# **Supporting Information**

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

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#### **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-2carboxaldehyde, TEMPO and vanillyl alcohol) were purchased from commercial suppliers and used without further purification. For recording NMR spectra, CDCl<sub>3</sub> was purchased from Sigma-Aldrich and used without further purification. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at Bruker AV-400 and JEOL-400 spectrometer (<sup>1</sup>H at 400 MHz and <sup>13</sup>C at 101 MHz). <sup>1</sup>H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethylsilane ( $\delta$ 0.00 ppm) and  ${}^{13}C{}^{1}H$  NMR chemical shifts are referenced in ppm with respect to CDCl<sub>3</sub> ( $\delta$ 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.<sup>S1</sup>

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<sub>3</sub>.OEt<sub>2</sub> (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. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub> solution (100 mL) and extracted with chloroform (3 x 20 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. All volatiles were evaporated under high vacuum to yield 2-(benzhydrylthio)ethanamine (2.381 g, 98%) as light yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>1</sub>). 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<sub>1</sub> (1.297 g, 98%) as a reddish brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> Calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>S 333.1425, Found 333.1417. Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>S (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 ν<sub>max</sub> (cm<sup>-1</sup>): 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<sub>2</sub>). A solution of L<sub>1</sub> (1.328 g, 4.00 mmol) in methanol (30 mL) was cooled down to 0 °C in an ice-bath. Solid NaBH<sub>4</sub> (0.341 g, 9.00 mmol) was then added in small quantity to the solution at 0 °C under vigorous stirring. The resultant reaction mixture was stirred at 0 °C 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<sub>2</sub>SO<sub>4</sub> and dried under high vacuum to get L<sub>2</sub> (1.321 g, 99%) as brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  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]<sup>+</sup> Calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>2</sub>S 335.1582, Found 335.1577. Anal. Calcd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>S (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 v<sub>max</sub> (cm<sup>-1</sup>): 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 L<sub>1</sub> (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]<sup>+</sup> 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  $v_{max}$  (cm<sup>-1</sup>): 2880–3120 (C–H), 1650 (CH = N), 1405–1610 (C=N, py; C=C, ph), 1080 and 620 (ClO<sub>4</sub><sup>-</sup>), 680–790 (C–S).

**Synthesis of 1b.** A solution of Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.093 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of L<sub>2</sub> (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]<sup>+</sup> 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  $v_{max}$  (cm<sup>-1</sup>): 3182 and 3270 (N–H), 2820–3100 (C–H), 1400–1610 (C=N, py; C=C, ph), 1079 and 620 (ClO<sub>4</sub><sup>-</sup>), 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  $L_1$  (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]<sup>+</sup> 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 v<sub>max</sub> (cm<sup>-1</sup>): 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<sub>2</sub> (0.033 g, 0.25 mmol) in methanol (10 mL) was added dropwise to a solution of  $L_2$  (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]<sup>+</sup> 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  $v_{max}$  (cm<sup>-1</sup>): 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<sub>3</sub> (0.5 mL). The solution was transferred in a NMR tube. Required amount of THF (40.6  $\mu$ L, 0.50 mmol) as external standard was added to the CDCl<sub>3</sub> solution and <sup>1</sup>H NMR spectrum was recorded. Occasionally the CDCl<sub>3</sub> 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:**

Isolated yield = 
$$\frac{\text{weight of isolated vanillin/molecular weight of vanillin}}{\text{weight of vanillyl alcohol used/molecular weight of vanillyl alcohol}} \times 100\%$$
$$= \frac{\text{moles of isolated vanillin}}{\text{moles of used vanillyl alcohol}} \times 100\%$$
For example, isolated yield = 
$$\frac{1.520 \text{ g/152.15 g/mol}}{1.520 \text{ g/152.15 g/mol}} \times 100\% = \frac{10 \text{ mmol}}{100\%} \times 100\%$$

10 mmol

**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<sub>2</sub> peak (four protons) at 1.58 ppm, vanillyl alcohol: benzyl peak (two protons) at 4.58 ppm and vanillin:

1.541 g/154.17 g/mol

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.<sup>*a*</sup>

_0	Н				H	0
	air,	Cu catalyst:	5/2.5 mol	%, TEMP	O: 20 mol%	
		sol	lvent, 40 <sup>c</sup>	°C, time		
ОН					(	DH
Ent	Cu	TEMPO	Temp.	Time	Solvent	Conv. <sup>b</sup>
	(mol%)	(mol%)	(°C)	(h)	(1:1 mixture)	(%) <sup>c</sup>
1	<b>1a</b> (5)	20	40	6	MeCN	6 (6 <sup>c</sup> )
2	<b>1b</b> (5)	20	40	6	MeCN	$6(5^{c})$
3	<b>2a</b> (2.5)	20	40	6	MeCN	$24(21^{c})$
4	<b>2b</b> (5)	20	40	6	MeCN	34 (32 <sup>c</sup> )
5	<b>1a</b> (5)	20	40	3	water	6
6	<b>1b</b> (5)	20	40	3	water	8
7	<b>2a</b> (2.5)	20	40	3	water	26 (24 <sup>c</sup> )
8	<b>2b</b> (5)	20	40	3	water	34 (33 <sup>c</sup> )
9	<b>1a</b> (5)	20	40	6	ethanol	5
10	<b>1b</b> (5)	20	40	6	ethanol	6
11	<b>2a</b> (2.5)	20	40	6	ethanol	25 (23 <sup>c</sup> )
12	<b>2b</b> (5)	20	40	6	ethanol	32 (30 <sup>c</sup> )
13	<b>1a</b> (5)	20	40	6	acetone	<5
14	<b>1b</b> (5)	20	40	6	acetone	<5
15	<b>2a</b> (2.5)	20	40	6	acetone	13
16	<b>2b</b> (5)	20	40	6	acetone	16
17	<b>1a</b> (5)	20	40	6	THF	6
18	<b>1b</b> (5)	20	40	6	THF	7
19	<b>2a</b> (2.5)	20	40	6	THF	26 (23 <sup>c</sup> )
20	<b>2b</b> (5)	20	40	6	THF	$31(30^{\circ})$

<sup>*a*</sup>Reactions conducted in a vial (10 ml) with 0.50 mmol of vanillyl alcohol, 5/2.5 mol% of Cucat and 20 mol% of TEMPO (16 mg) in 2 mL of solvent at 40 °C. <sup>*b*</sup>Conversions of vanillyl alcohol to vanillin were determined by <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard. <sup>*c*</sup>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<sub>2</sub>SO<sub>4</sub>. 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 <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) 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, 10 mol%, TEMP

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<sub>2</sub>SO<sub>4</sub>. 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<sub>2</sub>SO<sub>4</sub>. 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<sub>3</sub>. Slow evaporation of the CHCl<sub>3</sub> 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<sub>3</sub> (0.5 mL). Required amount of THF as standard was added and <sup>1</sup>H NMR spectrum was recorded. Finally, the CDCl<sub>3</sub> solution was dried under high vacuum and the product vanillin was purified by column chromatography.



Figure S1. <sup>1</sup>H NMR of 2-(benzhydrylthio)-ethanamine hydrochloride in CDCl<sub>3</sub> at r.t.



Figure S2: <sup>1</sup>H NMR of 2-(benzhydrylthio)-ethanamine in CDCl<sub>3</sub> at r.t.



Figure S3: <sup>1</sup>H NMR of N-(2-(benzhydrlthio) ethyl)-1-(pyridine-2-yl) methanimine ( $L_1$ ) in CDCl<sub>3</sub> at r.t.



Figure S4: <sup>13</sup>C NMR of N-(2-(benzhydrlthio) ethyl)-1-(pyridine-2-yl) methanimine  $(L_1)$  in CDCl<sub>3</sub> at r.t.



Figure S5: <sup>1</sup>H NMR of 2-(benzhydrylthio)-N-(pyridine-2-ylmethyl) ethan-1-amine ( $L_2$ ) in CDCl<sub>3</sub> at r.t.



Figure S6: <sup>13</sup>C NMR of 2-(benzhydrylthio)-N-(pyridine-2-ylmethyl) ethan-1-amine  $(L_2)$  in CDCl<sub>3</sub>.



Figure S7: FTIR Spectrum of Ligand L<sub>1</sub>.



Figure S8: FTIR Spectrum of Ligand L<sub>2</sub>.



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<sup>[S2]</sup> using an INCOATEC micro source (Cu-K $\alpha$  radiation,  $\lambda = 1.54$  Å, multilayer optics) and Al filtered.<sup>[S3]</sup> 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  $\omega$  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*<sup>[S2]</sup> 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*<sup>[S2]</sup> was applied. Data collection and refinement parameters are given in Table 1.

The structure was solved by direct methods using *SHELXT*<sup>[S4]</sup>, 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*<sup>[S5]</sup> program.

