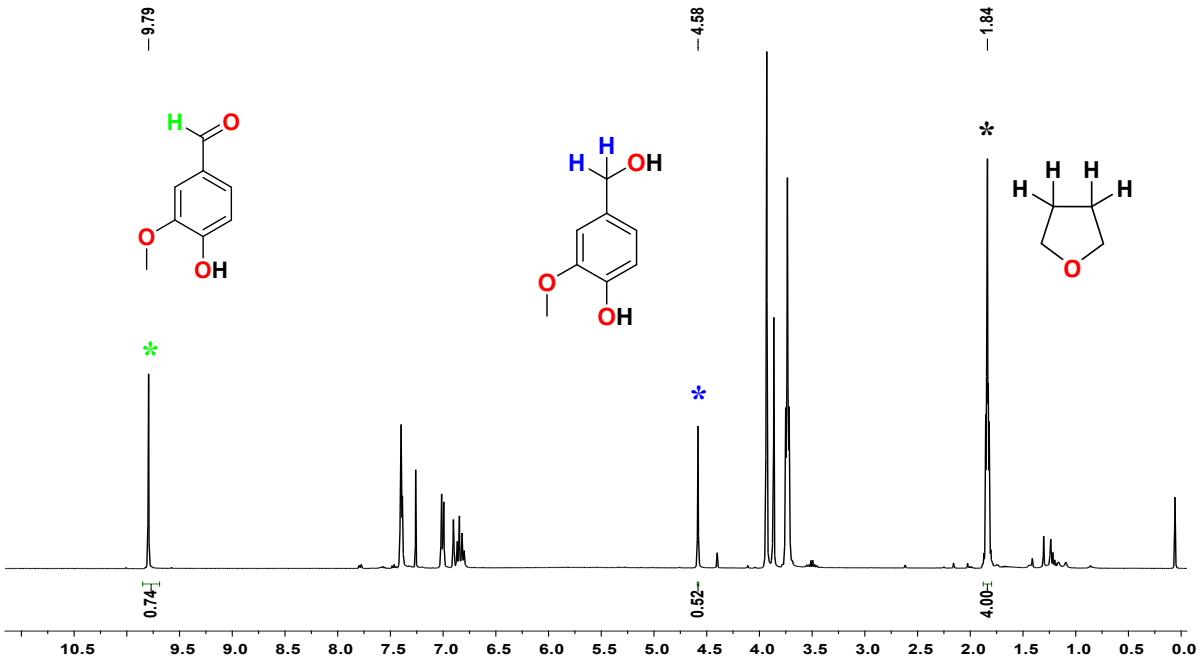



**Figure S17.** $^{1}$H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 20 mol% of TEMPO and 5 mol% of **2b** in ethanol/water (1:1) mixture. Conversion of vanillyl alcohol to vanillin were determined by $^{1}$H NMR spectroscopy using THF (0.50 mmol) as external standard.

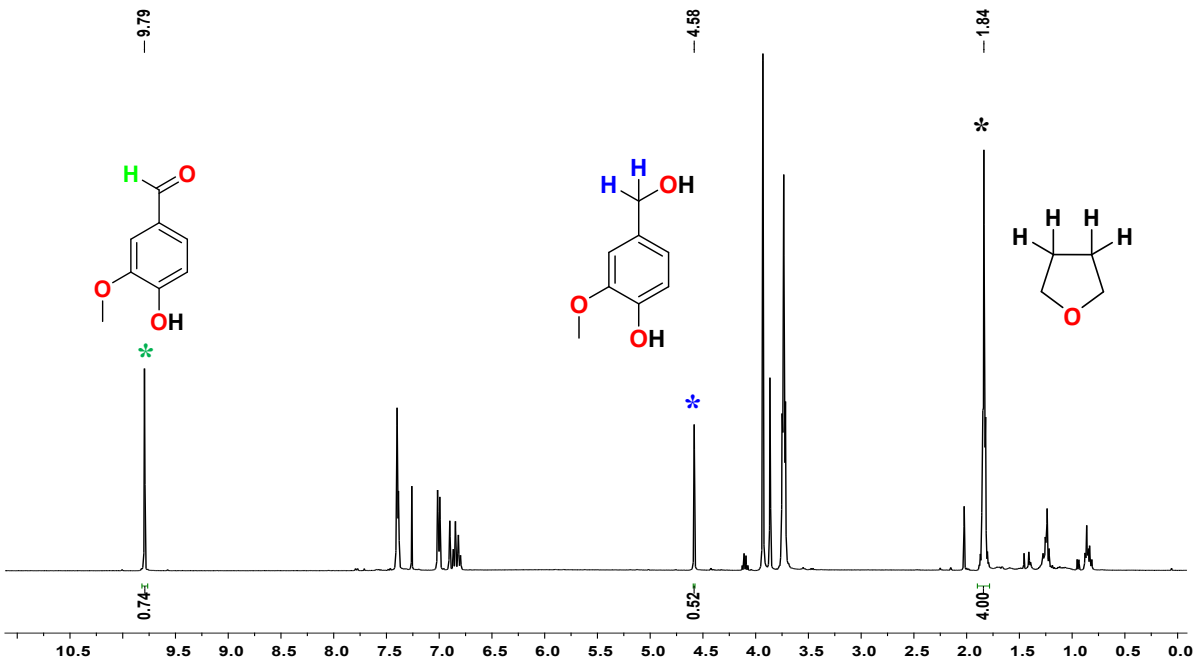



**Figure S18.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 20 mol% of TEMPO and 5 mol% **2b** in ethanol/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin was determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

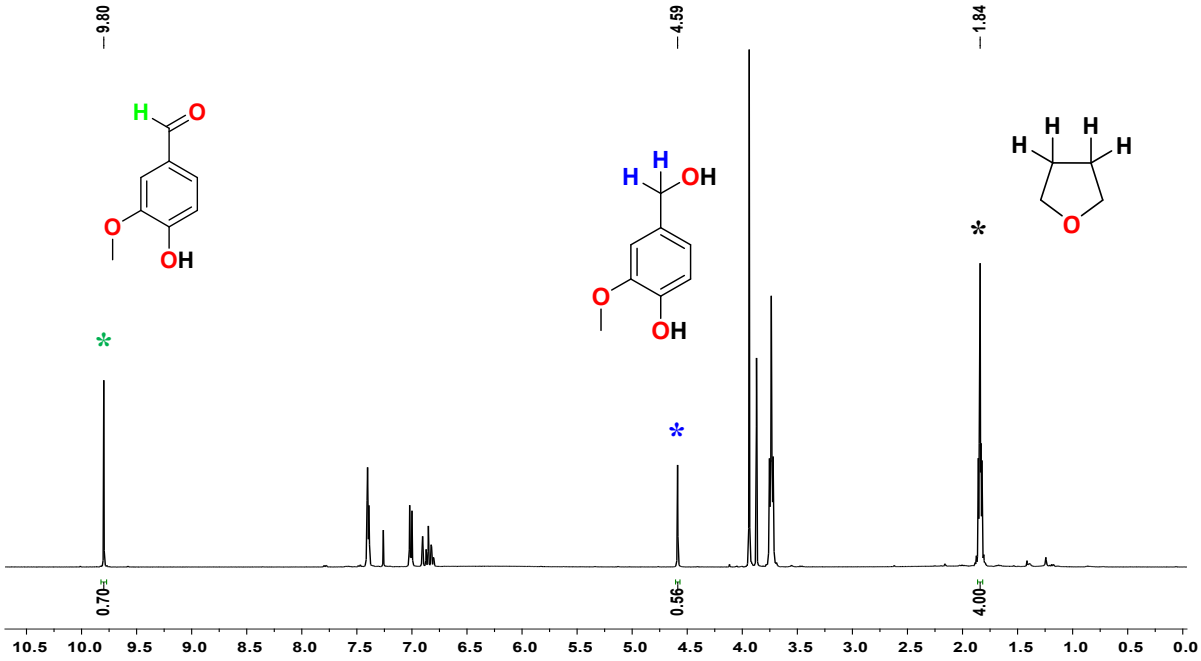



**Figure S19.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 10 mol% of TEMPO and 5 mol% of **2b** in acetonel/water (1:2) mixture. Conversion of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

