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Supporting Information

Cooperative Nanoscale ZnO-NiO-Ni Heterojunction for Sustainable Catalytic Amidation of Aldehydes with Secondary Amines

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1. Experimental Section

1.1 Materials and Method

Commercially sourced solvents were used for material synthesis and catalytic reactions without further purification. The reagents used in the studies were commercially available and used as received. To optimize reactions and examine substrate scope in oxidation reactions, studies were carried out in a pressure tube attached to a reaction station, which maintained a dry, oxygen-free environment. PXRD analysis was performed using a Philips X'pert X-ray powder diffractometer with Cu Kα radiation (λ = 1.54178 Å). The JEOL JSM 7100F microscope was used to generate high-resolution scanning electron microscopy (HR-SEM) pictures. To avoid charging, samples were coated with a thin layer of gold via sputtering before imaging. For HR-SEM examination, materials were ultrasonically dispersed in a methanol-acetone mixture for 30 minutes before being deposited onto aluminum stubs with a micropipette. After the solvent had completely evaporated, the samples were dried in a vacuum desiccator for 12 hours. Thermo-Scientific's NEXSA device was used to perform X-ray photoelectron spectroscopy (XPS). The analyzer was calibrated to 284.8 eV for the binding energy of the C1s peak, and the pass energy was held constant at 20 eV. An electron flood cannon with low energy was used to reduce sample charging. Data was processed using the CasaXps program. Samples were placed on 300-mesh carbon-coated copper grids, and JEOL JEM-2100 high-resolution transmission electron microscopy (HR-TEM) pictures were obtained. Following 30 minutes of sonication to disperse the samples in ethanol, capillary action was used to deposit the samples onto copper grids. For two hours, grids were vacuum-dried in a desiccator. To perform the GC-MS analysis, the Shimadzu GCMS QP 2020 system was employed. The Perkin Elmer Optima 2000 apparatus was used to perform inductively coupled plasma (ICP) analysis. Each sample was prepared by mixing it with aqua regia (HCl: HNO3 = 3:1) and letting it evaporate on a hot plate until it was completely dry, which allowed the metals to dissolve. This was done three

times, evaporating and dissolving. To digest the residual material for ICP-MS analysis, it was dissolved in strong nitric acid, heated to eliminate extra nitric acid, and then diluted nitric acid was used. The content of zinc and nickel was determined by doing three consecutive ICP-MS tests on each sample at three distinct concentrations.

2. Synthesis of Materials

2.1 General Procedure for Synthesis of Materials

The materials used in this study have already been synthesized and reported by us.[1, 2] Zinc acetate sodium acetate [CH_3COONa] (1.6 g, 20 mmol) and [$Zn(OAc)_2.H_2O$] (2.2 g, 10 mM) in methanol (30 mL) at ambient temperature for an hour was the first step in the synthesis of **ZN-O**. An additional hour of stirring at ambient temperature was then required after adding 1.5 g (10 mmol) of nickel sulfate [$NiSO_4.6H_2O$] to the reaction mixture. After completing the first stage, a solution containing 2 mL of 42 mM hydrazine hydrate was added, and the resulting mixture was heated for 4 hours at 90 °C with reflux in an oil bath. Subsequently, the reaction mixture was moved into a 150 mL steel jar lined with Teflon, sealed firmly, and heated under autogenous pressure for 12 hours at 130 °C. Centrifugation was used to extract the final product once the reaction was finished and the steel vessel was cool. A white substance (**ZN-O**, 1.5 g) was obtained from the collected material when it was repeatedly washed with methanol and water and dried in an oven heated at 60 °C for 12 hours. Using a solution of methanol (10 mL) containing sodium borohydride ($NaBH_4$, 5 mM, 190 mg), a dropwise addition of **ZN-O** (0.3 g) in methanol (30 mL) at 25 °C produced **ZN-R**. Under an argon environment, the addition was carried out gradually and carefully. The same temperature was kept for four hours throughout the reaction. Following the completion of the reaction, the resulting black material was separated by centrifugation and subsequently cleaned with methanol and water. The final product was obtained by vacuum-drying the solid black material (**ZN-R**).

2.2 Method of Pyrolysis for ZN-O and ZN-R Catalyst: After completing the previous procedure, the (**ZN-O**/**ZN-R**) solid materials were transferred to a crucible and then put inside a furnace for pyrolysis. Employing a temperature gradient of 80 °C per minute, the pyrolysis process was carried out for three hours in standard air conditions. The materials were assigned sample codes based on the specific pyrolysis conditions and their initial composition (**ZN-O**/**ZN-R**). **ZN-O-6** and **ZN-R-6** were the labels utilized for the products of pyrolysis at 600 °C.

2.3 Method of Pyrolysis for ZN-O and ZN-R was directed under diverse atmospheric conditions. With a temperature gradient of 5 °C every minute, the pyrolysis process included changing the atmosphere's pressure and temperatures. Throughout the whole pyrolysis process, a constant argon gas combination was maintained. The (**ZN-O**/**ZN-R**) parent material, the temperature at which pyrolysis took place, and the particular environment used were used to categorize the materials. For the materials, the following sample codes were assigned: **ZN-O-A-7** (pyrolyzed in an argon environment at 700°C).

3. General Procedure for Oxidative Coupling of Benzaldehyde and Amine to Synthesize Amide

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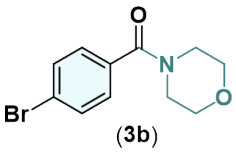
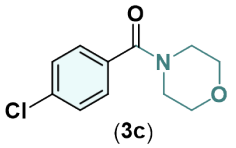
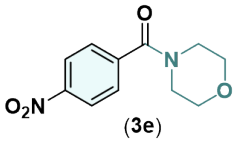
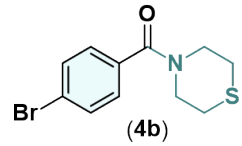
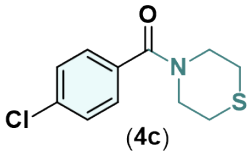
The reaction was conducted in a pressure tube equipped with simultaneous heating/cooling, stirring, and refluxing capabilities under an inert atmosphere using the Carousel 12 Plus reaction station. A dry and oxygen-free argon/nitrogen atmosphere was maintained throughout the process. In the reaction vessel, 0.5 mM of substituted benzaldehyde derivatives and 0.5 mM of secondary amine (morpholine, thiomorpholine, piperazine, pyrrolidine, piperidine, etc) were combined with 5-6 M TBHP in dodecane (112 µL, approximately 0.5 mM) and **ZN-O-A-7**

catalyst (7.1 mol%, 10 mg) dissolved in 3 mL of THF. The mixture was then refluxed at 90°C for 2 hours. Upon completion of the reaction, the solid catalyst was separated *via* centrifugation. The THF solvent was evaporated, and 50 mL of water was added. The resulting mixture was extracted with ethyl acetate (50 mL × 3), followed by washing with water (50 mL × 2) and brine (50 mL × 1). The organic phase was dried over anhydrous Na_2SO_4 (5 g). After solvent removal under reduced pressure, the crude product was subjected to gas chromatography-mass spectrometry (GC-MS) analysis. The pure product was isolated via column chromatography using hexane: ethyl acetate as the eluent. The isolated product was characterized using ^1H and ^{13}C NMR spectroscopy.