	1a	1b	2a	2b	<b>2b</b> (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 <sub>22</sub> H <sub>23</sub> Cl <sub>5</sub> CuN <sub>2</sub> S
CCDC	2088325	2088326	2088327	2088328	2088330
Formula weight (g mol <sup>-1</sup> )	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>I</i> 2/a	$P2_1/c$	Pī	$P2_1/c$	Pbca
<i>a</i> (Å)	21.1362(6)	15.46340(11)	8.7543(2)	17.0171(3)	19.10688(11)
<i>b</i> (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
$\gamma(\text{deg})$	90	90	113.730(2)	90	90
volume (Å <sup>3</sup> )	8819.7(6)	4499.68(6)	1002.26(6)	2076.00(5)	4916.61(5)
Z	1	4	2	4	8
$D_{\text{calc}} (\text{g cm}^{-3})$	1.407	1.422	1.547	1.500	1.589
$\mu \text{ (mm}^{-1})$	3.172	3.130	5.022	4.849	7.156
F(000)	3856	2004	478	964	2392
Crystal Size	$0.3 \times 0.2 \times 0.1 \text{ mm}^3$	$0.4 \times 0.3 \times 0.2 \text{ mm}^3$	$0.12 \times 0.11 \times 0.1 \text{ mm}^3$	$0.3 \times 0.2 \times 0.1 \text{ mm}^3$	$0.2\times0.1\times0.1~\text{mm}^3$
$\theta$ Range (deg)	4.096-68.248	3.668-68.247	5.456-68.249	5.228-68.232	3.352-68.250
Index Ranges	$-24 \le h \le 25, -12 \le k \le 13, -$	$-18 \le h \le 15, -19 \le k \le 19, -$	$-10 \le h \le 10, -10 \le k \le 8, -17$	$-20 \le h \le 19, -11 \le k \le 11, -10$	$-23 \le h \le 23, -10 \le k \le 11, -$
	$45 \le l \le 46$	$21 \le 1 \le 22$	$\leq l \leq l /$	$16 \le l \le 16$	$31 \le 1 \le 28$
Reflections collected	604/1	66480	14/01	29160	83189
Independent reflections ( $R_{int}$ )	8076 (0.1078)	8238 (0.0439)	3667(0.0485)	3790(0.0828)	4495(0.1195)
Completeness to theta = $66.9/^{\circ}$	99.94	99.96	99.93	99.95	99.96
Refinement method	Full-matrix least-squares on	Full-matrix least-squares on	Full-matrix least-squares on	Full-matrix least-squares on	Full-matrix least-squares on
	F <sup>2</sup>	F <sup>2</sup>	F <sup>2</sup>	F <sup>2</sup>	F <sup>2</sup>
Data/Restraints/parameters	8076/0/575	8238/2/557	3667/0/244	3790/0/244	4495/0/280
Goodness-of-fit on F2	1.058	1.083	1.194	1.042	1.098
Final <i>R</i> indices $[I>2\sigma(I)]$	$R_1 = 0.1106, wR_2 = 0.2839$	$R_1 = 0.0734, wR_2 = 0.2103$	$R_1 = 0.0853, wR_2 = 0.2628$	$R_1 = 0.0406, wR_2 = 0.1082$	$R_1 = 0.0513, wR_2 = 0.0988$
R indices (all data)	$R_1 = 0.1247, wR_2 = 0.2952$	$R_1 = 0.0764, wR_2 = 0.2132$	$R_1 = 0.0873, wR_2 = 0.2633$	$R_1 = 0.0423, wR_2 = 0.1098$	$R_1 = 0.0539, wR_2 = 0.1001$
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

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

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

PLAT306\_ALERT\_2\_B Isolated Oxygen Atom (H-atoms Missing ?) ..... 09 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	<b>2</b> b	2b·CHCl <sub>3</sub>
Cu–N (pyridine)	2.078(6) 2.257(8)	2.016(3) 2.012(3)	2.035(8)	2.0166(19)	2.023(3)
Cu–N (imine)	1.941(7) 2.004(7)	_	2.025(8)	_	
Cu–N (secondary amine)	_	2.059(3) 2.040(3)	_	2.0345(18)	2.040(2)
Cu–S (thioether)	2.410(8) 2.943(8)	2.8099(8)	_	2.7991(6)	2.829(8)
Cu–Cl (bridge)	_	_	2.590(3) 2.288(3)	_	
Cu–Cl (terminal)	_	_	2.251(3)	2.2567(6) 2.2622(6)	2.2818(8) 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.** <sup>1</sup>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.** <sup>13</sup>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.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S17.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S18.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S19.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S20.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S21.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S22.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S23.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S24.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S25.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S26.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S27.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S28.** <sup>1</sup>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 <sup>1</sup>H NMR spectroscopy using THF (0.50 mmol) as external standard.



**Figure S29.** <sup>1</sup>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 <sup>1</sup>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.<sup>[S6, S7]</sup> Complex **2b** (0.010 g, 0.02 mmol) was dissolved in a degassed 1:1 mixture of acetone and water (4 mL) under N<sub>2</sub> 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<sub>2</sub>SO<sub>4</sub> 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<sub>3</sub><sup>-</sup> was detected by UV-Vis spectrophotometer due to the development of the characteristic I<sub>3</sub><sup>-</sup> 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<sub>2</sub>.



Figure S31. EPR spectrum of 2b in a 1:1 mixture of acetone and water at 77K under N<sub>2</sub>.

The effect of temperature has also been examined by EPR spectroscopy (Figure S30). The Xband EPR spectra of **2b** in 1:1 acetone water mixture at 77K exhibit axial symmetry with  $g_1 > g_{\perp}$  suggesting that the unpaired electron resides in the  $d_{x^2-y^2}$  ground state. The hyperfine coupling constant  $A_1$  of 167 is also very similar as observed in ternary Cu(II) complexes having square pyramidal geometry.<sup>[S8]</sup> Moreover, all these  $g_1, g_{\perp}$  and  $A_1$  values are very close to the Cu(II) square pyramidal complexes reported by Halcrow and co-workers.<sup>[S9]</sup>



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 vanilly 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 vanilly 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  $F([M_F - 2C1]^+ \text{ for } C_{21}H_{24}N_2CuO_3S)$ .

Supplementary Informa	tion: App	endix 2		Summary o	f Zero Pas	s Metrics Toolkit											
Yield, conversion, select	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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
								Flag									
molecular	weight	of product	t v 10	0		Yield	99.9	99.9									
$AE = \frac{1}{total molecua}$	lr weigh	t of reacte	ints × 10	U		Conversion	100.0	100.0									
	Selectivity 99.9						99.9					mass	mw	mol			
$RME = \frac{mass \ of \ iso}{mass \ of \ iso}$	$ME = \frac{mass of isolated product}{100} \times 100$					AE	81.7					Product	1.521	152.150	0.0099967		
total mass	$ME = \frac{Mass of issues product }{total mass of reactants} \times 100$					RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)											_	reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any o	of the follow	ving)			L	ist Highly Hazardo	us Solvents	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofo	rm, DCE, nit	tromethane,	CS <sub>2</sub> , HMPA	1		Nor	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	ig for any	of the follov	ving)			L	ist substa	nces plus the red fl	agged H-co	des below							
Highly ex	Highly explosive H200, H201, H202, H2							None									
Explosive thermal runaway H240								None									
Fatally	toxic		H3	00, H310, H3	30			None									
Mutag	enic			H350				None									
Repro-	Repro-toxic			H360				None									
Serious environme	ntal impli	cations		H420				None									