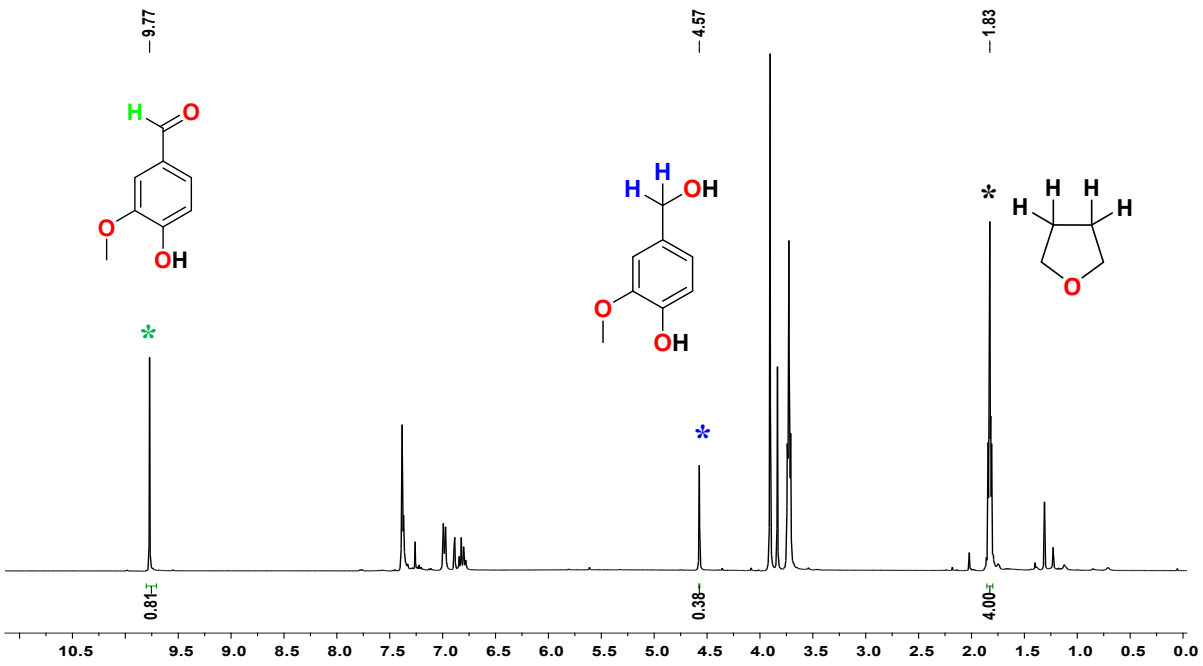



**Figure S20.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 20 mol% of TEMPO and 5 mol% of **2b** in acetone/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

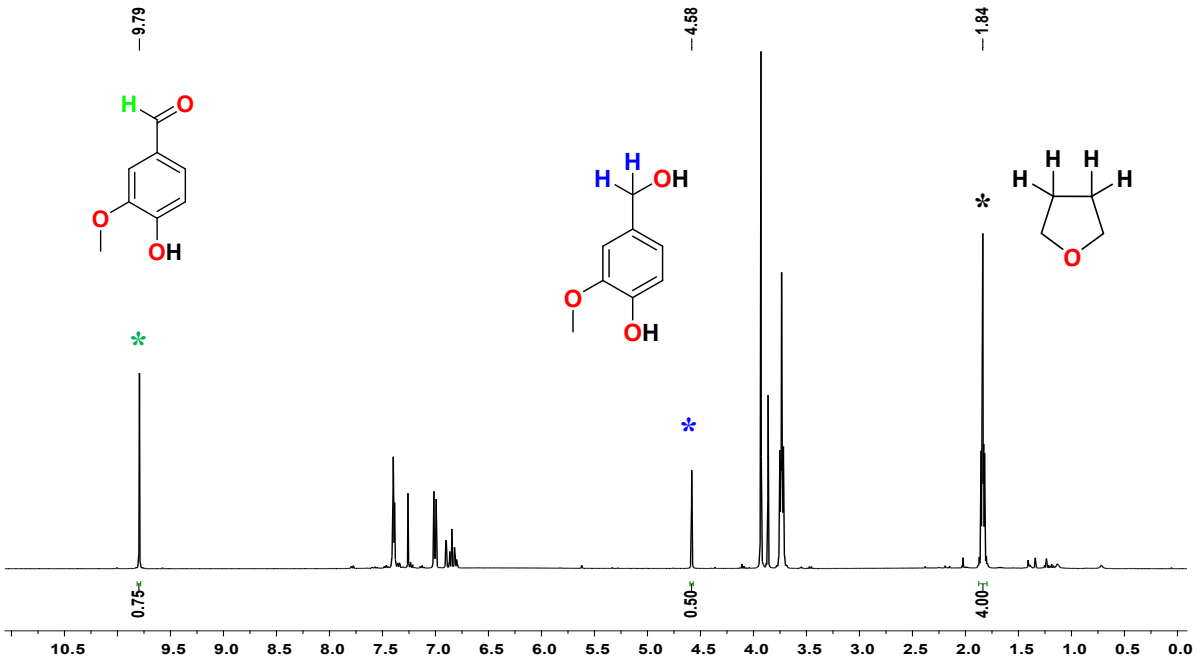



**Figure S21.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 20 mol% of TEMPO and 5 mol% of **2b** in THF/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

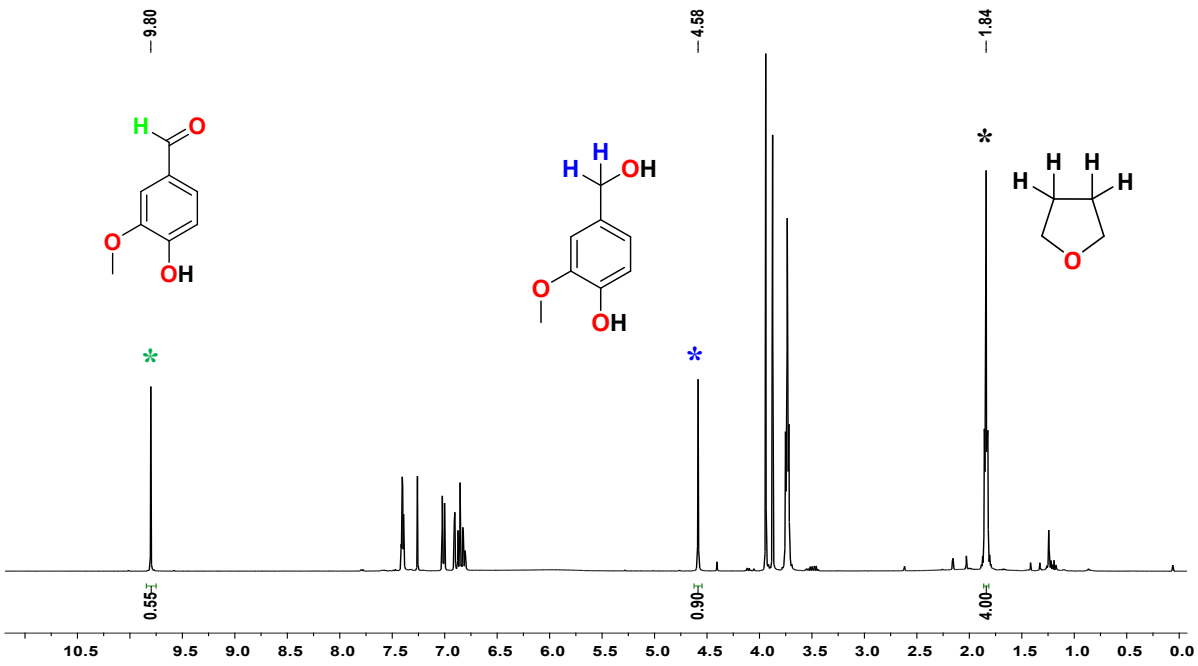



**Figure S22.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 3 h with 20 mol% of TEMPO and 5 mol% of **2b** in ethanol/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

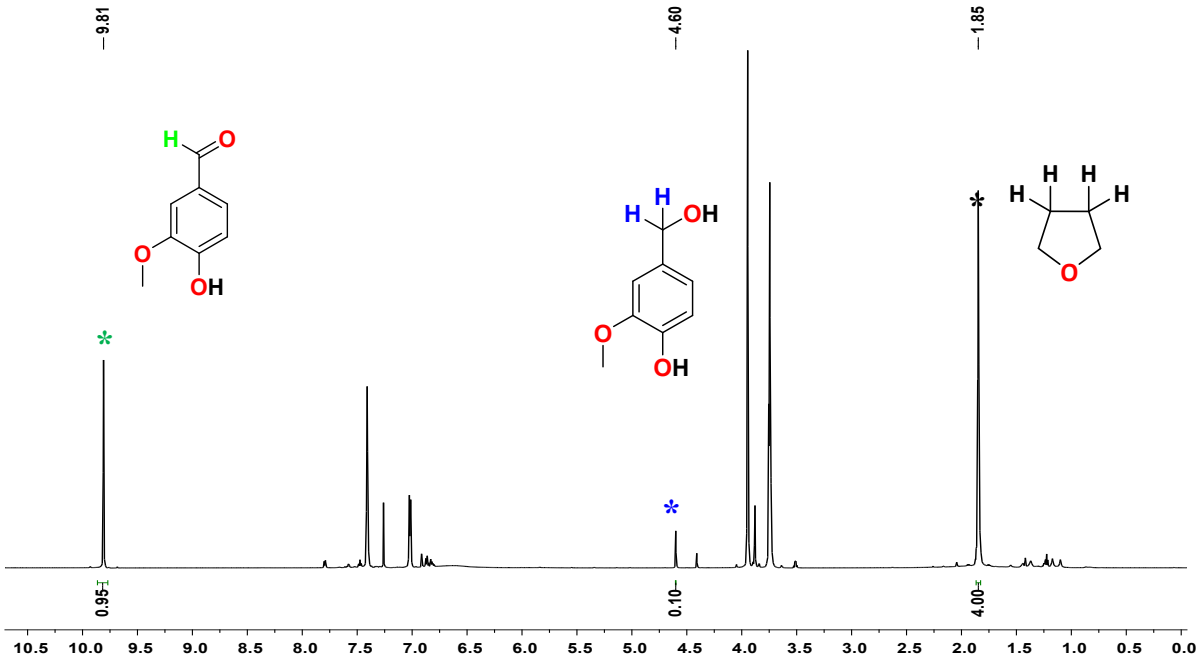



**Figure S23.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 12 h with 20 mol% of TEMPO and 5 mol% of **2b** in ethanol/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