4. ^1H and ^{13}C NMR data of products

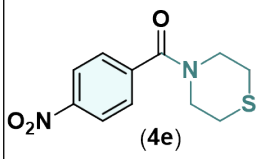
 (**3b**)	*(4-bromophenyl)(morpholino)methanone* (**3b**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 3.75 – 3.70 (m, 4H), 3.60 (d, J = 5.8 Hz, 2H), 3.45 – 3.37 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 134.1, 131.9, 128.9, 124.4, 66.9, 29.8.
 (**3c**)	*(4-chlorophenyl)(morpholino)methanone* (**3c**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 3.81 – 3.66 (m, 4H), 3.61 – 3.57 (m, 2H), 3.44 – 3.37 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 136.1, 133.7, 128.9, 128.8, 66.9, 29.8.
 (**3e**)	*morpholino(4-nitrophenyl)methanone* (**3e**): ^1H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 3.86 – 3.75 (m, 4H), 3.69 – 3.59 (m, 2H), 3.47 – 3.30 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 136.1, 133.7, 128.9, 128.8, 66.9, 29.8.
 (**4b**)	*(4-bromophenyl)(thiomorpholino)methanone* (**4b**): ^1H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 2H), 7.23 (dd, J = 8.4, 2.9 Hz, 2H), 3.97 (s, 2H), 3.63 (s, 2H), 2.68 (s, 2H), 2.55 (s, 2H). ^{13}C NMR (151 MHz,

$CDCl_3$) δ 169.8, 134.6, 131.9, 128.6, 124.2, 50.2, 44.8.



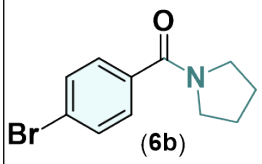
(4c)

(4-chlorophenyl)(thiomorpholino)methanone (**4c**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.33 – 7.29 (m, 2H), 3.98 (s, 2H), 3.75 – 3.57 (m, 2H), 2.69 (s, 2H), 2.56 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 136.0, 134.2, 129.0, 128.4, 29.8.



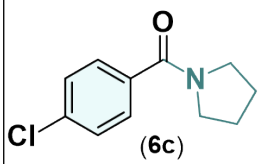
(4e)

(4-nitrophenyl)(thiomorpholino)methanone (**4e**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 4.02 (s, 2H), 3.59 (s, 2H), 2.73 (s, 2H), 2.54 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.5, 148.5, 141.9, 127.9, 124.1, 50.1, 44.7, 28.1, 27.4.



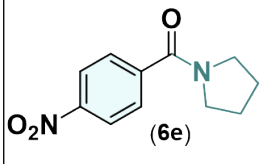
(6b)

(4-bromophenyl)(pyrrolidin-1-yl)methanone (**6b**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 3.58 (t, J = 7.0 Hz, 2H), 3.36 (t, J = 6.7 Hz, 2H), 1.91 (p, J = 6.8 Hz, 2H), 1.83 (p, J = 6.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 136.0, 131.5, 128.9, 124.2, 49.7, 46.4, 26.5, 24.5.



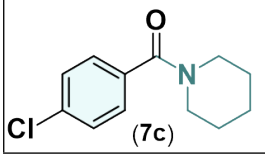
(6c)

(4-chlorophenyl)(pyrrolidin-1-yl)methanone (**6c**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.60 (t, J = 7.1 Hz, 2H), 3.38 (t, J = 6.6 Hz, 2H), 1.92 (p, J = 6.8 Hz, 2H), 1.85 (p, J = 6.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 135.9, 135.5, 128.8, 128.6, 49.7, 46.4, 26.5, 24.5.



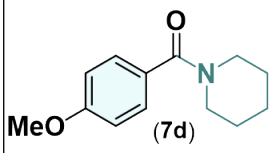
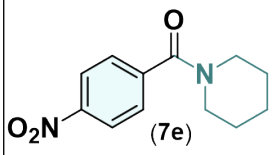
(6e)

(4-nitrophenyl)(pyrrolidin-1-yl)methanone (**6e**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 3.66 (t, J = 7.1 Hz, 2H), 3.37 (t, J = 6.8 Hz, 2H), 1.98 (p, J = 6.9 Hz, 2H), 1.91 (p, J = 6.6 Hz, 2H). 13C NMR (151 MHz, $CDCl_3$) δ 167.5, 148.5, 143.2, 128.2, 123.8, 49.5, 46.5, 26.5, 24.4.



(7c)

(4-chlorophenyl)(piperidin-1-yl)methanone (**7c**): ^{1}H NMR (600 MHz,

$CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 3.67 (d, J = 8.2 Hz, 2H), 3.30 (d, 2H), 1.69 – 1.63 (m, 2H), 1.50 – 1.47 (m, 2H), 1.23 (t, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 135.5, 134.8, 131.4, 128.8, 48.9, 43.4, 29.8, 26.6, 24.6.
 (7d) *(4-methoxyphenyl)(piperidin-1-yl)methanone* (**7d**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.5, 1.5 Hz, 2H), 6.90 (dd, 2H), 3.83 (s, 3H), 3.68 – 3.64 (m, 2H), 3.43 (s, 2H), 1.70 – 1.65 (m, 2H), 1.58 (d, J = 25.8 Hz, 2H), 0.88 (t, 1H).
 (7e) *(4-nitrophenyl)(piperidin-1-yl)methanone* (**7e**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 3.74 (d, J = 6.0 Hz, 2H), 3.29 (d, 2H), 1.75 – 1.67 (m, 2H), 1.54 (d, J = 7.7 Hz, 2H), 0.88 (t, J = 6.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.3, 148.6, 143.1, 128.2, 124.2, 49.0, 43.6, 30.1, 26.9, 24.8.