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

Yield, conversion, select	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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									
malecular	weight a	of product				Yield	99.9	99.9									
total molecua	tr weigh	t of reacte	mts × 10			Conversion	100.0	100.0									
						Selectivity	99.9	99.9					mass	mw	mol		
-RME - mass of iso	lated pro	$\frac{oduct}{\times 10}$	0			AE	81.7					Product	1.521	152.150	0.0099967		
total mass	of react	ants				RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any c	of the follov	ving)				List Highly Hazardou	is Solvents I	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofo	rm, DCE, nit	romethane,	CS <sub>2</sub> , HMPA	۱ <u>ــــــــــــــــــــــــــــــــــــ</u>		Non	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	ng for any	of the follow	ving)			L	ist substa	nces plus the red fl	agged H-coc	les below							
Highly ex	plosive		H200,	H201, H202,	H203			None									
Explosive therr	mal runaw	/ay		H240				None									
Fatally	toxic		H3	00, H310, H3	30			None									
Mutagenic H350								None									
Repro-		H360				None											
Serious environme	ntal impli	cations		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, select	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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									
malecular	weight a	of <del>produc</del> i				Yield	99.9	99.9									
total molecua	tr weigh	t of reacto	mts × 10			Conversion	100.0	100.0									
						Selectivity	99.9	99.9					mass	mw	mol		
-RME - mass of iso	lated pro	$oduct \times 10$	0			AE	81.7					Product	1.521	152.150	0.0099967		
total mass	of react	ants				RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any c	of the follov	ving)				List Highly Hazardou	is Solvents I	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofo	rm, DCE, nit	romethane,	CS <sub>2</sub> , HMPA	1		Non	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	ag for any	of the follow	ving)			L	ist substa	nces plus the red fl	agged H-coc	les below							
Highly ex	plosive		H200,	H201, H202,	H203			None									
Explosive therr	mal runaw	vay		H240				None									
Fatally	toxic		H3	00, H310, H3	30			None									
Mutagenic H350								None									
Repro-			H360				None										
Serious environme	ntal impli	cations		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, selec	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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									
malacular	weight a	of product	t			Yield	99.9	99.9									
total molecua	i <mark>tr weig</mark> h	t of reacte	mts 🔨 🗖	-		Conversion	100.0	100.0									
						Selectivity	99.9	<b>9</b> 9.9					mass	mw	mol		
-RME-	HE = mass of isolated product total mass of reactants					AE	81.7					Product	1.521	152.150	0.0099967		
total mass	total mass of reactants					RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solve	nts (Red f	lag for any o	of the follow	wing)				List Highly Hazardo	us Solvents	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofor	rm, DCE, ni	tromethane,	CS <sub>2</sub> , HMPA	\		Nor	ne								
Health and Safety (Zero	o Pass)																
Health & safety (Red fla	ag for any	of the follov	ving)				List substa	inces plus the red fl	agged H-coo	les below							
Highly ex	plosive		H200,	H201, H202,	H203			None									
Explosive there	ay		H240				None										
Fatally	toxic		H3	00, H310, H3	30			None									
Mutag	genic			H350				None									
Repro-	toxic			H360				None									
Serious environme	ntal impli	cations		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, select	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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									
malecular	weight	of <del>produc</del>	ŧ			Yield	99.9	99.9									
total molecua	lr weigh	t of react	mts × 10			Conversion	100.0	100.0									
						Selectivity	99.9	99.9					mass	mw	mol		
-RME-mass of iso	lated pr	oduct × 10	10			AE	81.7					Product	1.521	152.150	0.0099967		
total mass	of react	ants				RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)											_	reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any o	of the follow	ving)				List Highly Hazardou	is Solvents I	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofo	rm, DCE, nit	tromethane,	CS <sub>2</sub> , HMPA	۱ <u>ــــــــــــــــــــــــــــــــــــ</u>		Non	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	ag for any	of the follow	wing)			L	ist substa	nces plus the red fl	agged H-coc	les below							
Highly ex	plosive		H200,	H201, H202,	H203			None									
Explosive therr	mal runaw	vay		H240				None									
Fatally	toxic		H3	00, H310, H3	30			None									
Mutagenic H350								None									
Repro-	toxic			H360				None									
Serious environme	ntal impli	cations		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, select	tivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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
								Flag									
malecular	weight (	of <del>produci</del>				Yield	99.9	99.9									
total molecua	tr weigh	t of reacte	mts × 10			Conversion	100.0	100.0									
						Selectivity	99.9	99.9					mass	mw	mol		
mass of iso	lated pro	oduct × 10				AE	81.7					Product	1.521	152.150	0.0099967		
total mass	of react	ants				RME	89.4						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any c	of the follov	ving)				List Highly Hazardou	is Solvents I	Below							
Et <sub>2</sub> O, Be	enzene, CO	Cl <sub>4</sub> , chlorofo	rm, DCE, nit	romethane,	CS <sub>2</sub> , HMPA	\\		Non	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	ag for any	of the follow	ving)			L	ist substa	nces plus the red fl	agged H-coc	les below							
Highly ex	plosive		H200,	H201, H202,	H203			None									
Explosive therr	mal runaw	/ay		H240				None									
Fatally	toxic		H3	00, H310, H3	30			None									
Mutagenic H350								None									
Repro-		H360				None											
Serious environme	ntal impli	cations		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, AE, RME, MI/PMI	and OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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
										Flag								
							Yield		99.9	99.9								
							Conversior	۱	100.0	100.0								
mass of isola	ted product	400					Selectivity		99.9	➡ 99.9			Duad		Mass	MW	Mol	
I total mass of	reactants	100					RMF		81.7	OF	109 3		Prod	uci	1.52 mass	152.15	0.01	
									05.4	0L	105.5		Unreacted	limiting	111035			
AF-	weight of pr	winct .	100				PMI total		55.9				react	ant	0.00			
total molecua	ir weight of 1	reactants	a, se se				PMI Reacti	on	24.9									
							PMI reacta	nts,										
mass intensity = -	otal mass in	a process or	process s	tep			reagents, c	atlyst	1.5									
	ma	ass of proau	cı				PMI reaction	on										
RME VION							solvents		23.5									
$OE = \frac{1}{AE} \times 100$																		
							PMI Worku	цр	30.9									
							PMI Worku	ıp										
							chemical		0.0									
							PMI worku	р										
							solvents		30.9									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	tBuOH, BnC	OH, nBuOF DH, ethylen	e glycol, acet sulfolane	one, MEK, I	vie, MeOH, VIBK, <b>AcOEt,</b>	water	, aceto	ne, <b>AcOEt</b>									
Problematic solvents: only if substitution do advantages	(acceptable es not offer )	DMSO, cyc AcOMe, TI MTBE, <b>cycl</b>	clohexanor HF, heptan ohexane, c	e, DMPU, Ac e, Me-cyclohe hlorobenzen	OH, Ac2O, A exane, tolue e. formic ac	Acetonitrile, ene, xylene, id. pyridine,												
	,		, .	Me-THF				non	e									
Hazardous solvents: Th have significant health a concerns	ese solvents and/or safety	dioxane, pe I	ntane, TEA DMA, NMP,	diisopropyl methoxyeth	ether, DMI anol, hexar	E, DCM, DMF, ne												
Highly bazardous sol	vente. The	Et O Bonz		hlarafarm D	CE nitrom	othana CS			e									
solvents which are agre	ed not to be	L120, Del12	.ene, cci <sub>4</sub> , c	нмра	CL, III. 0110	ethane, co <sub>2</sub> ,												
used, even in scr	eening			TIMITA														
	-																	
Catalyst/enzyme (First P	ass)			Tick							Tick	1						
Catalyst or enzyme use	Talyst/enzyme (Hrst Pass) Tick Talyst/enzyme (Hrst Pass) Tick Tick Talyst/enzyme (Hrst Pass) Tick Tick Tick Tick Tick Tick Tick Tick			Facile re	ecovery of c	atalyst/	/enzyme	Green Flag	x									
Use of stoichiometric	without any catalyst/reagents. Flag A C Catalyst/reagents. Flag C Catalyst/reagents. Catalyst/reagents C Catalyst C Catal				cataly	st/enzyme i	not reco	overed	Amber Flag									
Use of reag	gents in excess	s	Red Flag															