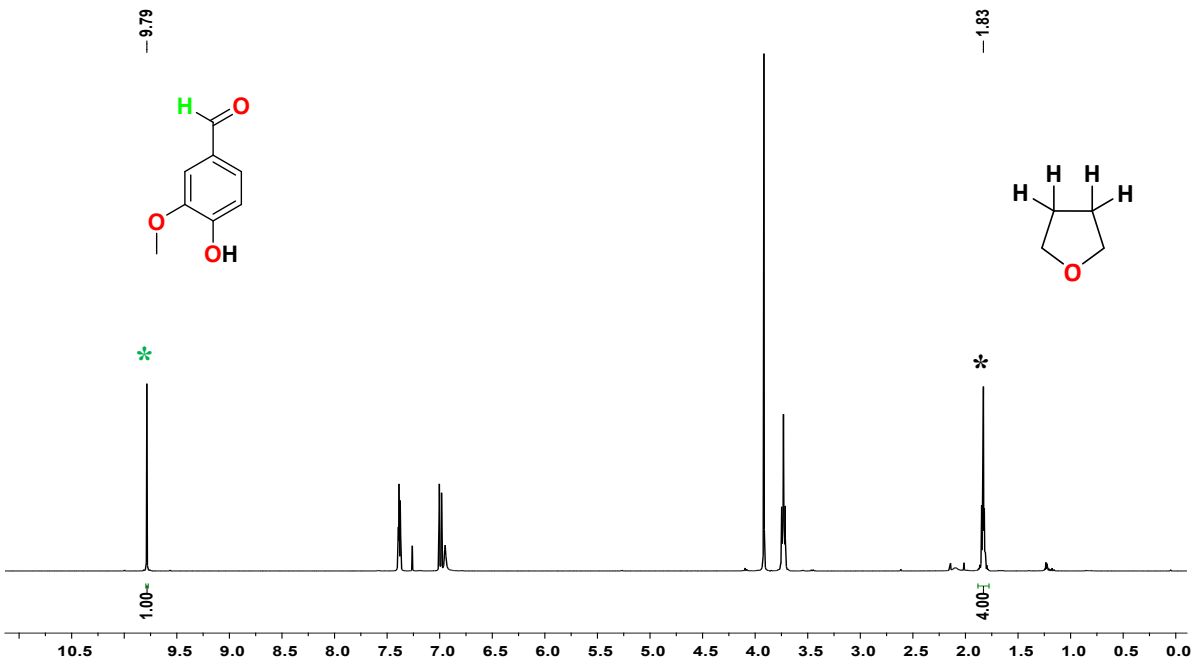



**Figure S24.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 15 h with 20 mol% of TEMPO and 5 mol% of **2b** in ethanol/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

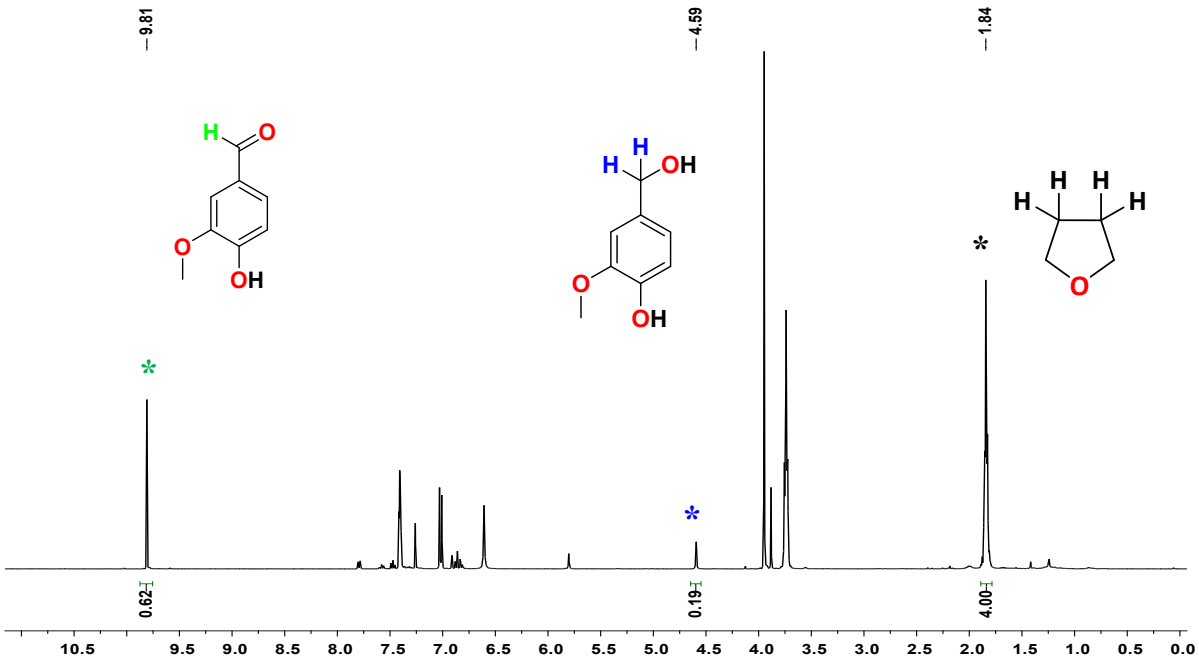



**Figure S25.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 3 h with 20 mol% of TEMPO and 5 mol% of **2b** in acetone/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

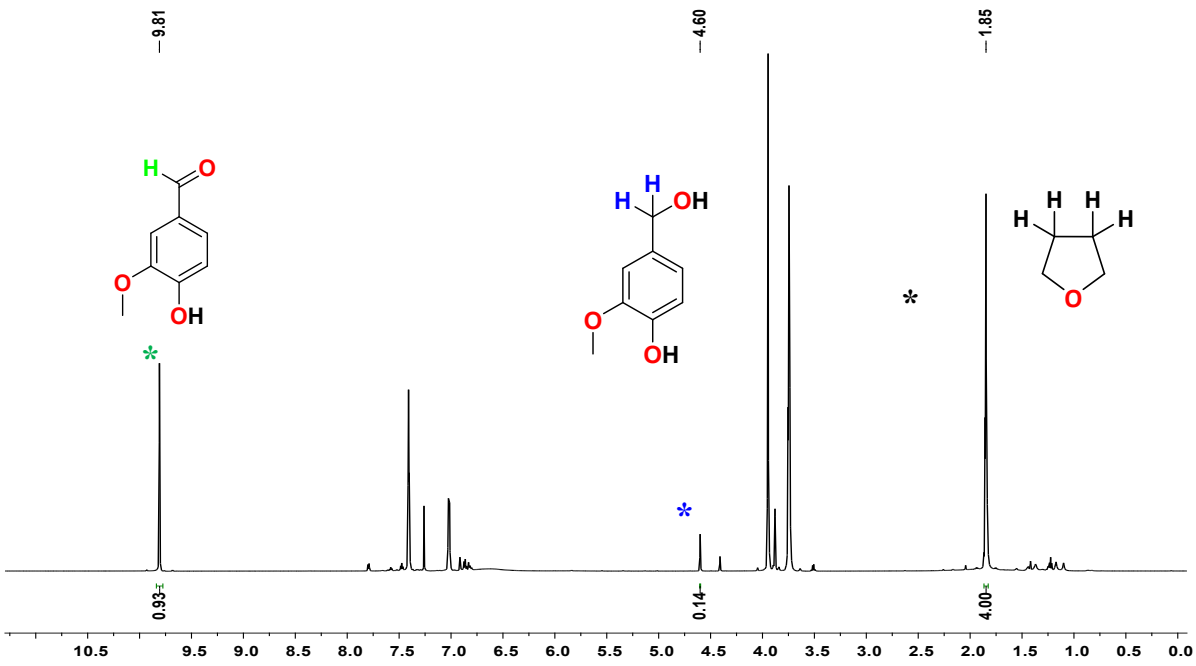



**Figure S26.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 9 h with 20 mol% of TEMPO and 5 mol% of **2b** in acetone/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

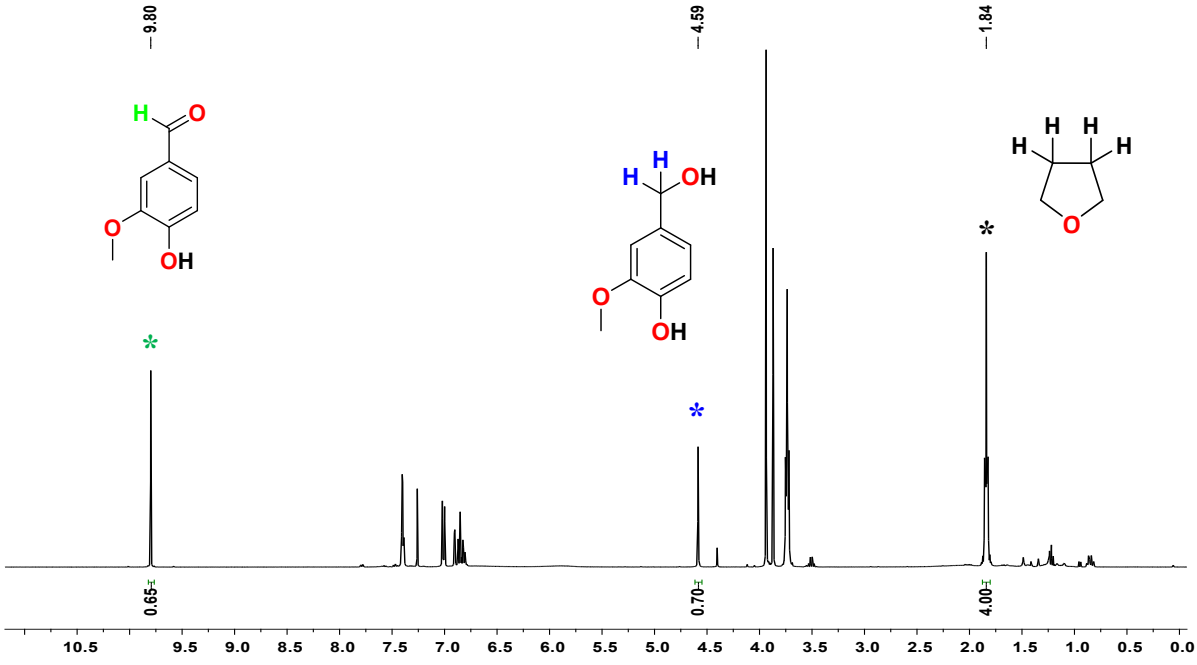



**Figure S27.** [1]H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 6 h with 10 mol% of TEMPO and 3 mol% of **2b** in ethanol/water (1:1) mixture. Conversion of vanillyl alcohol to vanillin were determined by [1]H NMR spectroscopy using THF (0.50 mmol) as external standard.