5. ^{1}H and ^{13}C NMR spectra of products

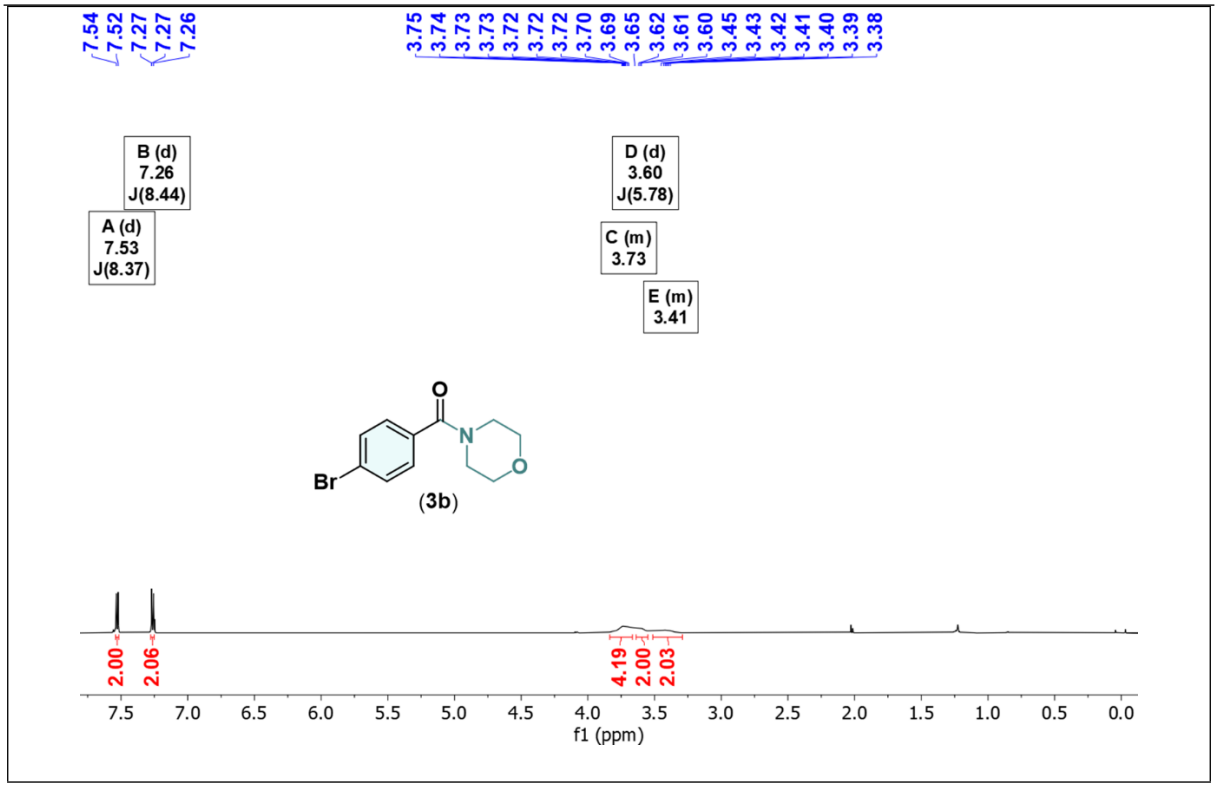


Fig. S1. ^{1}H–NMR of **3b** in $CDCl_3$ at 298K.

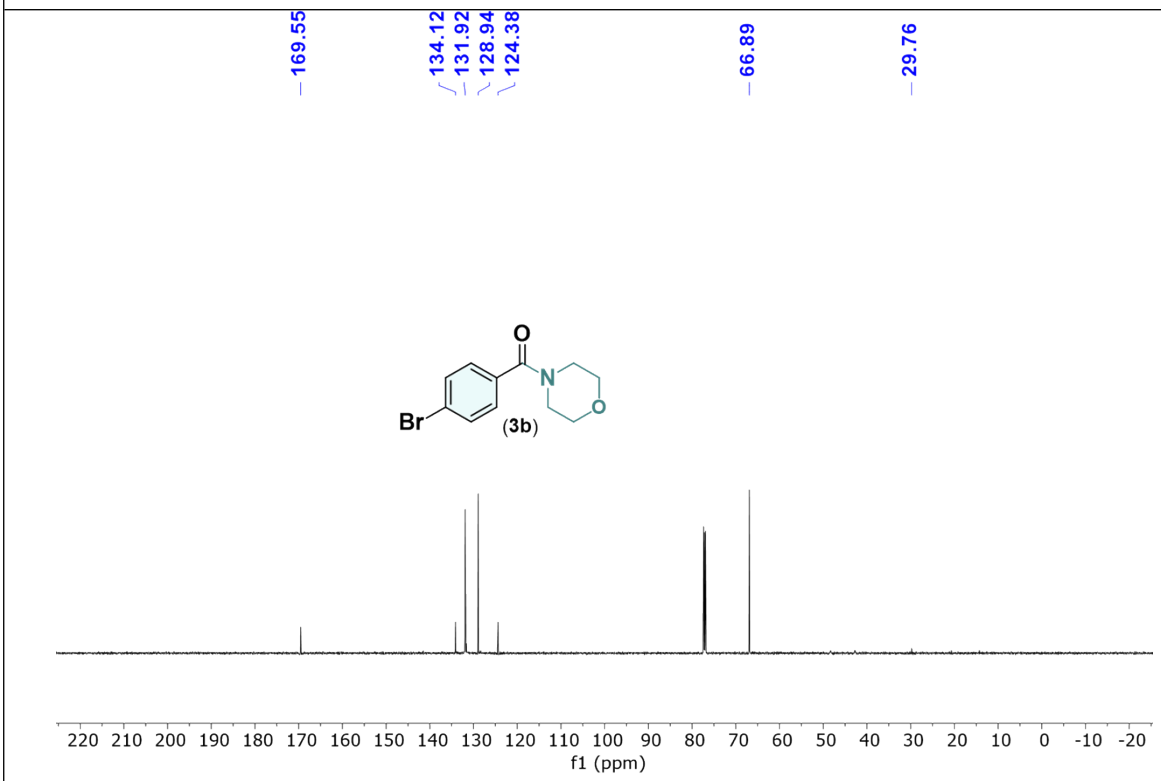


Fig. S2. ^{13}C–NMR of **3b** in $CDCl_3$ at 298K.