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

Critical elements														
Supply remaining	Flag colour	Note element	1	H 204	Remaining years until depletion of known reserves				He					
5-50 years	Red Flag		3	i Be	(based on current rate of extraction)		B C	7 8 9 1 N O F	° Ne					
50-500 years	Amber Flag	Cu	6.94 11	1 9.012182 12 Ia Mg	50-100 years 100-500 years		10.811 12.01 13 14 AI S	07 14.00674 15.9994 18.99840 2 35 16 17 1 i P S Cl	0.1797 8 Ar					
+500 years	Green Flag		22.5	8977 24.3050 20 21 K Ca Sc	22 23 24 27 26 Ti V Cr Mn Fe	27 28 29 Co Ni Cu	26 98 153 28.08 90 81 17 Zn Ga G	55 39.97376 32.066 35.4527 3 31 34 35 3 e As Se Br	9.948 6 Kr					
			39.0 <b>37</b>	983 40.078 44.95591 38 39	47.867         50.9415         51.9961         50.93804         55.845           40         41         42         43         64	58.93320         58.6934         63.346           45         46         47	05.30 09.723 73.65 48 49 50	78.92180         78.96         79.904         8           51         52         53         5	4					
			F 85.4	Sr         Y           678         \$7.61         \$85.085	Zr         Nb         Mo         Tc         Ru           91.224         92.90638         95.94         (98)         101.01	Rh         Pd         Ag           102.9055         106.42         107.8082	Cd In St	n Sb Te l 3232,760 127,60 126,9044 1	Xe 31.29					
			132	56 57 <b>Ba La*</b> 9054 137.327 138.9055	22         23         24         25         25           Hf         Ta         W         Re         Os           176.4%         180.9429         188.84         166.207         196.247	77         78         79           Ir         Pt         Au           192.257         195.076         196.9665	80         81         82           Hg         Ti         Pi           200.59         204.3833         270.2	N)         84         85         8           Bi         Po         At         2000 (200)         (210)         <	6 Rn 222)					
			87	r Ra Ac‡	104         105         106         107         108           Rf         Db         Sg         Bh         Hs	109 110 111 Mt Ds Rq	112 113 114 Uub Uut Uu	115 116 117 1 Iq Uup Lv Uus	18 Uuo					
			(22)	226.025 (227)	(257) (266) (263) (262) (265)	(266) (271) (272)	(285) (284) (289)	(288) (292)						
				Lanthanic	des * Ce Pr Nd Pm	62 60 64 Sm Eu Gd	65 66 67 Tb Dy Ho	68 69 70 7 Er Tm Yb	Lu					
			_		140.9077         144.24         (145)         150.36           90         91         92         93	153.964         157.25         158.9253           94         95         96	158.9253         162.50         164.93           97         98         99	03         167.26         168.9342         173.04         1           100         101         102         1	<b>74.967</b> 03					
				Actinid	es ‡ Th Pa U Np 232.0381 231.0289 218.0284 (237)	Pu         Am         Cm           (244)         (243)         (247)	Bk Cf Es (247) (251) (252)	Fm Md No (257) (258) (259) (2	Lr (62)					
France (First Dass)			Tiel					Tiek						
Reaction run between	0 to 70°C		LICK					LICK						
		Green Flag	Х		Reaction run at	t reflux	Red Flag							
Reaction run between -: to 140°C	20 to 0 or 70	Amber Flag			Departies run F <sup>0</sup> C er m	ara balaw tha								
Reaction run below -2	0 or above				solvent boiling	ore below the g point	Green Flag	x						
140°C		Red Flag												
<b>D</b> · · · · ///				_										
Batch/flow	Groot	n Flag	Tick		Work Up	a		List						
Batch/flow Flow Batch	Gree	n Flag	Tick		Work Up quenchin filtration	g		List						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up quenchin filtration centrifugat	g 1		List Filtration,						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up quenchin filtration centrifugat crystallisati	g 1 ion	Green Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Gree Ambe	n Flag er Flag 2	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera	g ion ion ature	Green Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag :	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange. ou	g ion ion ature / sublimation (< uenching into	Green Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greet Ambe	n Flag :	Tick		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol	g ion ature / sublimation (< ienching into vent	Green Flag Amber Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Gree Ambe	n Flag Pr Flag Pr	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io	g ion ature / sublimation (< uenching into vent in exchange	Green Flag Amber Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greet Ambe	n Flag Pr Flag S	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recret	ig ion ion ture / sublimation (< uenching into vent in exchange ature allication	Green Flag Amber Flag Red Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greet Ambe	n Flag	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta	ig ion ion sture / sublimation (< uenching into vent in exchange ature allisation	Green Flag Amber Flag Red Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greet Ambe	n Flag	Tick X		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta	g ion ion ature / sublimation (< ienching into vent in exchange ature allisation	Green Flag Amber Flag Red Flag	List Filtration, Evaporation						
Batch/flow Flow Batch Health & safety	Greet Ambe	n Flag	Tick		Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta	g ion ion ature / sublimation (< ienching into vent in exchange ature allisation	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	d H-codes	List su	bstances and H	-codes		
Batch/flow Flow Batch Health & safety	Gree Ambe	n Flag print flag prin	Tick X Am	ber Flag	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/ioo high tempera multiple recrysta	g ion ion ature / sublimation (< renching into vent in exchange ature ature allisation	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	Ind H-codes	List su	bstances and H	-codes		
Batch/flow Flow Batch Health & safety Highly explosive	Gree Ambe	Flag H202, H203	Tick X Ann H205,	ber Flag_ H220, H224	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta Green Flag If no red or amber flagged H codes	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	Id H-codes	List su	bstances and H	1-codes		
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway	Gree: Ambe 4 1200, H201, H230, H2	Flag H202, H203 240, H250	Tick X H205,	ber Flag H220, H224	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	ad H-codes	List su Vanillyl al	bstances and H	4-codes		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic	Gree: Ambe Ambe H200, H201, H200, H201, H230, H2	Flag H202, H203 240, H250	Tick X H205, H301.	bber Flag H220, H224 H241 H311, H331.	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	Id H-codes	List su Vanillyl al Vanill	bstances and H cohol: H315, H in: H317, H319 ne: H225, H310	4-codes 319, H336; , H302;		
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity	Gree Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H340, H350,	Flag H202, H203 40, H250 10, H330 H360, H370, H370 172	Tick X Am H205, H301, H301, H341,	ber Flag H220, H224 H311, H331, H351, H361, H351, H361,	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/ioo high temper- multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	d H-codes	List su Vanillyl al Vanill Acetor Ethylace	bstances and H cohol: H315, H in: H317, H319 ne: H225, H319 tate: H225, H319	H-codes 319, H336; H302; I, H336; 19, H336.		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	Gree Ambe Ambe 1200, H201, H200, H201, H230, H2 H300, H3 H340, H350, H3	Flag H202, H203 440, H250 10, H330 H360, H370, 172 H411, H420	тіск К Ам Н205, Н301, Н	Image: state	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation List substances ar none	Id H-codes	List su Vanillyl al Vanill Acetor Ethylace	cohol: H315, H in: H317, H319 ne: H225, H310 tate: H225, H3	<b>1-codes</b> <b>319, H336;</b> <b>H302;</b> J, H336; 19, H336.		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	Green Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	Flag Flag H202, H203 H202, H203 H360, H370, H360, H370, H370, H370, H370, H370, H370, H370, H370, H370, H370, H370, H370, H370	Tick X Ann H205, H301, H	ber Flag H220, H224 H241 H311, H331, H351, H361, V1, H373 D1, H412	Work Up quenchin filtration centrifugat crystallisati Low tempera- distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera- multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	ig ion ion iture / sublimation (< uenching into vent un exchange ature allisation List substances	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation List substances an none	d H-codes	List su Vanillyl al Vanill Aceto Ethylace	cohol: H315, H in: H317, H319 ne: H225, H319 tate: H225, H3	<b>319, H336;</b> <b>H302;</b> J, H336; 19, H336.		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	Gree Ambe Ambe H200, H201, H200, H201, H230, H2 H300, H3 H300, H300, H30	Flag Flag Flag Flag Flag Flag Flag Flag	тіск К К Н205, Н301, Н301, Н301,	http://www.actionality.org/act	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/ioo high tempera multiple recrysta Green Flag If no red or amber flagged H codes present then green flag	g ion ion iture / sublimation (< uenching into vent in exchange ature allisation List substances non	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation List substances are none	Id H-codes	List su Vanillyl al Vanill Aceto Ethylace	bstances and H cohol: H315, H in: H317, H319 ne: H225, H315 tate: H225, H3	<b>319, H336;</b> <b>H302;</b> J, H336; 19, H336.		
Batch/flow Flow Batch Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica Chemical identified as S	Gree Ambe Ambe Particle H200, H201, H200, H200, H200, H200, H200, H200, H200, H200, H200, H200, H200,	Flag         1           Flag         1           Flag         1           H202, H203         1           H202, H203         1           H360, H370, H360, H370, H360, H370, H360, H370, H370, H411, H420         1           Inental concerr         I           Very High Conviluence         1	Тіск К Алт Н205, Н301, Н341,	Image: state of the s	Work Up quenchin filtration centrifugat crystallisati Low tempera distillation/evaporation, solvent exchange, qu aqueous sol chromatography/io high tempera multiple recrysta Green Flag If no red or amber flagged H codes present then green flag List substances of vert	g	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation List substances ar none	Id H-codes	List su Vanillyl al Vanill Aceto Ethylace	bstances and H cohol: H315, H in: H317, H319 ne: H225, H315 tate: H225, H3	H-codes 319, H336; , H302; , H336; 19, H336.		

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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 <sup>3</sup> )	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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	1	100.0						Mass	N/\\/	Mol	
RMR - mass of isola	$\frac{ted product}{\vee}$	100					AE		81.7	55.5			Prod	uct	1.52	152.15	0.01	
total mass of	reactants						RME		89.4	OE	109.3				mass			
AR - molecular	weight of pr	oduct	00				PMI total		55.7				Unreacted	l limiting ant	0.00			
total molecua	ir weight of t	reactants					PMI Reacti	on	24.8				. Cutt		0.00			
ý.	atal marc in			tem			PMI reacta	nts,										
mass intensity = -	TR	ass of produ	CL				reagents, c	atlyst	1.3									
DME							PMI reaction solvents	on	23.5									
$OE = \frac{100}{AE}$																		
							PMI Worku	ıp	30.9									
							PMI Worku	μ	0.0									
							PMI worku	a										
							solvents		30.9									
Solvents (First Pass)				A - O'r - A - (		4- 14-011	List	solvent	s below									
Preterred solve	ents	tBuOH, BnC	OH, NBUOH )H, ethylen	e glycol, acet sulfolane	one, MEK, I	viibk, <b>AcOEt,</b>	water	, aceto	ne, <b>AcOEt</b>									
Problematic solvents: only if substitution do advantages	(acceptable es not offer )	DMSO, cyc AcOMe, TI MTBE, <b>cycl</b>	clohexanon HF, heptane ohexane, cl	e, DMPU, Ac e, Me-cyclohe nlorobenzen	OH, Ac2O, A exane, tolue e, formic ac	Acetonitrile, ene, xylene, id, pyridine,												
				Me-THF				non	e									
Hazardous solvents: Th have significant health a concerns.	iese solvents and/or safety	dioxane, pe	ntane, TEA, DMA, NMP,	diisopropyl methoxyeth	ether, DMI anol, hexar	E, DCM, DMF, 1e												
Highly hazardous sol	vents: The	Et <sub>-</sub> O Benz	ene CCL c	hloroform D	CF nitrom	ethane CS-												
solvents which are agre	ed not to be	2120, 00112	ciic, cci <sub>4</sub> , c	НМРА		culture, co <sub>2</sub> ,												
								- Holli										
Catalyst/enzyme (First P	ass)			Tick							Tick	1						
Catalyst or enzyme use without any ca	ed, <b>or</b> reaction	n takes place nts.	Green Flag	х		Facile re	ecovery of c	atalyst/	/enzyme	Green Flag	x							
Use of stoichiometric	c quantities o	f reagents	Amber Flag			cataly	st/enzyme i	not reco	overed	Amber Flag								
Use of reag	gents in exces	S	Red Flag															