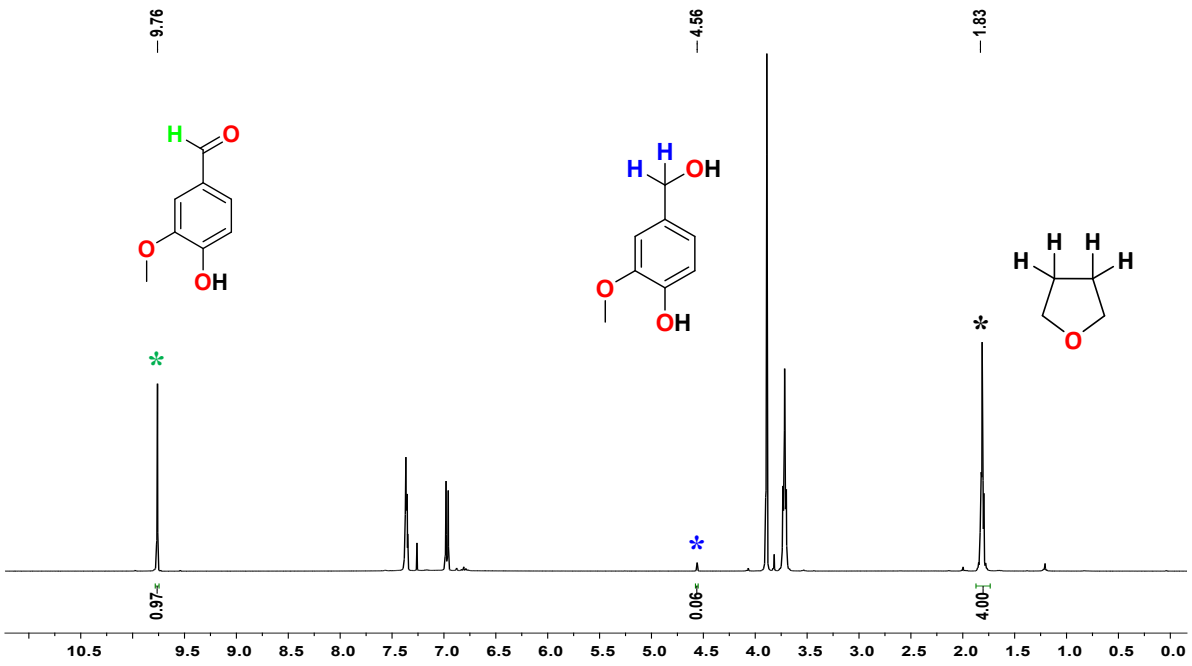



**Figure S28.** $^{1}$H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 50 °C for 18 h with 10 mol% of TEMPO and 3 mol% of **2b** in acetone/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by $^{1}$H NMR spectroscopy using THF (0.50 mmol) as external standard.

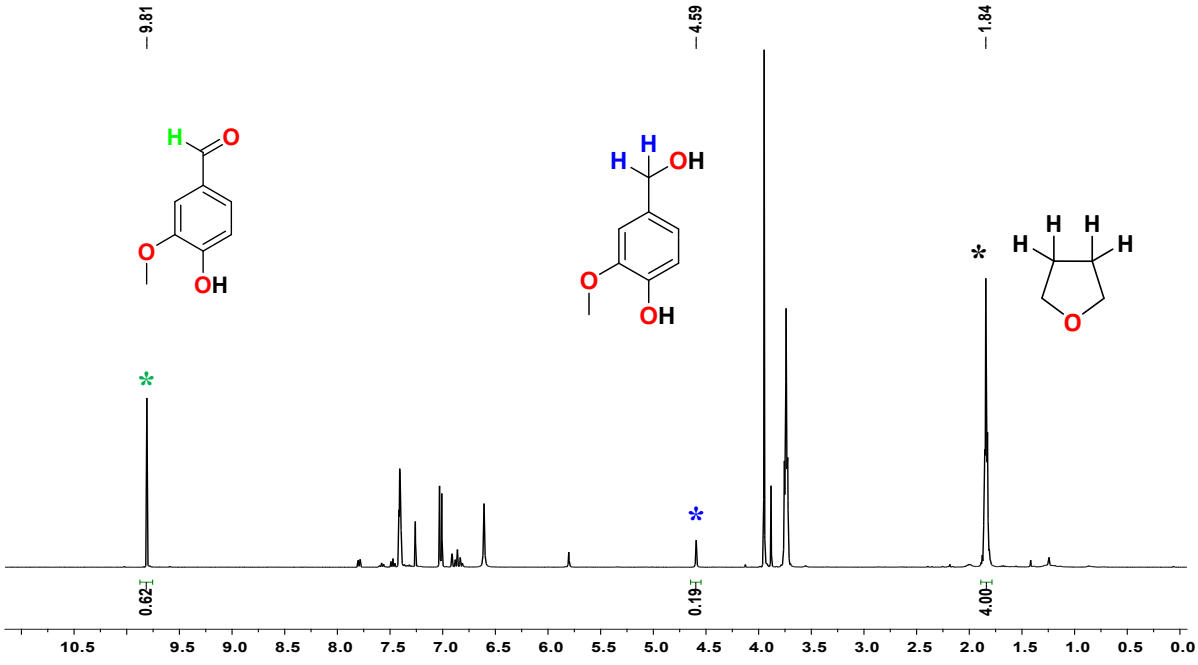



**Figure S29.** $^{1}$H NMR (400 MHz) spectrum of crude reaction mixture obtained from the aerobic oxidation of vanillyl alcohol (0.50 mmol) at 40 °C for 12 h with 10 mol% of TEMPO and 3 mol% of **2b** in acetone/water (1:1) mixture. Conversions of vanillyl alcohol to vanillin were determined by $^{1}$H NMR spectroscopy using THF (0.50 mmol) as external standard.

## Mechanistic analysis

**Experimental process.** Complex **2b** (0.010 g, 0.02 mmol) was dissolved in a degassed 1:1 mixture of acetone and water (4 mL) under $N_2$ atmosphere. EPR spectrum was recorded from the solution (Figure S29). Same reaction mixture was subjected to measure at low temperature (77K) to observe the temperature effect on EPR signals (Figure S30). TEMPO radical (0.006 g, 0.04 mmol) was added to the solution of **2b** under inert condition and EPR spectrum was recorded (Figure S30). Vanillyl alcohol (0.030 g, 0.2 mmol) as substrate was added to the above reaction mixture under inert condition and EPR spectra were recorded at regular time interval (Figure S31). Four hours later, the above reaction mixture was opened in air and EPR spectra were recorded at regular time interval (Figure S32). The above reaction mixture was also subjected to mass analysis.

**Detection of hydrogen peroxide in the aerobic oxidation of vanillyl alcohol.**[S6, S7] Complex **2b** (0.010 g, 0.02 mmol) was dissolved in a degassed 1:1 mixture of acetone and water (4 mL) under $N_2$ atmosphere. TEMPO radical (0.006 g, 0.04 mmol) was added to the solution of **2b** under inert condition followed by the addition of vanillyl alcohol (0.030 g, 0.2 mmol) under inert condition. Four hours later, the above reaction mixture was opened in air. After another 3 h of reaction, an equal volume of water was added and vanillin was extracted with dichloromethane (3 x 5 mL). The aqueous layer was acidified with $H_2SO_4$ to pH = 2 to stop further oxidation. Thereafter 1 mL of a 10% solution of KI and three drops of 3% solution of ammonium molybdate were added to the aqueous reaction mixture. In the presence of hydrogen peroxide, the following reaction 1 occurs. With an excess of iodide ions, the triiodide ion is formed according to reaction 2. Overall mixture renders the reaction almost instantaneously. The formation of $I_3^-$ was detected by UV-Vis spectrophotometer due to the development of the characteristic $I_3^-$ band with $\lambda_{max}$ = 353 nm (Figure S33).