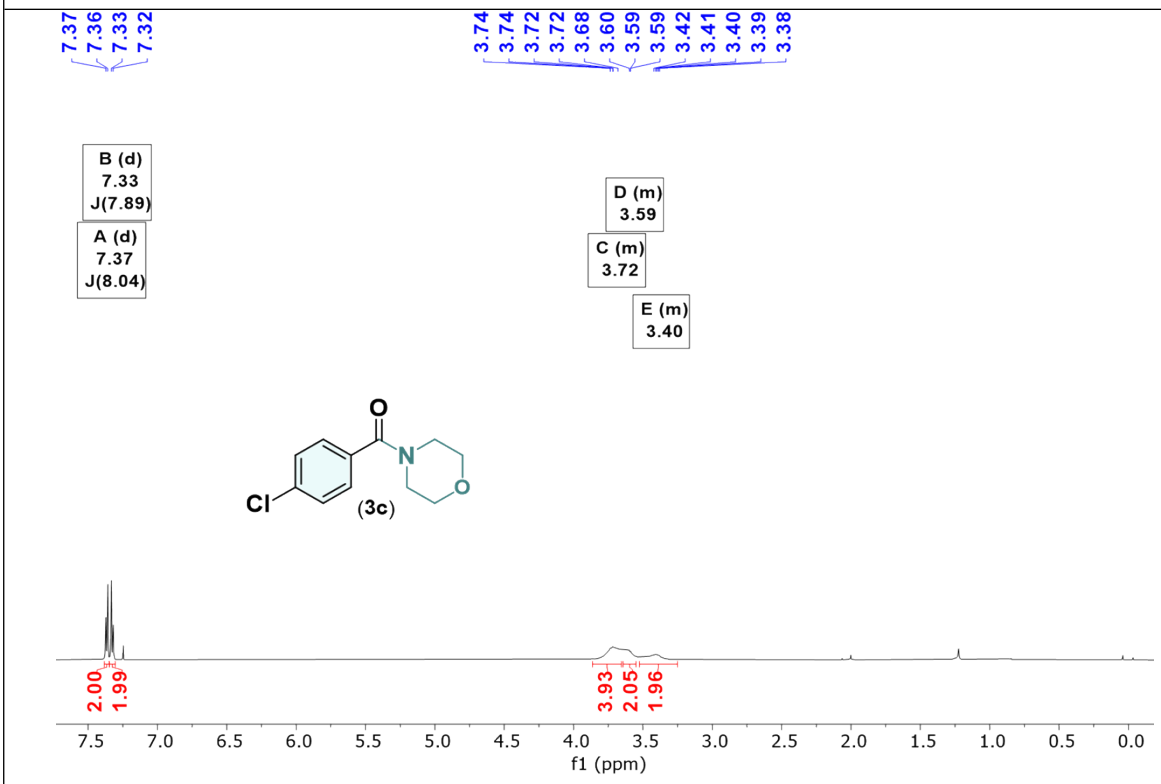


Fig. S3. ^{1}H–NMR of **3c** in $CDCl_3$ at 298K.

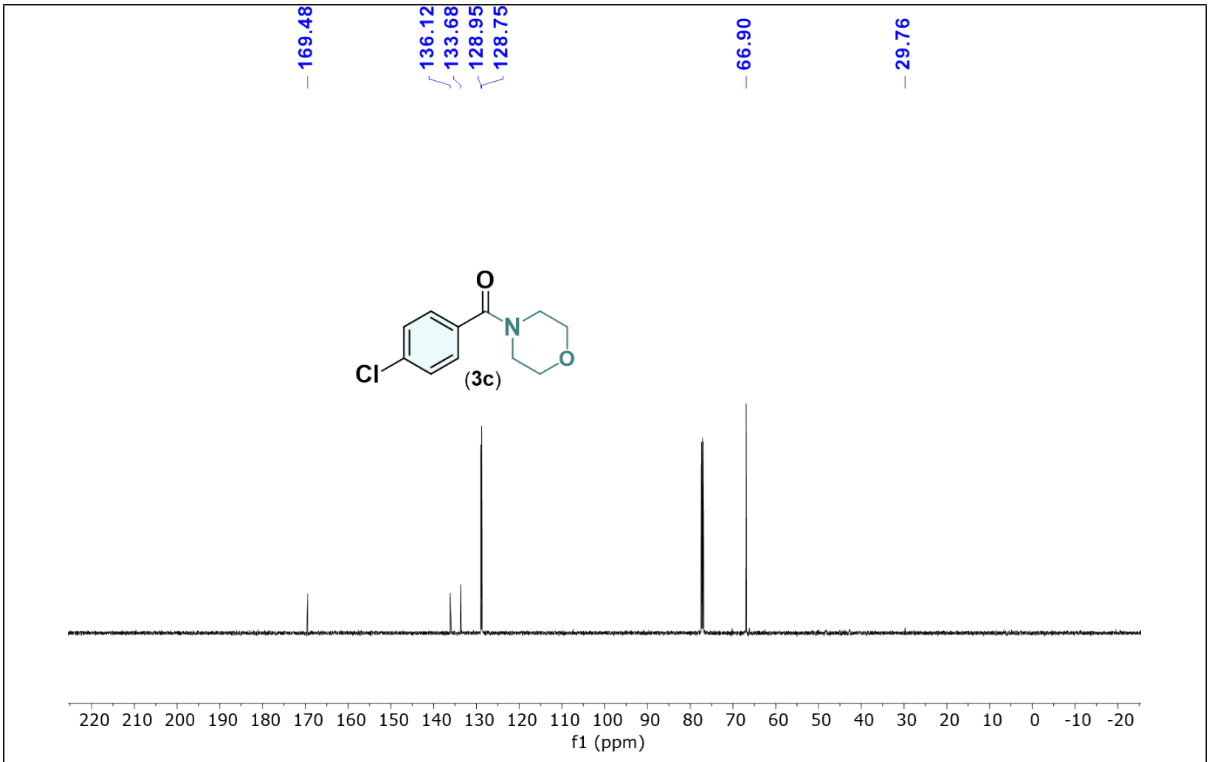


Fig. S4. ^{13}C–NMR of **3c** in $CDCl_3$ at 298K.