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

Supply remaining       Pig colour       Note (1)       Note (2)	Supply containing       Reg close       Note (see (see (see (see (see (see (see (s	Supply remaining         Flag colo           5-50 years         Red Fla           50-500 years         Amber Flag           +500 years         Green Flag	ur Note element ag Cu ag					CALLER'S		Part Part						
5-30 (par)       iseling       iseling <td>5-50 yars     Anile Tig     Cu     <td< td=""><td>5-50 years Red Fla 50-500 years Amber Fl +500 years Green Fla</td><td>g Cu ag Cu ag</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<></td>	5-50 yars     Anile Tig     Cu     Cu <td< td=""><td>5-50 years Red Fla 50-500 years Amber Fl +500 years Green Fla</td><td>g Cu ag Cu ag</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	5-50 years Red Fla 50-500 years Amber Fl +500 years Green Fla	g Cu ag Cu ag													
50:500 years       Amber Nag       Cu	94:00 yant       Andor Ag       Cu       Image Provided State       Ima	50-500 years Amber Fl +500 years Green Fl	ag Cu ag													
-300 years       Green Flag       Image: Second Se	1:500 µtans       0reen hig       0	+500 years Green Fla	ag													
Second field       Note Field	indication       indication <td></td>															
Image: Section run between 00 07/0° (reen ring to the section run at reflux to 100 °C (reen ring to the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 r/0 root or and the section run between 20 to 00 root or and the sectin run between 20 to 00 root or and the section run between 20 to 0	A   A   A   A   A   A   A   A   A															
Image: Section run between 10:0 70°C       Green Flag       X       Amber Flag	Image: Section of the sectin the sectin the secting of the secting the section o															
Image: Section run between 0:0 07/C       Green Flag       X       Reaction run at reflux       Bed Bias       C	$   \   \   \   \   \   \   \   \   \   $															
Image: State in the state	$ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$															
Image: Section run between 0 to 70°C       Green Flag       X       Reaction run at reflux       Red flag       Image: Section run at reflux       Red flag         Reaction run between 0 to 70°C       Green Flag       X       Reaction run at reflux       Red flag       Image: Section run at reflux       Red flag <td></td>																
Image: Section 1/10       Image: Section 1/10<																
Energy (First Pas)         Tick         Reaction run at reflux         Red Flag         Control         Control <th< td=""><td>Image: prime prima prime prima prime prima prime prima prima prima prima prima prim</td><td></td><td></td><td>_</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	Image: prime prima prime prima prime prima prime prima prima prima prima prima prim			_												
Energy (First Pass)       Tick       Tick       Reaction run between 0 to 70°C       Green Flag       X       Reaction run at reflux       Red Flag       Image: Second content of the	Energy (First Pass)         Tick         Tick         Reaction run between 0 to 77°C         Green Flag         X         Reaction run S*C or more below the solvent boiling point         Read flag         Control 1000         Contro			_												
Energy (First Pass)         Tick         Tick         Reaction run betwen 0 to 70°         Green Flag         X         Reaction run at reflux         Red Flag         Image: Control of 0 and the control of 0	trace       Tech       Image: constraint of the section run between 0 to 70°C       Green Flag       X       Image: constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Constraint of the section run at refux       Field size       Field size <th< td=""><td></td><td></td><td>_</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>			_												
Reaction run between 0 to 70°C       Green Flag       X       Reaction run at reflux       Red Flag       C <thc< th="">       C       C</thc<>	Reaction run between 0 to 07 70       Kee Flag       X       Reaction run at refux       Red flag       Constraint of the source of the	Energy (First Pass)		Tick						Tick						
Reaction run between -20 to 0 or 70 to 140°C     Amber Flag     Reaction run 5°C or more below thoiling point     Green Flag     Reaction run below -20 to 20 r about thoiling point     Green Flag     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 to 20 r about thoiling point     Reaction run below -20 r about thoiling point     Reacting run run below -20 r abou	Reaction un between -20 to 20 or 7 to 140°C       Inder Flag       Inder	Reaction run between 0 to 70°C	Green Flag	x		F	Reaction run at	t reflux	Red Flag							
Reaction run S L of more below run       Green Flag       X         Reactor run S L of more below run       Green Flag       X       Image: Solvent boling point       Image: Solvent point point       Image: Solvent point point       Image: Solvent point point       Image: Solvent point poin	Reaction run below -20 or above 140°C       Reatting point       Green Flag solvent boiling point       X       <	Reaction run between -20 to 0 or to 140°C	70 Amber Flag			Desetier	5°C	ana halawaha								
140°C     Red Rag     Work Up     Image: Control or and the second or and th	140°C         Red Flag         Tick         Work Up         Ist	Reaction run below -20 or above	e			Reaction	solvent boiling	g point	Green Flag	x						
Batch/flow       Image: Constraint of the sector of the sec	Bath/flow       Green Flag       Inck       Work Up       More Up       Ist       <	140°C	Red Flag													
Batch // How     Green Flag     Itek     Work Up     List     List     Image: Constraint of the state o	Batch         Green Flag         X         Quenching         Itext         List         Control         Contro         Contro         Contro </td <td></td>															
Internation       Outcome flag       X       Outcome flag       Z       Z       Outcome flag       Z <thz< th="">       Z       Z       <thz< th=""> <thz< td=""><td>Image: Constraint of the second of</td><td>Batch/flow</td><td>reen Elag</td><td>Tick</td><td></td><td>Work Up</td><td>quenchin</td><td>ng .</td><td></td><td>List</td><td></td><td></td><td></td><td></td><td></td><td></td></thz<></thz<></thz<>	Image: Constraint of the second of	Batch/flow	reen Elag	Tick		Work Up	quenchin	ng .		List						
Image: Construct of the safety	Image: Section of the secting of the secting of th	Batch An	nber Flag	x			filtration	י <u>ה</u> ו								
Image: Construct of the second of the se	Image: Construct of the second of the sec						centrifugat	tion	Green Flag	Filtration,						
Low temperature distillation/evaporation/ sublination (< distillation/evaporation sublination (< distillation/eva	Image: Constraint of the						crystallisat	ion	Green ridg	Evaporation						
Amber Flag Amber Flag   Health & safety Amber Flag   Red Flag Amber Flag   Health & safety Amber Flag   Health & safety Imaged Flag   Health & safety H200, H201, H202, H203   H200, H201, H202, H203 H205, H220, H224   Imaged H codes   present then green flag	indication       indication <td></td> <td></td> <td></td> <td></td> <td>distillation</td> <td>Low tempera n/evaporation</td> <td>ature i/ sublimation (&lt;</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>					distillation	Low tempera n/evaporation	ature i/ sublimation (<								
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$					solven	t exchange, qu aqueous sol	uenching into Ivent	Amber Flag							
Image: high temperature     Ked Flag       high temperature     Ked Flag       multiple recrystallisation     Image: high temperature       Health & safety     Image: high temperature       Health & safety     Image: high temperature       Red Flag     Amber Flag       Highly explosive     H200, H201, H202, H220       H200, H201, H202, H230     H205, H220, H224       If no resent then green flag       Present then green flag	Image: Main and					chror	natography/io	on exchange	Ded Stee							
Health & safety       Red Flag       Amber Flag       Green Flag       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       If no red or amber flagged H codes       Vanilly alcohol: H315, H319,	Health & safety       Red Flag       Amber Flag       Green Flag       List substances and H-codes       List substances       List substan					m	nigh temper ultiple recrysta	ature allisation	Red Hag							
Health & safety       Red Flag       Amber Flag       Green Flag       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       Fragged H codes       Fragged H codes         Explosive thermal       H230, H240, H250       H241       present the green flag       Vanilly lakehol: H315, H319, H3	Health & safetyNew FlagAmber FlagGreen FlagList substances and H-codesList substances and H-codesList substances and H-codesList substances and H-codesHighly explosiveH200, H201, H202, H203H205, H220, H224If no ed or amber flagged H codes present H=r green flagIf no ed or amber flagged H codes present H=r green flagIf no ed or amber flagged H codes present H=r green flagNoneNanily alcohol: H315, H319, H336; Vanily alcohol: H315, H319, H336; Codes Codes Codes H300, H300, H300, H300, H301, H311, H331, H341, H351, H341, H351, H371, H373Nanily HNoneNanily alcohol: H315, H319, H336; Codes Present H=r green flag Present H=r green flag Present H=r green flag Present H=r green flagNoneNanily alcohol: H315, H319, H336; Codes Codes Ethylacetate: H225, H319, H336; Ethylacetate: H226, H310, H310, H310, H310, H310						e je									
Health & safety     Red Flag     Amber Flag     Green Flag       Highly explosive     H200, H201, H202, H203     H205, H220, H224     If no red or amber flagged H codes       Explosive thermal     H230, H240, H250     H241     present then green flag	Health & safety       Red Flag       Amber Flag       Green Flag       If no red or amber flagged H codes       If no red or amber flagged H codes       Vanilly alcohol: H315, H319, H336;       Main H310, H330       H201, H311, H331       Freen flag       If no red or amber flagged H codes       Present then green flag       None       Vanilly alcohol: H315, H319, H336;       Vanilly alcohol: H315, H319, H336;       Vanilly alcohol: H315, H319, H336;       If no red or amber flagged H codes       Present then green flag       Present then green flag       None       Vanilly alcohol: H315, H319, H336;       Vanilly alcohol: H315, H319, H336;       If no red or amber flagged H codes       Present then green flag       Present then green flag       Present then green flag       None       Vanilly alcohol: H315, H319, H336;       If no red or amber flagged H codes       Present then green flag       Present then gree							List substances a	and H-codes	List substances an	d H-codes	List sul	stances and H	l-codes		
Highly explosive     H200, H201, H202, H203     H205, H220, H224     If no red or amber flagged H codes       Explosive thermal     H230, H240, H250     H241     present then green flag	Highly explosive fragged H200, H201, H202, H203       H205, H202, H224       If no red or amber flagged H codes present then green flag present then green flag       None       Vanilly alcohol: H315, H319, H336; Vanillin: H317, H319, H302;         Toxic       H300, H310, H330       H301, H311, H331, H300, H300, H300, H300, H300, H301, H317, H303, H300, H310, H330       H301, H311, H331, H311, H331, H311, H373       If no red or amber flagged H codes       none       none       Vanilly alcohol: H315, H319, H302; Vanillin: H317, H319, H302;       Vanilly alcohol: H315, H319, H302;         Iong Term toxicity       H340, H350, H360, H370, H372       H341, H351, H361, H372       H401, H411, H420       H401, H412	Health & safety	Pod Flag	Ambor	r Flog	Gro	on Elog									
Explosive thermal H230, H240, H250 H241 present then green flag	Explosive thermal runaway       H230, H240, H250       H241       present then green flag present then green flag         Toxic       H300, H310, H330       H301, H311, H331, H372       H301, H311, H331, H371, H373       Present then green flag         Environmental implications       H400, H411, H420       H401, H411, H420       H401, H412	Highly explosive H200, H2	201, H202, H203	H205, H22	20, H224	If no rec	d or amber									
	runaway       Vanillin: H317, H319, H302;         Toxic       H300, H310, H330       H301, H311, H331,         Long Term toxicity       H340, H350, H360, H370, H341, H351, H361, H373       H372       H371, H373         Environmental implications       H400, H410, H411, H420       H401, H412       H401, H412	Explosive thermal H230,	, H240, H250	H24	41	present th	en green flag					Vanillyl ald	ohol: H315, H	319, H336;		
Trunaway Name None None None Name Name Name Name Name Name Name Nam	Long Term toxicity         H340, H350, H360, H370, H31, H361, H361, H361, H371, H373           Environmental implications         H400, H410, H411, H420         H401, H412	Toxic H300	H310 H330	H301 H31	11 H331			none	e	none		Vanilli	n: H317, H319,	H302;		
Long Term toxicity H340, H350, H360, H370, H341, H351, H361, H371,	Environmental implications     H400, H411, H420     H401, H412	Long Term toxicity H340, H3	50, H360, H370, H372	H341, H35	51, H361, H373							Ethylacet	ate: H225, H315	19, H336.		
Environmental H400, H411, H420 H401, H412	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Environmental H400, H4	410, H411, H420	H401,	H412											
	Use of chemicals of environmental concern List substances of very high concern	Use of chemicals of envir	onmental concerr	1		List sub	stances of ver	y high concern								
Use of chemicals of environmental concern List substances of very high concern	Chemical identified as Substances of Very High Concern by Red Flag none	Chemical identified as Substance ChemSec which a	s of Very High Cor re utilised	ncern by	Red Flag		none									