**Reaction 1:** $H_2O_2 + 2I^- + 2H^+ \rightarrow 2H_2O + I_2$. **Reaction 2:** $I_2 + I^- \rightarrow I_3^-$.

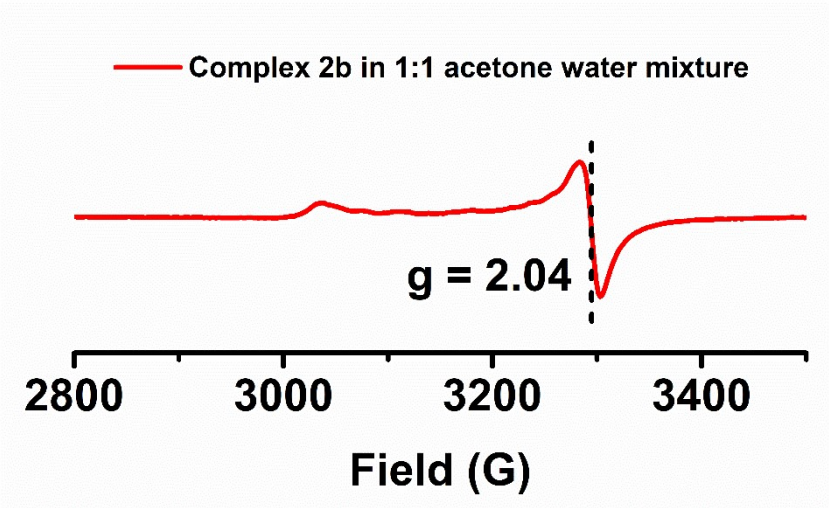



**Figure S30.** EPR spectrum of **2b** in a 1:1 mixture of acetone and water at r.t. under $N_2$.

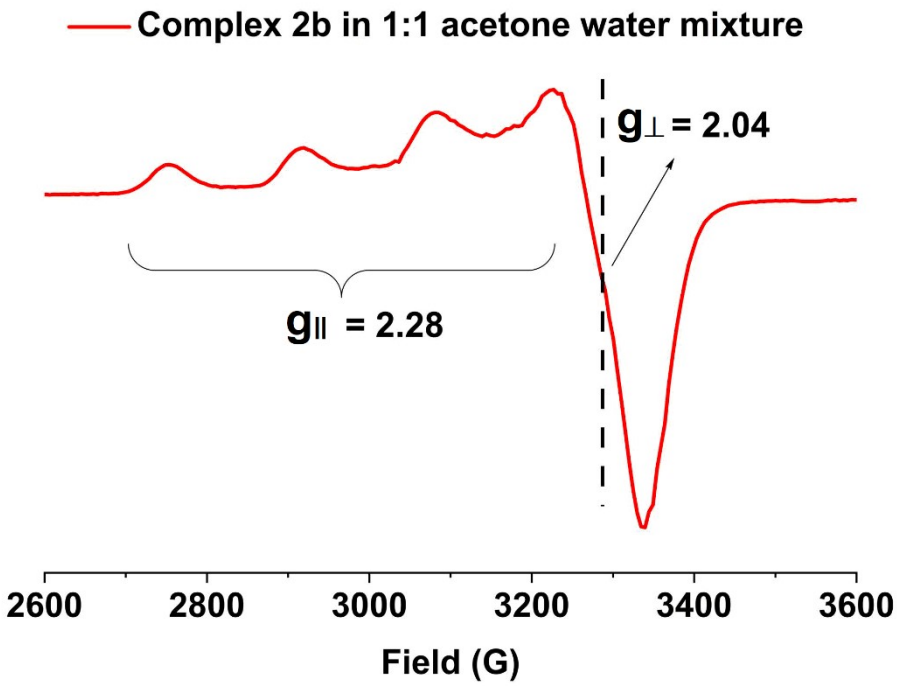



**Figure S31.** EPR spectrum of **2b** in a 1:1 mixture of acetone and water at 77K under $N_2$.

The effect of temperature has also been examined by EPR spectroscopy (Figure S30). The X-band EPR spectra of **2b** in 1:1 acetone water mixture at 77K exhibit axial symmetry with $g_{\parallel} > g_{\perp}$ suggesting that the unpaired electron resides in the $d_{x^2-y^2}$ ground state. The hyperfine coupling constant $A_{\parallel}$ of 167 is also very similar as observed in ternary Cu(II) complexes having square pyramidal geometry.[S8] Moreover, all these $g_{\parallel}$, $g_{\perp}$ and $A_{\parallel}$ values are very close to the Cu(II) square pyramidal complexes reported by Halcrow and co-workers.[S9]

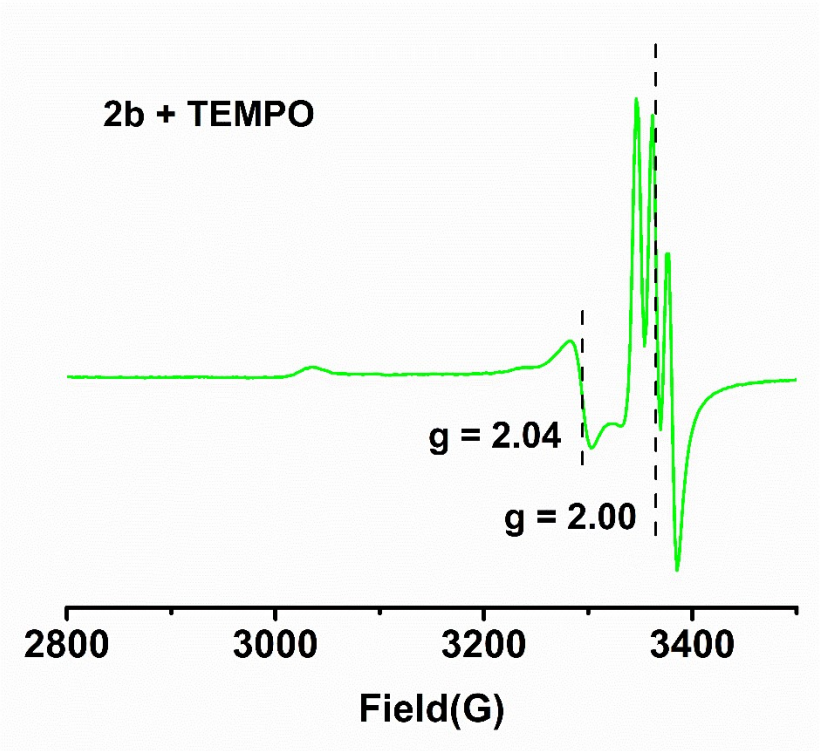



**Figure S32.** EPR spectrum of **2b** and TEMPO radical in a 1:1 mixture of acetone and water at r.t. under $N_2$.

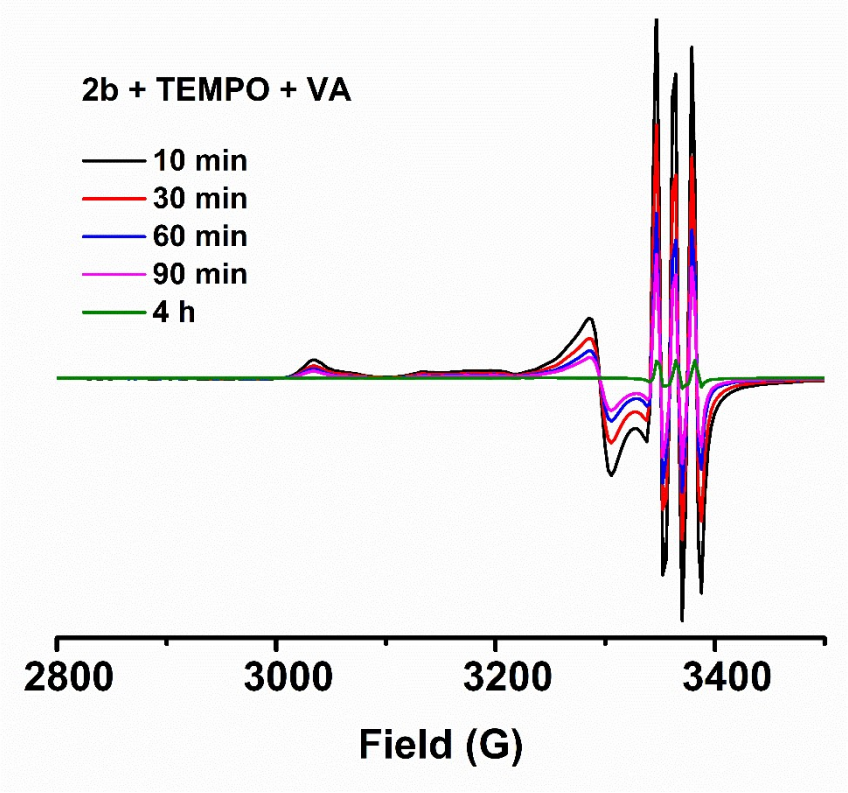



**Figure S33.** EPR spectrum of complex **2b**, TEMPO radical and vanillyl alcohol in a 1:1 mixture of acetone and water at r.t. under $N_2$.