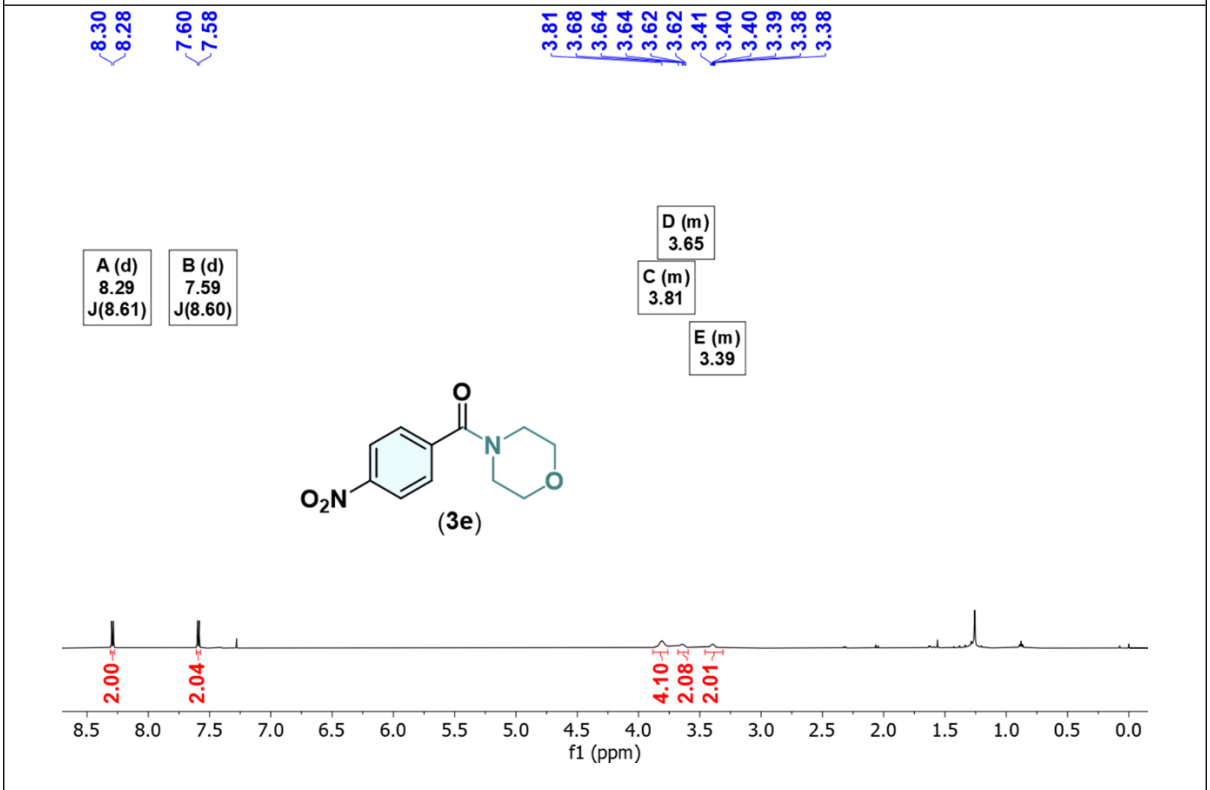


Fig. S5. ^{1}H–NMR of **3e** in $CDCl_3$ at 298K.

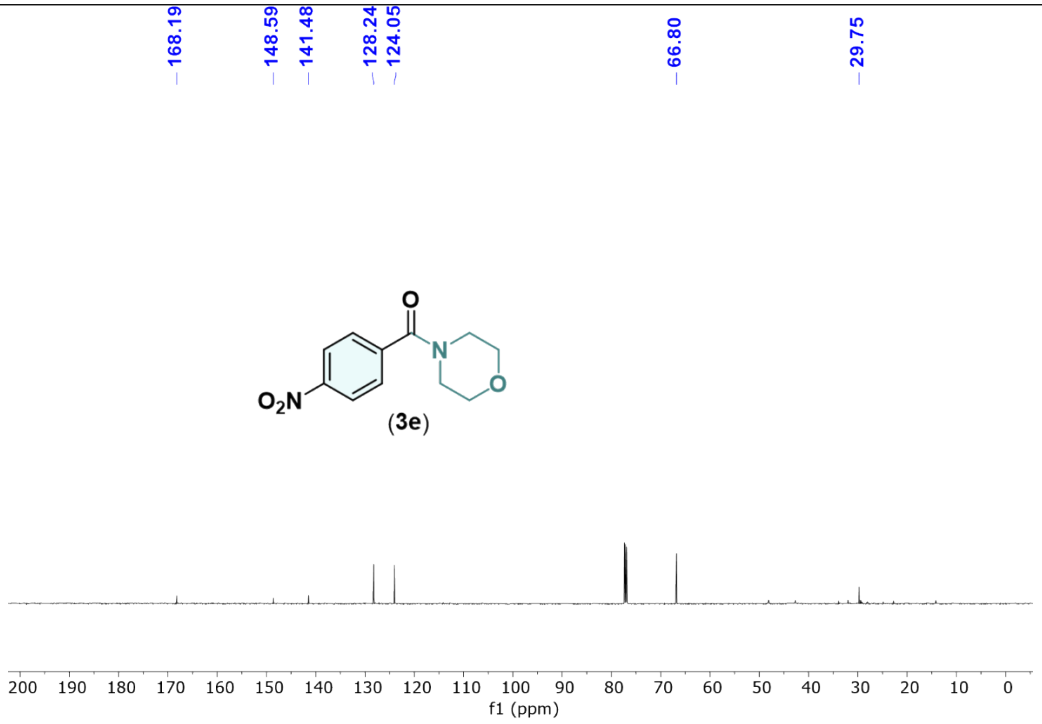


Fig. S6. ^{13}C–NMR of **3e** in $CDCl_3$ at 298K.

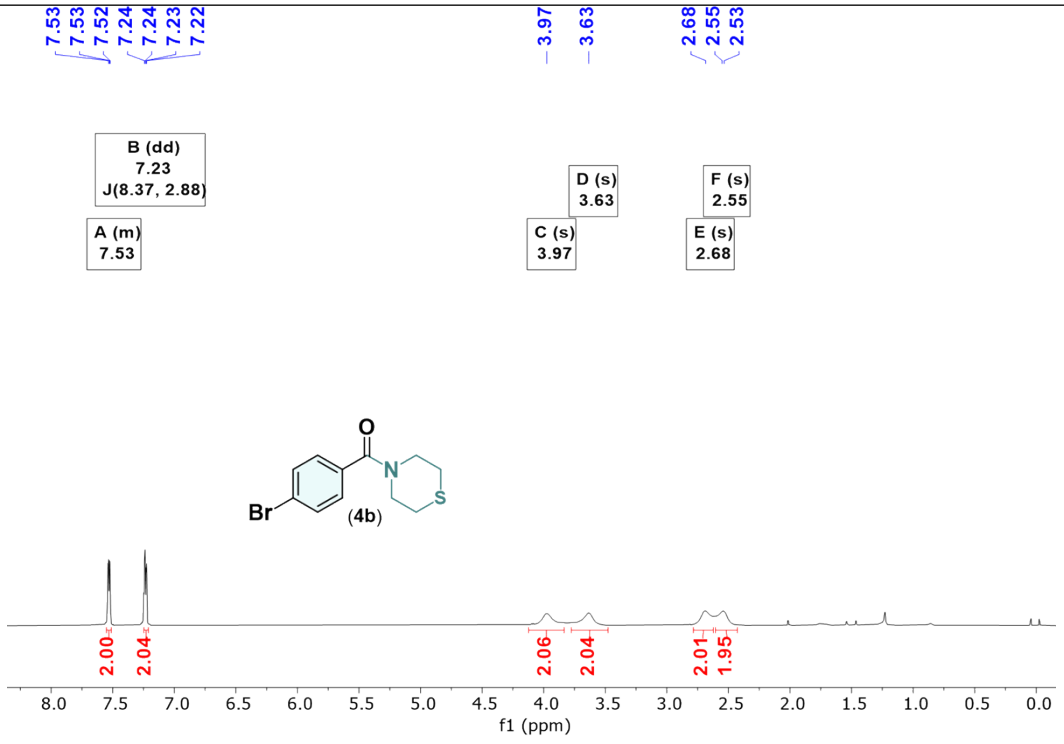


Fig. S7. ^{1}H–NMR of **4b** in $CDCl_3$ at 298K.