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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 <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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								
							Conversior	า	100.0	100.0						5.0347	84-1	
mass of isola	ted product	100					Selectivity		99.9	99.9			Brod	uct		152.15	0.01	
total mass of	reactants						RMF		89.4	OF	109 3		FIOU		mass	132.13	0.01	
malania	weight of m	minut								02	205.5		Unreacted	limiting				
AE = total molecula	incigne of pr	X	100				PMI total		55.9				react	ant	0.00			
CDGGL INDICCIDA	n weight of	7 Gall-Gallona					PMI Reacti	on	25.0									
8	otal mass in	a process or	process s	tep			PMI reacta	nts,										
mass intensity = -	π	oss of produ	L				reagents, c	atlyst	1.5									
							PMI reaction	on										
$OE = \frac{2ME}{4F} \times 100$							solvents		23.5									
							PIMI Worku	цр	30.9									
							PIMI Worku	цр	0.0									
							DMLworku		0.0									
							solvents	ib	30.9									
							301761163		50.5									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, Et tBuOH, BnC	:OH, nBuOH DH, ethylen	l, AcOipr, AcO e glycol, acet sulfolane	OnBu, PhON one, MEK, N	/le, MeOH, MIBK, <b>AcOEt,</b>	wate	er, EtOl	⊣, AcOEt									
Problematic solvents: only if substitution do advantages	(acceptable es not offer )	DMSO, cyc AcOMe, TI MTBE, <b>cycl</b>	clohexanon HF, heptane Iohexane, cl	e, DMPU, Ac e, Me-cyclohe hlorobenzen Me-THF	OH, Ac2O, A exane, tolue e, formic ac	Acetonitrile, ene, xylene, cid, pyridine,		non	e									
Hazardous solvents: Th have significant health a concerns.	ese solvents and/or safety	dioxane, pe I	ntane, TEA, DMA, NMP,	diisopropyl methoxyeth	ether, DME anol, hexar	E, DCM, DMF, ne		non	e									
Highly hazardous solvents which are agree used, even in scree	vents: The eed not to be eening	Et <sub>2</sub> O, Benz	ene, CCl <sub>4</sub> , c	hloroform, D HMPA	CE, nitrome	ethane, CS <sub>2</sub> ,		non	e									
C-4-1	<b>\</b>			71-1-							<b>T</b> 1-1-							
Catalyst or enzyme use	ass)	takes nlace	Green	ПСК				_	ļ		TICK	1						
without any ca	atalyst/reage	nts.	Flag	х		Facile re	ecovery of c	atalyst,	/enzyme	Green Flag	x							
Use of stoichiometric	c quantities o	f reagents	Amber Flag			cataly	st/enzyme i	not rec	overed	Amber Flag								
Use of reag	gents in exces	S	Red Flag															

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

Critical elements															
Supply remaining	Flag colour	Note element													
5-50 years	Red Flag														
50-500 years	Amber Flag	Cu													
+500 years	Green Flag														
										_					
				1			1								
Energy (First Pass)			Tick						Tick	]					
Reaction run betweer	n 0 to 70°C	Green Flag	х			Reaction run a	it reflux	Red Flag							
Reaction run between -	20 to 0 or 70	Amber Flag				5 <sup>9</sup> 0									
Reaction run below -7	0 or above				Reactio	solvent boilin	g point	Green Flag	х						
140°C		Red Flag					6 F								
Batch/flow			Tick		Work Up				List						
Flow	Green	n Flag	v			quenchir	ng								
Datch	AIIDE	I Flag	^			centrifuga	tion		Filtration.						
						crystallisat	tion	Green Flag	Evaporation						
					distillatio	Low temper on/evaporatior	ature n/ sublimation (<								
					solver	nt exchange, qu aqueous so	uenching into Ivent	Amber Flag							
					chro	matography/io	on exchange								
					-	high temper	rature	Red Flag							
						indiciple recryst	amsduun								
							List substances	and H-codec	List substances or	nd H-codec	List ou	hstances and l	-codes		
Health & safety								and n-coules	List substances an	nu n-coues	LIST SU	stances and i	-coues		
	Red	Flag	Amb	er Flag	Gre	en Flag								 	
Highly explosive	H200, H201,	H202, H203	H205, H	220, H224	flagge	d or amber d H codes									
Explosive thermal	H230, H2	40, H250	н	241	present th	nen green flag					Vanillyl al	cohol: H315, H	319, H336;		
Tullaway					-		non	e	none		H225 H	эт, пэтэ, пэ 19 <sup>.</sup> Ethvlaceta	te H225		
Toxic	H300 <u>. H3</u>	10, H330	H301, H	311, H331.								,			
Toxic Long Term toxicity	H300, H3 H340, H350, H3	10, H330 H360, H370,	H301, H3 H341, H3 H371	311, H331, 351, H361, L H373								Н319, Н336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H3 H341, H3 H371 H371 H401	311, H331, 351, H361, I, H373 ., H412	_							H319, H336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H H341, H H371 H371 H401	311, H331, 351, H361, I, H373 ., H412								Н319, Н336.			
Toxic Long Term toxicity Environmental implications Use of chemica	H300, H3 H340, H350, H3 H400, H410, Is of environn	10, H330 H360, H370, 72 , H411, H420 nental concer	H301, H3 H341, H3 H371 H401	311, H331, 351, H361, I, H373 ., H412	List sub	bstances of <u>ver</u>	ry high concern					Н319, Н336.			

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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 <sup>3</sup> )	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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	۱	100.0	100.0								
mass of isola	ted product	400					Selectivity		99.9	➡ 99.9			Dued		Mass	MW 1FD 1F	Mol	
I total mass of	reactionis	100					RMF		81.7	OF	109 3		Prod	uci	1.52 mass	152.15	0.01	
									05.4	0L	105.5		Unreacted	limiting	111035			
AF-	weight of pr	oduct	100				PMI total		55.8				react	ant	0.00			
total molecua	ir weight of t	eactants	1.5452				PMI Reacti	on	24.8									
	_						PMI reacta	nts.										
mass intensity = -	otai mass in	a process or	process s	tep			reagents, o	atlyst	1.3									
		ass of proau					PMI reaction	on										
ZME							solvents		23.5									
AE A. 100																		
							PMI Work	цр	30.9									
							PMI Work											
							chemical		0.0									
							PMI worku	р										
							solvents		30.9									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, Et tBuOH, BnC	OH, nBuOH DH, ethylen	l, AcOipr, AcO e glycol, acet sulfolane	OnBu, PhON one, MEK, I	Ле, MeOH, ЛIBK, <b>AcOEt,</b>	wate	er, EtOl	⊣, AcOEt									
Problematic solvents: only if substitution do advantages	(acceptable es not offer )	DMSO, cyc AcOMe, TI MTBE, <b>cycl</b>	clohexanon HF, heptane ohexane, cl	e, DMPU, Ac e, Me-cycloho nlorobenzen Me-THE	OH, Ac2O, A exane, tolue e, formic ac	Acetonitrile, ene, xylene, id, pyridine,												
Hazardous solvents: Th		diovano, no	ntano TEA	diicopropul	othor DM			non	e									
have significant health a	and/or safety	uloxalle, pe		methoxyeth	anol hevar													
concerns.	ind, or survey			memoxyeth	unoi, nexui													
Highly bazardous sol	vents. The	Et O Benz	ana CCL c	hloroform D	CE nitrom	athana CS			e									
solvents which are agre	ed not to be	L1 <sub>2</sub> 0, benz	.ene, cci <sub>4</sub> , c	ымал	CL, III. 0110	cinane, co <sub>2</sub> ,												
used, even in scr	eening			TIMITA														
Catalyst/enzyme (First P	ass)			Tick							Tick	1						
Catalyst or enzyme use	ed, or reaction	takes place	Green	v		Eacilore	acovery of c	atalyst	lenzume	Green Elag	v							
without any ca	atalyst/reage	nts.	Flag	^		Facilie II	ecoveryorc	ataiyst	enzyme	Green Flag	^							
Use of stoichiometric	c quantities o	f reagents	Amber Flag			cataly	st/enzyme	not rec	overed	Amber Flag								
Use of reag	gents in exces	S	Red Flag															