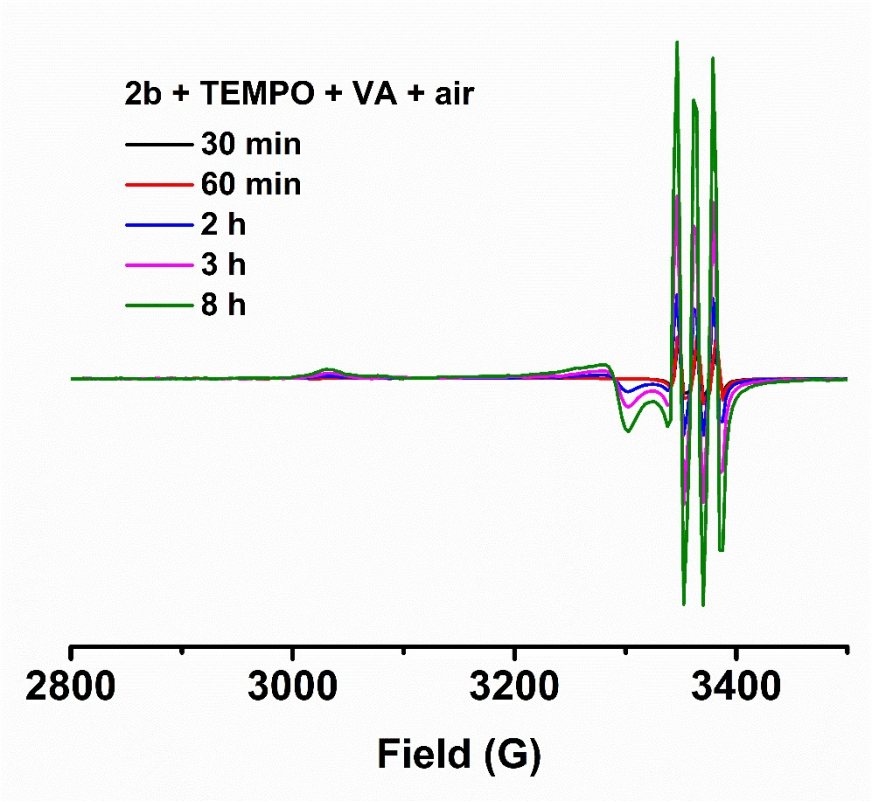



**Figure S34.** EPR spectrum of complex **2b**, TEMPO radical and vanillyl alcohol in a 1:1 mixture of acetone and water at r.t. in air.

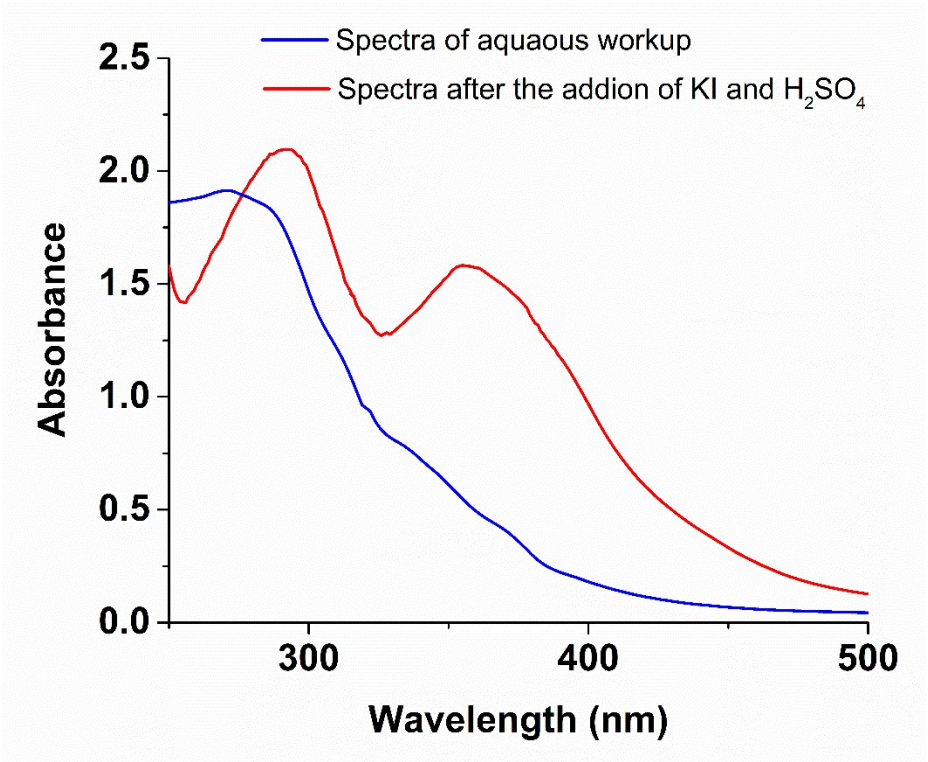



**Figure S35.** UV-vis spectrum of $I_3^-$, formed during the course of the reaction between reaction by-product $H_2O_2$ and excess KI.

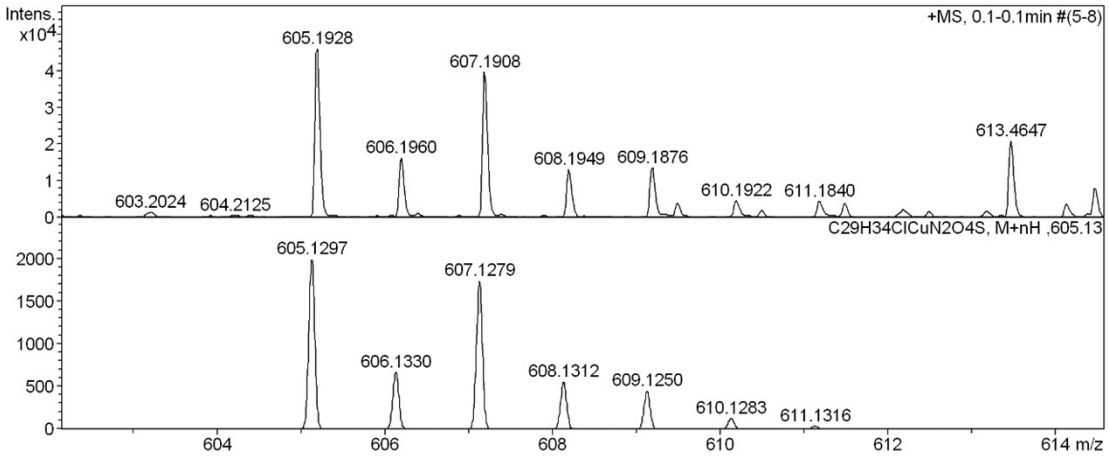



**Figure S36.** HR-MS of the species **B/C** ($[M_B - Cl]^+$ or $[M_C - Cl]^+$ for $C_{29}H_{34}ClCuN_2O_4S$).

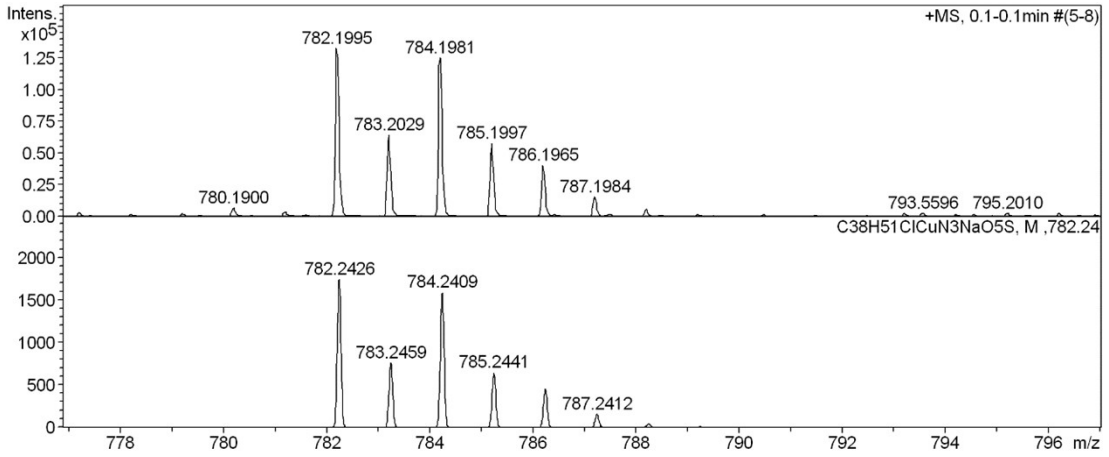



**Figure S37.** HR-MS of the species **D** $(M_D - Cl + Na]^+$ for $C_{38}H_{51}ClCuN_3NaO_5S$).

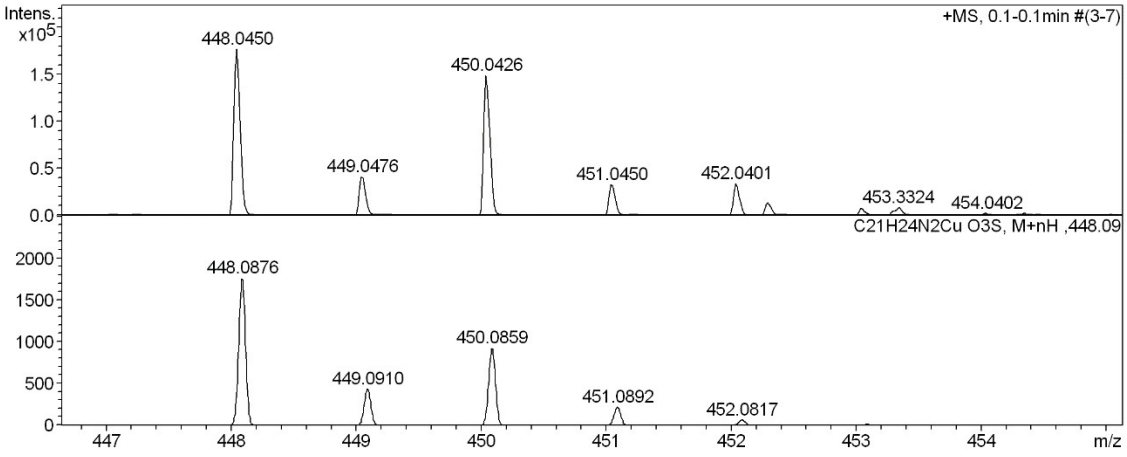



**Figure S38.** HR-MS of the species **F** ($[M_F - 2Cl]^+$ for $C_{21}H_{24}N_2CuO_3S$).

# Table S4. Method A (acetone/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 12 h): Zero Pass CHEM21 green metrics toolkit