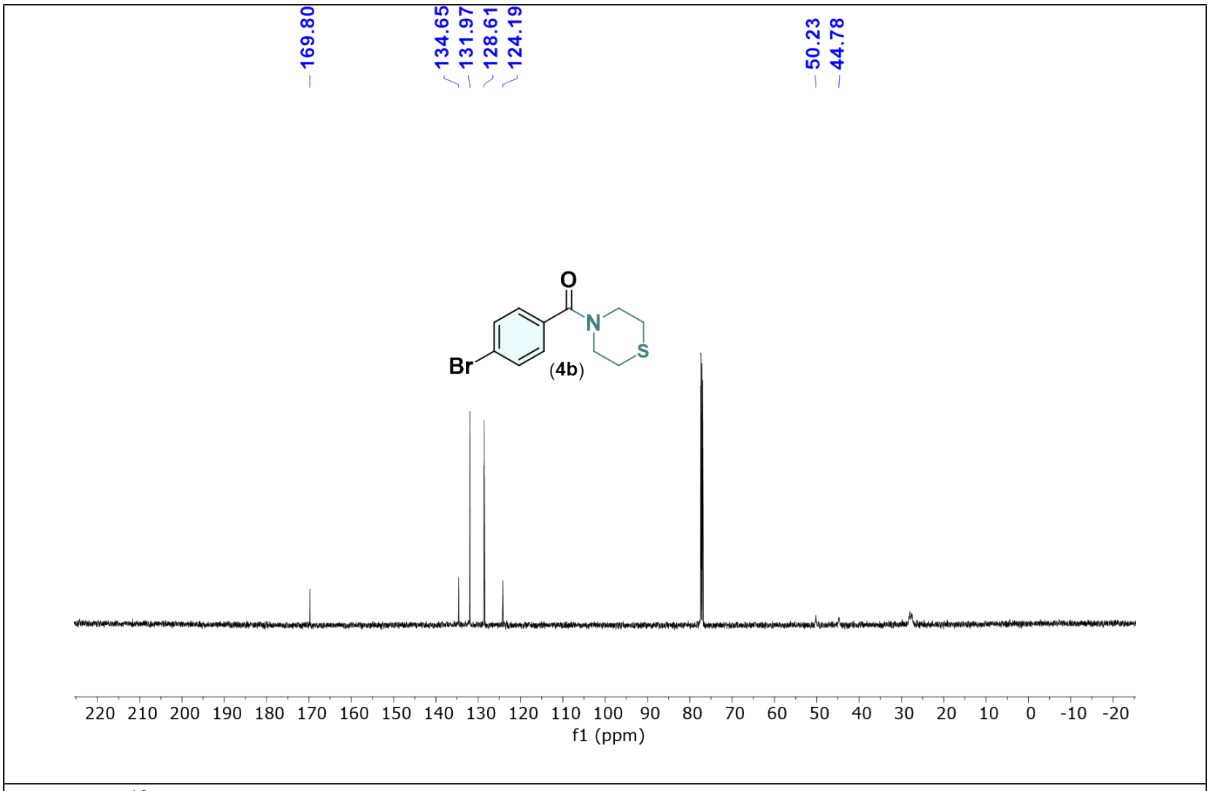


Fig. S8. ^{13}C–NMR of **4b** in $CDCl_3$ at 298K.

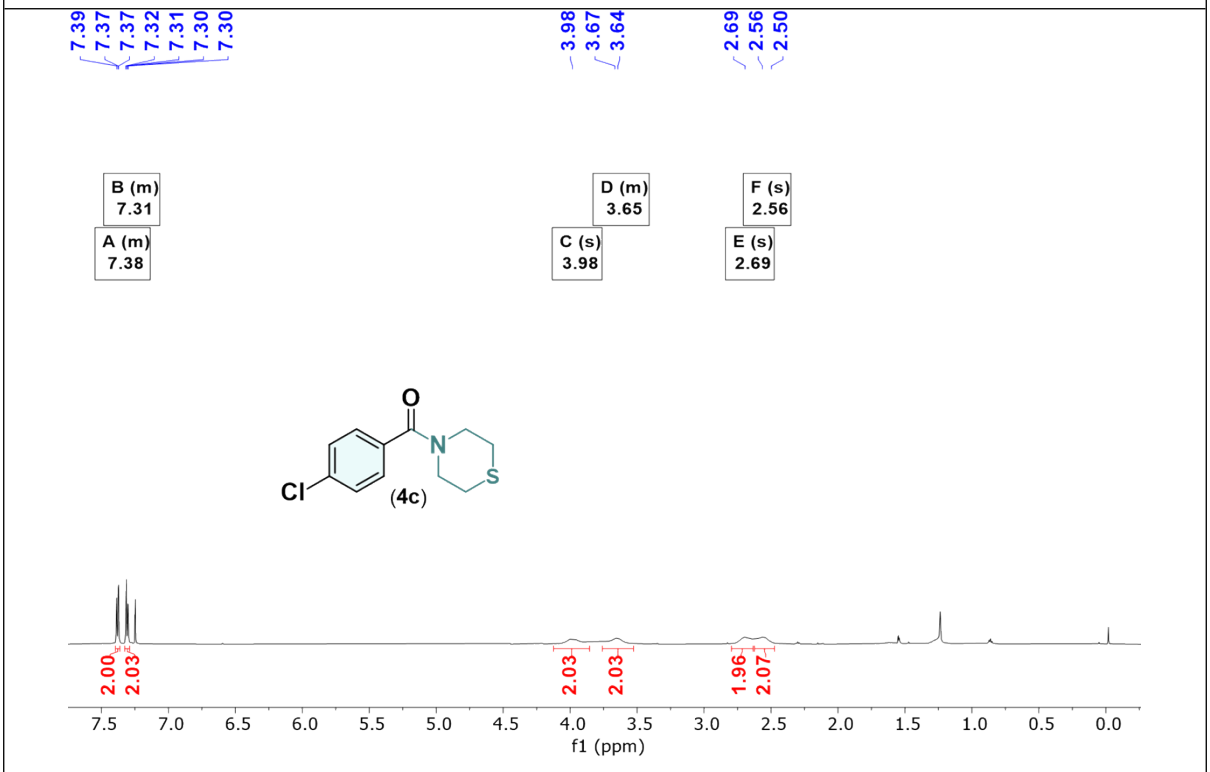


Fig. S9. ^{1}H–NMR of **4c** in $CDCl_3$ at 298K.