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

Critical elements															
Supply remaining	Flag colour	Note element													
5-50 years	Red Flag														
50-500 years	Amber Flag	Cu													
+500 years	Green Flag														
										_					
				1			1								
Energy (First Pass)			Tick						Tick	]					
Reaction run betweer	n 0 to 70°C	Green Flag	х			Reaction run a	it reflux	Red Flag							
Reaction run between -	20 to 0 or 70	Amber Flag				5 <sup>9</sup> 0									
Reaction run below -7	0 or above				Reactio	solvent boilin	g point	Green Flag	х						
140°C		Red Flag					6 F								
Batch/flow			Tick		Work Up				List						
Flow	Green	n Flag	v			quenchir	ng								
Datch	AIIDE	I Flag	^			centrifuga	tion		Filtration.						
						crystallisat	tion	Green Flag	Evaporation						
					distillatio	Low temper on/evaporatior	ature n/ sublimation (<								
					solver	nt exchange, qu aqueous so	uenching into Ivent	Amber Flag							
					chro	matography/io	on exchange								
					-	high temper	rature	Red Flag							
						indiciple recryst	amsduun								
							List substances	and H-codec	List substances or	nd H-codec	List ou	hstances and l	-codes		
Health & safety								and n-coules	List substances an	nu n-coues	LIST SU	stances and i	-coues		
	Red	Flag	Amb	er Flag	Gre	en Flag								 	
Highly explosive	H200, H201,	H202, H203	H205, H	220, H224	flagge	d or amber d H codes									
Explosive thermal	H230, H2	40, H250	н	241	present th	nen green flag					Vanillyl al	cohol: H315, H	319, H336;		
Tullaway					-		non	e	none		H225 H	эт, пэтэ, пэ 19 <sup>.</sup> Ethvlaceta	te H225		
Toxic	H300 <u>. H3</u>	10, H330	H301, H	311, H331.								,			
Toxic Long Term toxicity	H300, H3 H340, H350, H3	10, H330 H360, H370,	H301, H3 H341, H3 H371	311, H331, 351, H361, L H373								Н319, Н336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H3 H341, H3 H371 H371 H401	311, H331, 351, H361, I, H373 ., H412	_							H319, H336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H H341, H H371 H371 H401	311, H331, 351, H361, I, H373 ., H412								Н319, Н336.			
Toxic Long Term toxicity Environmental implications Use of chemica	H300, H3 H340, H350, H3 H400, H410, Is of environn	10, H330 H360, H370, 72 , H411, H420 nental concer	H301, H3 H341, H3 H371 H401	311, H331, 351, H361, I, H373 ., H412	List sub	bstances of <u>ver</u>	ry high concern					Н319, Н336.			

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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 <sup>3</sup> )	Density (g ml⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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	1	100.0	100.0								
mass of isola	ted product	400					Selectivity		99.9	➡ 99.9			Ducal		Mass	MW	Mol	
RME = iotal mass of	reacianis	100					RMF		81.7	OF	109 3		Prod	uci	1.52 mass	152.15	0.01	
									05.4	0L	105.5		Unreacted	limiting	111033			
AR-	weight of pr	winct	100				PMI total		55.8				react	ant	0.00			
total molecua	ir weight of 1	eactants	1.000				PMI Reaction	on	24.8									
	_						PMI reacta	nts.										
mass intensity = -	otai mass in	a process or	process s	tep			reagents, c	atlyst	1.3									
		uss of prout					PMI reaction	on										
ZME							solvents		23.5									
AE AE																		
							PMI Worku	р	30.9									
							PMI Worku	ıp										
							chemical		0.0									
							PMI worku	р										
							solvents		30.9									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, El tBuOH, Bni	tOH, nBuOH OH, ethylen	l, AcOipr, AcC e glycol, acet sulfolane	one, MEK, I	Me, MeOH, MIBK, <b>AcOEt,</b>	wate	er, EtOl	H, AcOEt									
Problematic solvents: only if substitution doe	(acceptable es not offer	DMSO, cy AcOMe, T	clohexanon HF, heptane	e, DMPU, Act e. Me-cyclohe	OH, Ac2O, J exane, tolu	Acetonitrile, ene. xylene.												
advantages	)	MTBE, cyc	lohexane, cl	nlorobenzen	e, formic a	cid, pyridine,												
				Me-THF				non	e									
Hazardous solvents: Th have significant health a	ese solvents and/or safety	dioxane, pe	entane, TEA, DMA, NMP,	diisopropyl methoxyeth	ether, DM anol. hexa	E, DCM, DMF, ne												
concerns.								non	<u>_</u>									
Highly hazardous sol	vents: The	Et <sub>2</sub> O, Benz	zene. CCL. c	hloroform. D	CE. nitrom	ethane. CS-			<u> </u>									
solvents which are agre	ed not to be			НМРА														
used, even in scre	eening							non	e									
Catalyst/enzyme (First P	'ass)			Tick							Tick							
Catalyst or enzyme use without <b>any</b> ca	d, <b>or</b> reaction	takes place	Green Flag	х		Facile re	ecovery of ca	atalyst,	/enzyme	Green Flag	x							
Use of stoichiometric	quantities of	f reagents	Amber Flag			cataly	st/enzyme r	not rec	overed	Amber Flag								
Use of reag	ents in exces	s	Red Flag															

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

Critical elements															
Supply remaining	Flag colour	Note element													
5-50 years	Red Flag														
50-500 years	Amber Flag	Cu													
+500 years	Green Flag														
										_					
				1			1								
Energy (First Pass)			Tick						Tick	]					
Reaction run betweer	n 0 to 70°C	Green Flag	х			Reaction run a	it reflux	Red Flag							
Reaction run between -	20 to 0 or 70	Amber Flag				5 <sup>9</sup> 0									
Reaction run below -7	0 or above				Reactio	solvent boilin	g point	Green Flag	х						
140°C		Red Flag					6 F								
Batch/flow			Tick		Work Up				List						
Flow	Green	n Flag	v			quenchir	ng								
Datch	AIIDE	I Flag	^			centrifuga	tion		Filtration.						
						crystallisat	tion	Green Flag	Evaporation						
					distillatio	Low temper on/evaporatior	ature n/ sublimation (<								
					solver	nt exchange, qu aqueous so	uenching into Ivent	Amber Flag							
					chro	matography/io	on exchange								
					-	high temper	rature	Red Flag							
						indiciple recryst	amsduun								
							List substances	and H-codec	List substances or	nd H-codec	List ou	hstances and l	-codes		
Health & safety								and n-coules	List substances an	nu n-coues	LIST SU	stances and i	-coues		
	Red	Flag	Amb	er Flag	Gre	en Flag								 	
Highly explosive	H200, H201,	H202, H203	H205, H	220, H224	flagge	d or amber d H codes									
Explosive thermal	H230, H2	40, H250	н	241	present th	nen green flag					Vanillyl al	cohol: H315, H	319, H336;		
Tullaway					-		non	e	none		H225 H	эт, пэтэ, пэ 19 <sup>.</sup> Ethvlaceta	te H225		
Toxic	H300 <u>. H3</u>	10, H330	H301, H	311, H331.								,			
Toxic Long Term toxicity	H300, H3 H340, H350, H3	10, H330 H360, H370,	H301, H3 H341, H3 H371	311, H331, 351, H361, L H373								Н319, Н336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H3 H341, H3 H371 H371 H401	311, H331, 351, H361, I, H373 ., H412	_							H319, H336.			
Toxic Long Term toxicity Environmental implications	H300, H3 H340, H350, H3 H400, H410,	10, H330 H360, H370, 72 , H411, H420	H301, H H341, H H371 H371 H401	311, H331, 351, H361, I, H373 ., H412								Н319, Н336.			
Toxic Long Term toxicity Environmental implications Use of chemica	H300, H3 H340, H350, H3 H400, H410, Is of environn	10, H330 H360, H370, 72 , H411, H420 nental concer	H301, H3 H341, H3 H371 H401	311, H331, 351, H361, I, H373 ., H412	List sub	bstances of <u>ver</u>	ry high concern					Н319, Н336.			