**Supplementary Information: Appendix 2** — **Summary of Zero Pass Metrics Toolkit**

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | Acetone | 20.00 | 0.79 | 15.70 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 35.70 | | 0.00 | | | | 47.06 |

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecualr\ weight\ of\ reactants} \times 100$$

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |

| | mass |
|---|---|
| Unreacted limiting reactant | 0.000 |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S5. Method B (acetone/water, [Cu] 3 mol%, TEMPO 10 mol%, 40 °C, 20 h): Zero Pass CHEM21 green metrics toolkit

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Acetone | 20.00 | 0.79 | 15.70 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.70 | | 0.00 | | | | 47.06 |

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |
| | mass | | |
| Unreacted limiting reactant | 0.000 | | |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S6. Method C (ethanol/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 15 h): Zero Pass CHEM21 green metrics toolkit

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |
| | mass | | |
| Unreacted limiting reactant | 0.000 | | |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S7. Method D (ethanol/water, [Cu] 3 mol%, TEMPO 10 mol%, 40 °C, 24 h): Zero Pass CHEM21 green metrics toolkit

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |
| | mass | | |
| Unreacted limiting reactant | 0.000 | | |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S8. Method E (acetone/water, [Cu] 3 mol%, TEMPO 10 mol%, 70 °C, 16 h): Zero Pass CHEM21 green metrics toolkit

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |
| | mass | | |
| Unreacted limiting reactant | 0.000 | | |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S9. Method F (THF/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 15 h): Zero Pass CHEM21 green metrics toolkit

**Yield, conversion, selectivity, AE, RME**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | THF | 20.00 | 0.89 | 17.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 37.78 | | 0.00 | | | | 47.06 |

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | |

| | mass | mw | mol |
|---|---|---|---|
| Product | 1.521 | 152.150 | 0.0099967 |
| | mass | | |
| Unreacted limiting reactant | 0.000 | | |

**Solvents (Zero Pass)**

| Highly hazardous solvents (Red flag for any of the following) | List Highly Hazardous Solvents Below |
|---|---|
| $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | None |

**Health and Safety (Zero Pass)**

| Health & safety (Red flag for any of the following) | | List substances plus the red flagged H-codes below |
|---|---|---|
| Highly explosive | H200, H201, H202, H203 | None |
| Explosive thermal runaway | H240 | None |
| Fatally toxic | H300, H310, H330 | None |
| Mutagenic | H350 | None |
| Repro-toxic | H360 | None |
| Serious environmental implications | H420 | None |

## Table S10. Method A (acetone/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 12 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | Acetone | 20.00 | 0.79 | 15.70 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 35.70 | | 0.00 | | | | 47.06 |

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecular\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | OE 109.3 |
| PMI total | 55.9 | |
| PMI Reaction | 24.9 | |
| PMI reactants, reagents, catlyst | 1.5 | |
| PMI reaction solvents | 23.5 | |
| PMI Workup | 30.9 | |
| PMI Workup chemical | 0.0 | |
| PMI workup solvents | 30.9 | |

| Product | Mass | MW | Mol |
|---|---|---|---|
| | 1.52 | 152.15 | 0.01 |
| | mass | | |
| Unreacted limiting reactant | 0.00 | | |

**Solvents (First Pass)**

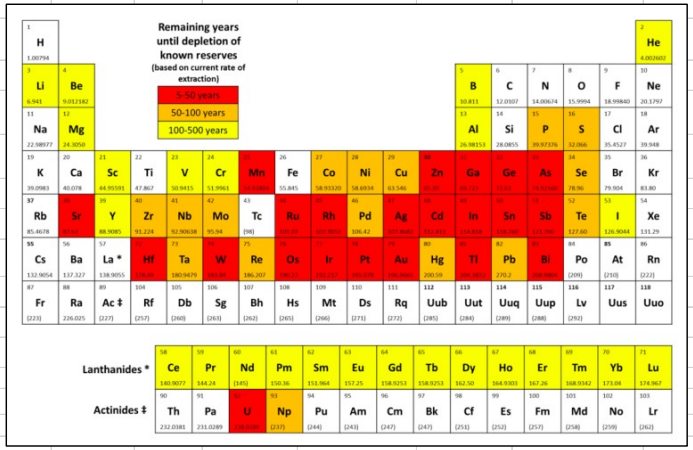
| | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water**, acetone, **AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | none |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| Catalyst/enzyme (First Pass) | | Tick |
|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X |
| Use of stoichiometric quantities of reagents | Amber Flag | |
| Use of reagents in excess | Red Flag | |

| | | Tick |
|---|---|---|
| Facile recovery of catalyst/enzyme | Green Flag | x |
| catalyst/enzyme not recovered | Amber Flag | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |




**Energy (First Pass)**

| | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

**Batch/flow**

| | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

**Work Up**

| | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **none** | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; Acetone:** H225, H319, H336; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# Table S11. Method B (acetone/water, [Cu] 3 mol%, TEMPO 10 mol%, 40 °C, 20 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Acetone | 20.00 | 0.79 | 15.70 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.70 | | 0.00 | | | | 47.06 |

| | | Flag |
|---|---|---|
| Yield | 99.9 | 99.9 |
| Conversion | 100.0 | 100.0 |
| Selectivity | 99.9 | 99.9 |
| AE | 81.7 | |
| RME | 89.4 | OE 109.3 |
| PMI total | 55.7 | |
| PMI Reaction | 24.8 | |
| PMI reactants, reagents, catlyst | 1.3 | |
| PMI reaction solvents | 23.5 | |
| PMI Workup | 30.9 | |
| PMI Workup chemical | 0.0 | |
| PMI workup solvents | 30.9 | |

| | Mass | MW | Mol |
|---|---|---|---|
| Product | 1.52 | 152.15 | 0.01 |
| | mass | | |
| Unreacted limiting reactant | 0.00 | | |

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

| Solvents (First Pass) | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water**, acetone, **AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | none |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| Catalyst/enzyme (First Pass) | | Tick |
|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X |
| Use of stoichiometric quantities of reagents | Amber Flag | |
| Use of reagents in excess | Red Flag | |

| | | Tick |
|---|---|---|
| Facile recovery of catalyst/enzyme | Green Flag | x |
| catalyst/enzyme not recovered | Amber Flag | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |

| Energy (First Pass) | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

| Batch/flow | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

| Work Up | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **none** | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; Acetone:** H225, H319, H336; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# Table S12. Method C (ethanol/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 15 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

| | | Flag | | | | |
|---|---|---|---|---|---|---|
| Yield | 99.9 | 99.9 | | | | |
| Conversion | 100.0 | 100.0 | | | | |
| Selectivity | 99.9 | 99.9 | | | | |
| AE | 81.7 | | | | | |
| RME | 89.4 | OE | 109.3 | | | |
| PMI total | 55.9 | | | | | |
| PMI Reaction | 25.0 | | | | | |
| PMI reactants, reagents, catlyst | 1.5 | | | | | |
| PMI reaction solvents | 23.5 | | | | | |
| PMI Workup | 30.9 | | | | | |
| PMI Workup chemical | 0.0 | | | | | |
| PMI workup solvents | 30.9 | | | | | |

| | Mass | MW | Mol |
|---|---|---|---|
| Product | 1.52 | 152.15 | 0.01 |
| | mass | | |
| Unreacted limiting reactant | 0.00 | | |

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

| Solvents (First Pass) | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water**, EtOH, **AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | none |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| Catalyst/enzyme (First Pass) | | Tick | | | Tick |
|---|---|---|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X | Facile recovery of catalyst/enzyme | Green Flag | x |
| Use of stoichiometric quantities of reagents | Amber Flag | | catalyst/enzyme not recovered | Amber Flag | |
| Use of reagents in excess | Red Flag | | | | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |

| Energy (First Pass) | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

| Batch/flow | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

| Work Up | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **none** | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; Ethanol:** H225, H319; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# Table S13. Method D (ethanol/water, [Cu] 3 mol%, TEMPO 10 mol%, 40 °C, 24 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

| | | Flag | | | | | |
|---|---|---|---|---|---|---|---|
| Yield | 99.9 | | 99.9 | | | | |
| Conversion | 100.0 | | 100.0 | | | | |
| Selectivity | 99.9 | | 99.9 | | | | |
| AE | 81.7 | | | | | Mass | MW | Mol |
| RME | 89.4 | OE | 109.3 | | Product | 1.52 | 152.15 | 0.01 |
| | | | | | | mass | | |
| PMI total | 55.8 | | | | Unreacted limiting reactant | 0.00 | | |
| PMI Reaction | 24.8 | | | | | | | |
| PMI reactants, reagents, catlyst | 1.3 | | | | | | | |
| PMI reaction solvents | 23.5 | | | | | | | |
| PMI Workup | 30.9 | | | | | | | |
| PMI Workup chemical | 0.0 | | | | | | | |
| PMI workup solvents | 30.9 | | | | | | | |