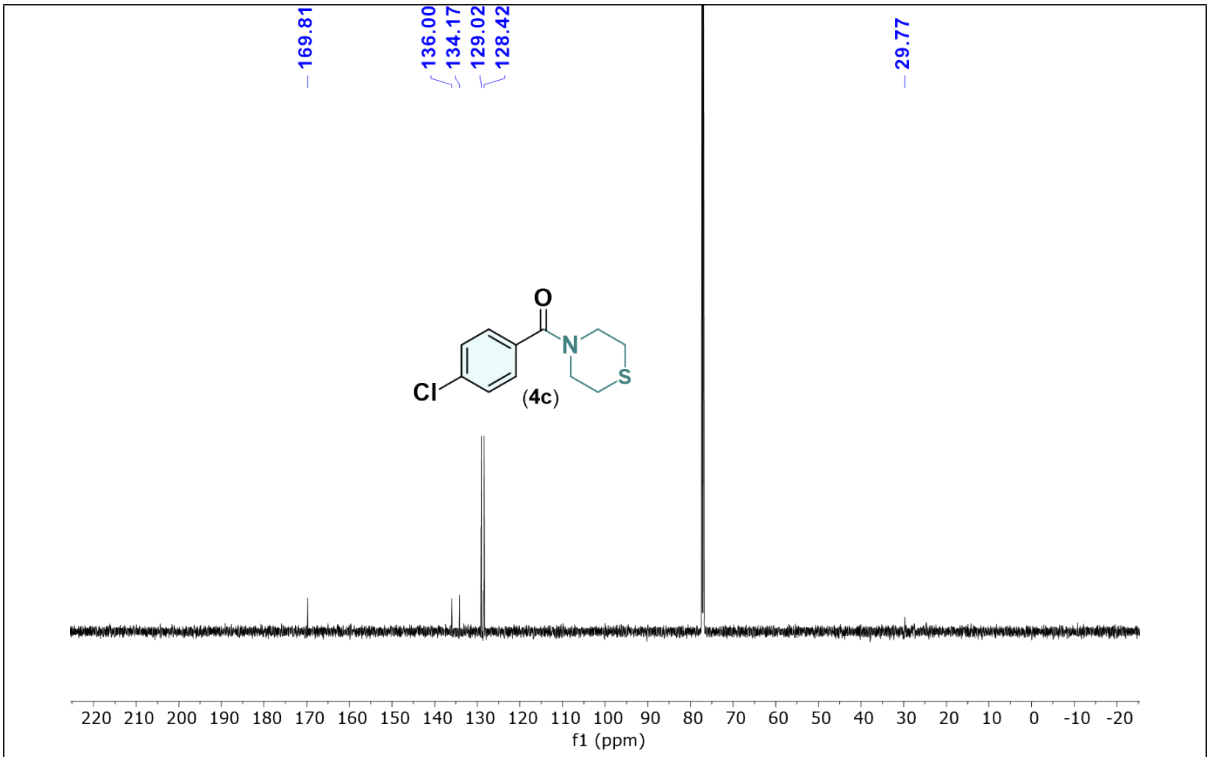


Fig. S10. ^{13}C–NMR of **4c** in $CDCl_3$ at 298K.

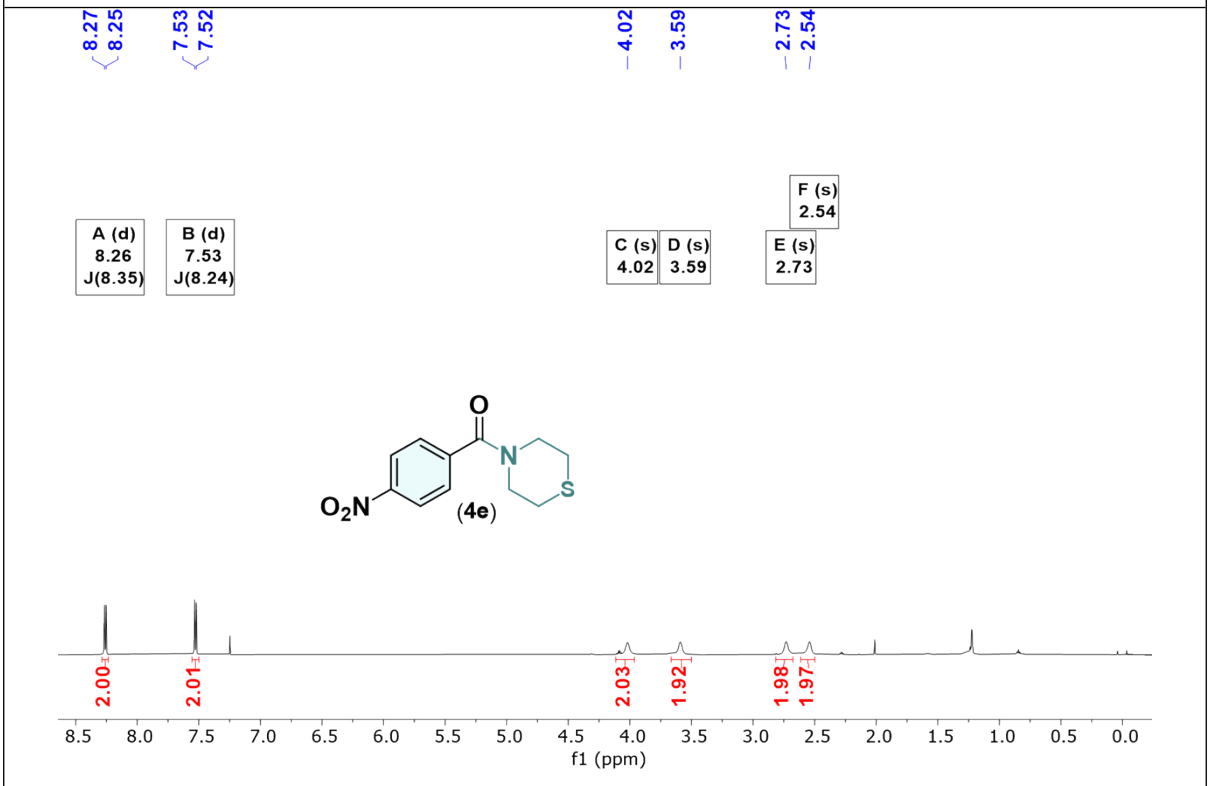


Fig. S11. ^{1}H–NMR of **4e** in $CDCl_3$ at 298K.