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Yield, AE, RME, MI/PMI	and OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm³)	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	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
										Flag								
							Yield		99.9	99.9								
							Conversion		100.0	100.0								
mass of isola	ted product						Selectivity		99.9	99.9					Mass	MW	Mol	L
RME =	reactants X						AE		81.7	05	100.0		Prod	uct	1.52	152.15	0.01	-
							RIVIE		89.4	UE	109.3		Unversion	live it in a	mass			
moleculor	weight of pr	oduct					PMI total		573				Unreacted	ant	0.00			
AE = total molecua	r weight of 1	eactants	100				PMI Reactio	n	26.3				Teact		0.00			
							PMI reactar	ate	2010									
mass intensity = -	otal mass in	a process or	process s	tep			reagents ca	atlyst	15									
	7720	iss of produ	ect.				DMAL reaction											
PMF							solvents	n	24.8									
0E = AE × 100							Solvents		24.0									
							PMI Worku	n	30.0									
							PMI Worku	p n	50.5									
							chemical	٢	0.0									
							PMI worku	n										
							solvents	,	30.9									
Solvents (First Pass)							List s	olvent	s below									
Preferred solve	ents	water, Ef tBuOH, Bn(	tOH, nBuOH OH, ethylen	, AcOipr, AcO e glycol, acet sulfolane	OnBu, PhON one, MEK, I	Me, MeOH, MIBK, <b>AcOEt,</b>	w	ater, A	cOEt									
Problematic solvents:	(acceptable	DMSO, cy	<mark>clohexanon</mark>	e, DMPU, Ac	ОН, Ac2O, /	Acetonitrile,												
only if substitution do	es not offer	AcOMe, T	HF, heptan	e, Me-cycloh	exane, tolu	ene, xylene,												
advantages	)	MTBE, CYC	lonexane, cl	Me-THF	e, formic ac	cia, pyriaine,		тнг										
Hazardous solvents: Th have significant health a concerns.	ese solvents ind/or safety	dioxane, pe	ntane, TEA, DMA, NMP,	diisopropyl methoxyeth	ether, DMI anol, hexai	E, DCM, DMF, ne		non	e									
Highly hazardous solv	vents: The	Et <sub>2</sub> O, Benz	zene, CCl <sub>4</sub> , c	hloroform, D	CE, nitrom	ethane, CS <sub>2</sub> ,												
solvents which are agre used, even in scre	ed not to be eening			HMPA				non										
Catalyst/enzyme (First P	ass)			Tick							Tick							
Catalyst or enzyme use without <b>any</b> ca	d, <b>or</b> reaction atalyst/reager	takes place nts.	Green Flag	х		Facile re	ecovery of ca	italyst/	/enzyme	Green Flag	x							
Use of stoichiometric	c quantities of	f reagents	Amber Flag			cataly	st/enzyme n	ot reco	overed	Amber Flag								
Use of reag	ents in excess	S	Red Flag															

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

Critical elements			10 A	and the second	M.C. San La Sa	The state of the		and the second							
Supply remaining	Flag colour	Note element							1.1.2.2.2.2.						
5-50 years	Red Flag														
50-500 years	Amber Flag	Cu													
+500 years	Green Flag														
			_							_					
				1											
Energy (First Pass)			Tick						Tick						
Reaction run betweer	n 0 to 70°C	Green Flag	х		F	Reaction run a	t reflux	Red Flag							
Reaction run between -	20 to 0 or 70	Amber Flag				0									
Reaction run below -2	0 or above				Reaction	n run 5°C or m solvent boilin	nore below the	Green Flag	х						
140°C		Red Flag				Solvene Solling	B point								
Batch/flow			Tick		Work Up				List						
Batch/flow Flow Batch	Green	n Flag	Tick		Work Up	quenchir	ng		List						
<b>Batch/flow</b> Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchir filtration centrifugat	ng n tion		List Filtration,						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchir filtratior centrifugat crystallisat	ng n tion	Green Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchir filtratior centrifugat crystallisat Low temper n/evaporation	ng n tion tion ature n/ sublimation (<	Green Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up distillation solven	quenchir filtratior centrifugar crystallisat Low temper n/evaporation t exchange, qu aqueous so	ng n tion ature / sublimation (< uenching into lvent	Green Flag Amber Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag rr Flag	Tick X		Work Up distillation solven chror	quenchir filtration centrifugat crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ice	ng n tion ature / sublimation (< uenching into lvent on exchange	Green Flag Amber Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag rr Flag	Tick X		Work Up distillation solven chror	quenchir filtration centrifugal crystallisat Low temper n/evaporation t exchange, qu aqueous so natography/icd high temper ultiple recryst	n tion ature J sublimation (< uenching into lvent on exchange rature allisation	Green Flag Amber Flag Red Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up distillation solven chror	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ic high temper ultiple recryst	ng n tion ature 1/ sublimation (< uenching into lvent pon exchange rature allisation	Green Flag Amber Flag Red Flag	List Filtration, Evaporation						
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up distillation solven chror m	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ici high temper ultiple recryst	ng	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul	ostances and I	H-codes		
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag er Flag	Tick X Amb		Work Up distillation solven chror m	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ici high temper ultiple recryst	18	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation		List sul	ostances and I	H-codes		
Batch/flow Flow Batch Health & safety Highly explosive	Greer Ambe	n Flag r Flag Flag Flag H202, H203	Tick X Amb H205, H	er Flag 220, H224	Work Up distillation solven chror m Gree fla gree	quenchir filtration centrifugal crystallisat Low temper n/evaporation t exchange, qu aqueous so natography/ic high temper ultiple recryst	n n tion ature of sublimation (< uenching into lvent on exchange rature allisation	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul	ostances and I	H-codes		
Batch/flow Flow Batch Health & safety Highly explosive Explosive thermal	Greer Ambe Ambe Red H200, H201, H230, H2	n Flag r Flag Flag H202, H203 40, H250	Tick X Amb H205, H	er Flag 2220, H224 224	Work Up distillation solven chror m Gree flaged present th	quenchir filtration centrifugal crystallisat Low temper n/evaporation t exchange, qi aqueous soo natography/ic high temper ultiple recryst en Flag d or amber I H codes en green flag	ng n	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul	ostances and l	H-codes		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic	Greer Ambe Ambe Red H200, H201, H230, H2 H300, H3	n Flag er Flag Flag H202, H203 40, H250	Тіск X Атв H205, H H301 H	er Flag 220, H224 241	Work Up distillation solven chror m Gree flagged present th	quenchir filtration centrifugat crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ic high temper ultiple recryst en Flag d or amber I H codes en green flag	n tion ature ature ature sublimation (< uenching into lvent on exchange rature allisation	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul Vanily al	2000 2000 2000 2000 2000 2000 2000 200	H-codes 1319, H336; 1302; THF: 10 H335-		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity	Green Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H340, H350, H340, H350,	n Flag r Flag Flag H202, H203 40, H250 40, H250 H360, H370, 72	Тіск Х Ата Н205, н Н 1301, н Н341, н Н341, н Н37	er Flag 220, H224 241 251, H331, 351, H361, L, H373	Work Up distillation solven chror m flagged present th	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so natography/icd high temper ultiple recryst d or amber I H codes en green flag	n tion cion ature t/ sublimation (< uenching into lvent on exchange ature allisation List substances	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul Vanillyl ale Vanillin: H225, H Ethylace	cohol: H315, H H317, H319, H 303, H316, H3 tate: H225, H3	H-codes <b>319, H336;</b> <b>1302; THF:</b> 19, H335; 119, H336.		
Batch/flow Flow Batch Health Safety Health Safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	Green Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H3	n Flag er Flag Flag H202, H203 40, H250 10, H330 H360, H370, 72 H411, H420	Tick X X H205, H H301, H H341,	er Flag 220, H224 241 311, H331, 351, H361, L, H373 ., H412	Work Up distillation solven chror m Gree flagged present th	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/iuc high temper ultiple recryst en Flag d or amber I H codes en green flag	n tion ature J sublimation (< uenching into lvent on exchange ature allisation	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul Vanillyi ala Vanillin: H225, H Ethylace	2000 2000 2000 2000 2000 2000 2000 200	H-codes 1319, H336; 1302; THF: 19, H335; 119, H336.		
Batch/flow Flow Batch Health Safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications	Green Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H340, H410	n Flag er Flag Flag H202, H203 40, H250 10, H330 H360, H370, 72 H411, H420	Tick X Amb H205, H H301, H H341, H H341, H H341, H H341, H H341, H H341, H	er Flag 220, H224 241 311, H331, 351, H361, L, H373 ., H412	Work Up distillation solven chror m Gree flagged present th	quenchir filtration centrifugai crystallisat Low temper n/evaporation t exchange, qu aqueous so matography/ici high temper ultiple recryst d or amber I H codes en green flag	n tion ature J sublimation (< uenching into lvent on exchange allisation List substances non	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation List substances an THF: H35	il.	List sul Vanillyl alu Vanillin: H225, H Ethylace	2000 2000 2000 2000 2000 2000 2000 200	H-codes 1319, H336; 1302; THF: 19, H335; 19, H336.		
Batch/flow Flow Batch Batch Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	Green Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H340, H410 H340, H410	n Flag r Flag Flag H202, H203 40, H250 10, H330 H360, H370, 72 H411, H420	Тіск X H205, H H301, H H341,	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 ., H412	Work Up distillation solven chror m Gree flaged present th	quenchir filtration centrifugal crystallisat Low temper n/evaporation t exchange, qu aqueous soo natography/ic high temper ultiple recryst en Flag d or amber I H codes en green flag	n tion ature y sublimation (< uenching into lvent on exchange allisation List substances non y high concern	Green Flag Amber Flag Red Flag and H-codes	List Filtration, Evaporation	nd H-codes	List sul Vanillyl alu Vanillin: H225, H Ethylace	25 20 20 20 20 20 20 20 20 20 20 20 20 20	H-codes 1319, H336; 1302; THF: 19, H335; 119, H336.		

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