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

| Solvents (First Pass) | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water**, EtOH, **AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | none |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| Catalyst/enzyme (First Pass) | | Tick | | | Tick |
|---|---|---|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X | Facile recovery of catalyst/enzyme | Green Flag | x |
| Use of stoichiometric quantities of reagents | Amber Flag | | catalyst/enzyme not recovered | Amber Flag | |
| Use of reagents in excess | Red Flag | | | | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |

| Energy (First Pass) | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

| Batch/flow | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

| Work Up | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **none** | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; Ethanol:** H225, H319; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# Table S14. Method E (acetone/water, [Cu] 3 mol%, TEMPO 10 mol%, 70 °C, 16 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.14 | | | Ethanol | 20.00 | 0.79 | 15.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.16 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.30 | | 0.00 | | | | 35.78 | | 0.00 | | | | 47.06 |

| | | Flag | | | | |
|---|---|---|---|---|---|---|
| Yield | 99.9 | 99.9 | | | | |
| Conversion | 100.0 | 100.0 | | | | |
| Selectivity | 99.9 | 99.9 | | | | |
| AE | 81.7 | | | | Mass | MW | Mol |
| RME | 89.4 | OE | 109.3 | Product | 1.52 | 152.15 | 0.01 |
| | | | | | mass | | |
| PMI total | 55.8 | | | Unreacted limiting reactant | 0.00 | | |
| PMI Reaction | 24.8 | | | | | | |
| PMI reactants, reagents, catlyst | 1.3 | | | | | | |
| PMI reaction solvents | 23.5 | | | | | | |
| PMI Workup | 30.9 | | | | | | |
| PMI Workup chemical | 0.0 | | | | | | |
| PMI workup solvents | 30.9 | | | | | | |

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

**Solvents (First Pass)**

| | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water**, EtOH, **AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | none |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| Catalyst/enzyme (First Pass) | | Tick | | | Tick |
|---|---|---|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X | Facile recovery of catalyst/enzyme | Green Flag | x |
| Use of stoichiometric quantities of reagents | Amber Flag | | catalyst/enzyme not recovered | Amber Flag | |
| Use of reagents in excess | Red Flag | | | | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |

| Energy (First Pass) | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

| Batch/flow | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

| Work Up | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **none** | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; Ethanol:** H225, H319; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# Table S15. Method F (THF/water, [Cu] 5 mol%, TEMPO 20 mol%, 40 °C, 15 h): First Pass CHEM21 green metrics toolkit

**Yield, AE, RME, MI/PMI and OE**

| Reactant (Limiting Reactant First) | Mass (g) | MW | Mol | Catalyst | Mass (g) | Reagent | Mass (g) | Reaction solvent | Volume ($cm^3$) | Density ($g\ ml^{-1}$) | Mass (g) | Work up chemical | Mass (g) | Workup solvent | Volume (cm3) | Density ($g\ ml^{-1}$) | Mass (g) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanillyl alcohol | 1.54 | 154.17 | 0.01 | [Cu] | 0.23 | | | THF | 20.00 | 0.89 | 17.78 | | | Ethyl acetate | 30.00 | 0.90 | 27.06 |
| Oxygen | 0.16 | 32.00 | 0.01 | TEMPO | 0.31 | | | Water | 20.00 | 1.00 | 20.00 | | | Water | 20.00 | 1.00 | 20.00 |
| Total | 1.70 | 186.17 | | | 0.55 | | 0.00 | | | | 37.78 | | 0.00 | | | | 47.06 |

$$RME = \frac{mass\ of\ isolated\ product}{total\ mass\ of\ reactants} \times 100$$

$$AE = \frac{molecular\ weight\ of\ product}{total\ molecular\ weight\ of\ reactants} \times 100$$

$$mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$$

$$OE = \frac{RME}{AE} \times 100$$

| | | Flag | | |
|---|---|---|---|---|
| Yield | 99.9 | | 99.9 | |
| Conversion | 100.0 | | 100.0 | |
| Selectivity | 99.9 | | 99.9 | |
| AE | 81.7 | | | |
| RME | 89.4 | OE | | 109.3 |
| PMI total | 57.3 | | | |
| PMI Reaction | 26.3 | | | |
| PMI reactants, reagents, catlyst | 1.5 | | | |
| PMI reaction solvents | 24.8 | | | |
| PMI Workup | 30.9 | | | |
| PMI Workup chemical | 0.0 | | | |
| PMI workup solvents | 30.9 | | | |

| | Mass | MW | Mol |
|---|---|---|---|
| Product | 1.52 | 152.15 | 0.01 |
| | mass | | |
| Unreacted limiting reactant | 0.00 | | |

**Solvents (First Pass)**

| | | List solvents below |
|---|---|---|
| **Preferred solvents** | **water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane | **water, AcOEt** |
| **Problematic solvents:** (acceptable only if substitution does not offer advantages) | DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF | THF |
| **Hazardous solvents**: These solvents have significant health and/or safety concerns. | dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane | none |
| **Highly hazardous solvents:** The solvents which are agreed not to be used, even in screening | $Et_2O$, Benzene, $CCl_4$, chloroform, DCE, nitromethane, $CS_2$, HMPA | none |

| **Catalyst/enzyme (First Pass)** | | **Tick** | | | **Tick** |
|---|---|---|---|---|---|
| Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents. | Green Flag | X | Facile recovery of catalyst/enzyme | Green Flag | x |
| Use of stoichiometric quantities of reagents | Amber Flag | | catalyst/enzyme not recovered | Amber Flag | |
| Use of reagents in excess | Red Flag | | | | |

**Critical elements**

| Supply remaining | Flag colour | Note element |
|---|---|---|
| 5-50 years | Red Flag | |
| 50-500 years | Amber Flag | Cu |
| +500 years | Green Flag | |

**Energy (First Pass)**

| | | Tick |
|---|---|---|
| Reaction run between 0 to 70°C | Green Flag | X |
| Reaction run between -20 to 0 or 70 to 140°C | Amber Flag | |
| Reaction run below -20 or above 140°C | Red Flag | |

| | | Tick |
|---|---|---|
| Reaction run at reflux | Red Flag | |
| Reaction run 5°C or more below the solvent boiling point | Green Flag | X |

**Batch/flow**

| | | Tick |
|---|---|---|
| Flow | Green Flag | |
| Batch | Amber Flag | X |

| Work Up | | List |
|---|---|---|
| quenching<br>filtration<br>centrifugation<br>crystallisation<br>Low temperature distillation/evaporation/ sublimation (< | Green Flag | Filtration, Evaporation |
| solvent exchange, quenching into aqueous solvent | Amber Flag | |
| chromatography/ion exchange<br>high temperature<br>multiple recrystallisation | Red Flag | |

**Health & safety**

| | Red Flag | Amber Flag | Green Flag | List substances and H-codes | List substances and H-codes | List substances and H-codes |
|---|---|---|---|---|---|---|
| **Highly explosive** | H200, H201, H202, H203 | H205, H220, H224 | If no red or amber flagged H codes present then green flag | none | **THF:** H351. | **Vanillyl alcohol: H315, H319, H336; Vanillin: H317, H319, H302; THF:** H225, H303, H316, H319, H335; **Ethylacetate**: H225, H319, H336. |
| **Explosive thermal runaway** | H230, H240, H250 | H241 | | | | |
| **Toxic** | H300, H310, H330 | H301, H311, H331, | | | | |
| **Long Term toxicity** | H340, H350, H360, H370, H372 | H341, H351, H361, H371, H373 | | | | |
| **Environmental implications** | H400, H410, H411, H420 | H401, H412 | | | | |

| Use of chemicals of environmental concern | | List substances of very high concern |
|---|---|---|
| Chemical identified as Substances of Very High Concern by ChemSec which are utilised | Red Flag | none |

# References

S1. O. M. Okunola-Bakare, J. Cao, T. Kopajtic, J. L. Katz, C. J. Loland, L. Shi and A. H. Newman, *J. Med. Chem.*, 2014, **57**, 1000–1013.

S2. Oxford Diffraction (2010). *CrysAlisPro* (Version 1.171.34.44). Oxford Diffraction Ltd., Yarnton, Oxfordshire, UK.

S3. P. Macchi, H.B. Bürgi, A. S. Chimpri, J. Hauser and Z. Gal, *J. Appl. Cryst.,* 2011, **44**, 763–771.

S4. G. M. Sheldrick, *Acta Cryst*., 2015, **A71**, 3–8.

S5. G. M. Sheldrick, *Acta Cryst*., 2015, **C71**, 3–8.

S6. E. Monzani, L. Quinti, A. Perotti, L. Casella, M. Gullotti, L. Randaccio, S. Geremia, G. Nardin, P. Faleschini and G. Tabbì, *Inorg. Chem.*, 1998, **37**, 553–562.

S7. A. Mandal, A. Sarkar, A. Adhikary, D. Samanta and D. Das, *Dalton Trans.*, 2020, **49**, 15461–15472.

S8. H.-H. Cui, W. Lv, W. Tong, X.-T. Chen and Z.-L. Xue, *Eur. J. Inorg. Chem.*, 2019, **2019**.

S9. (*a*) M. A. Halcrow, L. Mei LindyChia, X. Liu, E. J. L. McInnes, L. J. Yellowlees, F. E. Mabbs, I. J. Scowen, M. McPartlin and J. E. Davies, *J. Chem. Soc., Dalton Trans.*, 1999, 1753–1762; (*b*) M. A. Halcrow, E. J. L. McInnes, F. E. Mabbs, I. J. Scowen, M. McPartlin, H. R. Powell and J. E. Davies, *J. Chem. Soc., Dalton Trans.*, 1997, 4025–4036; (*c*) C. L. Foster, X. Liu, C. A. Kilner, M. Thornton-Pett and M. A. Halcrow, *J. Chem. Soc., Dalton Trans.*, 2000, 4563–4568.