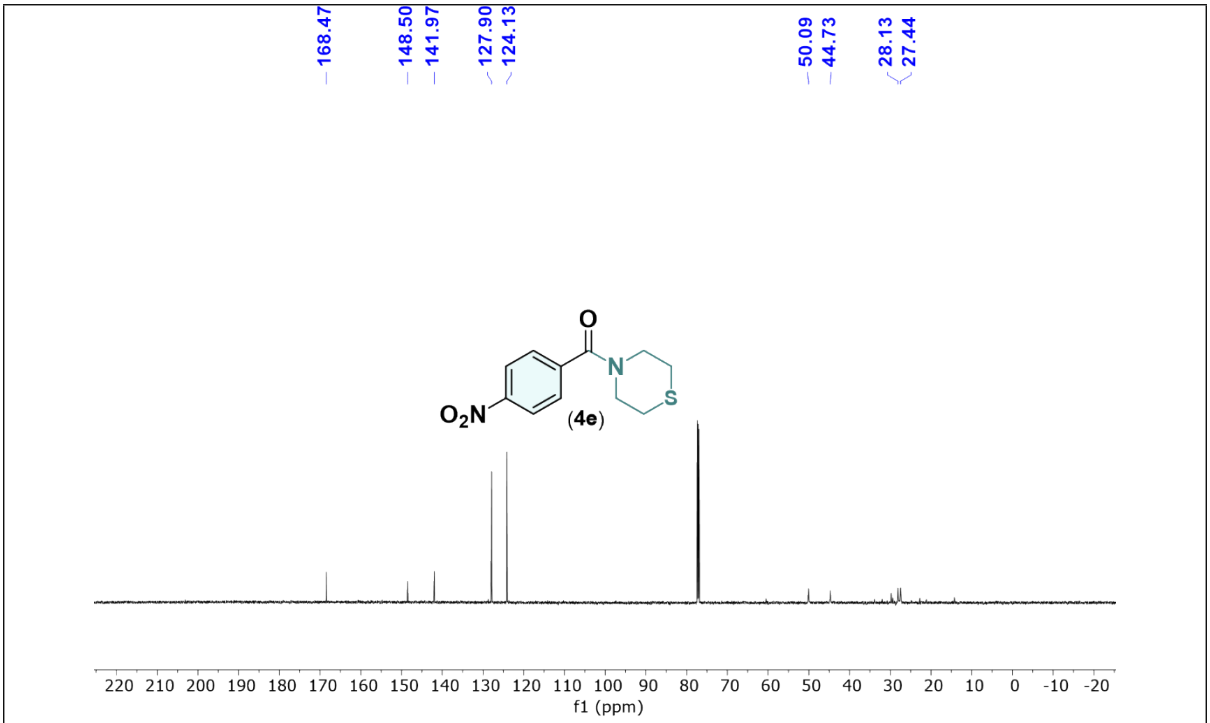


Fig. S12. ^{13}C–NMR of **4e** in $CDCl_3$ at 298K.

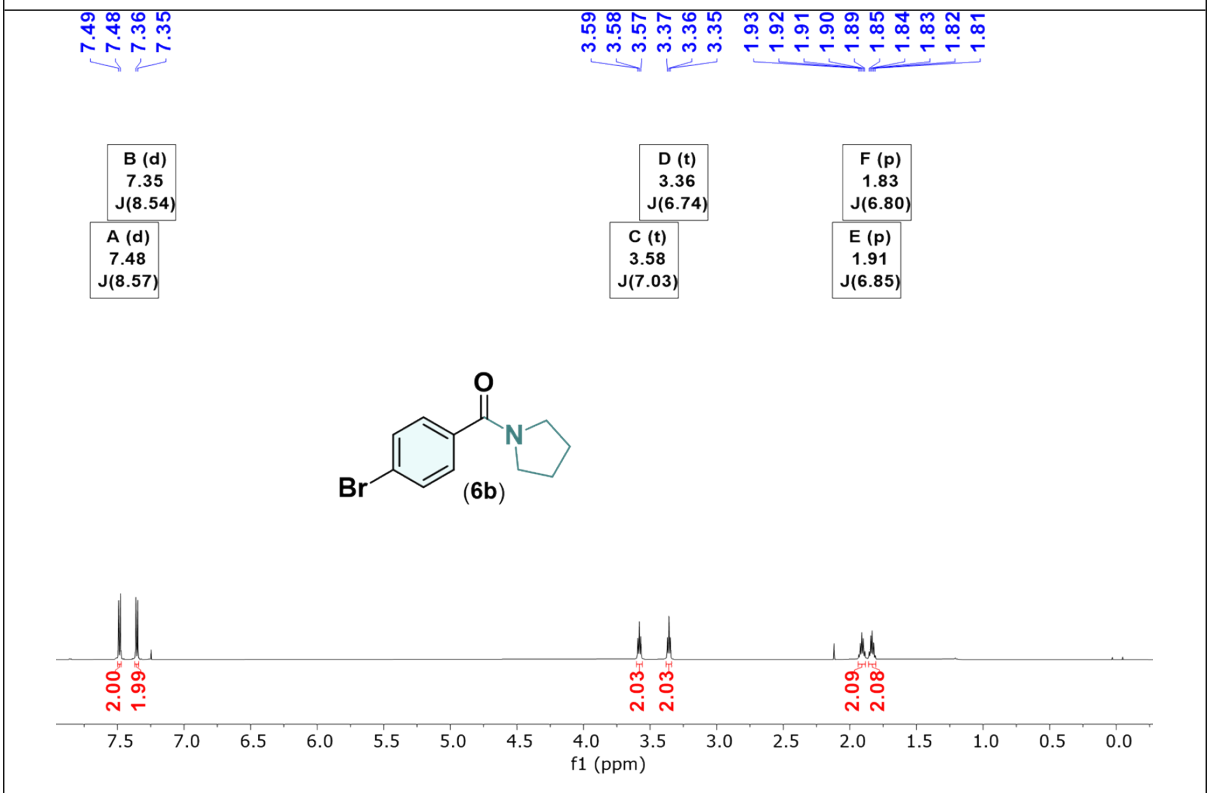


Fig. S13. ^{1}H–NMR of **6b** in $CDCl_3$ at 298K.

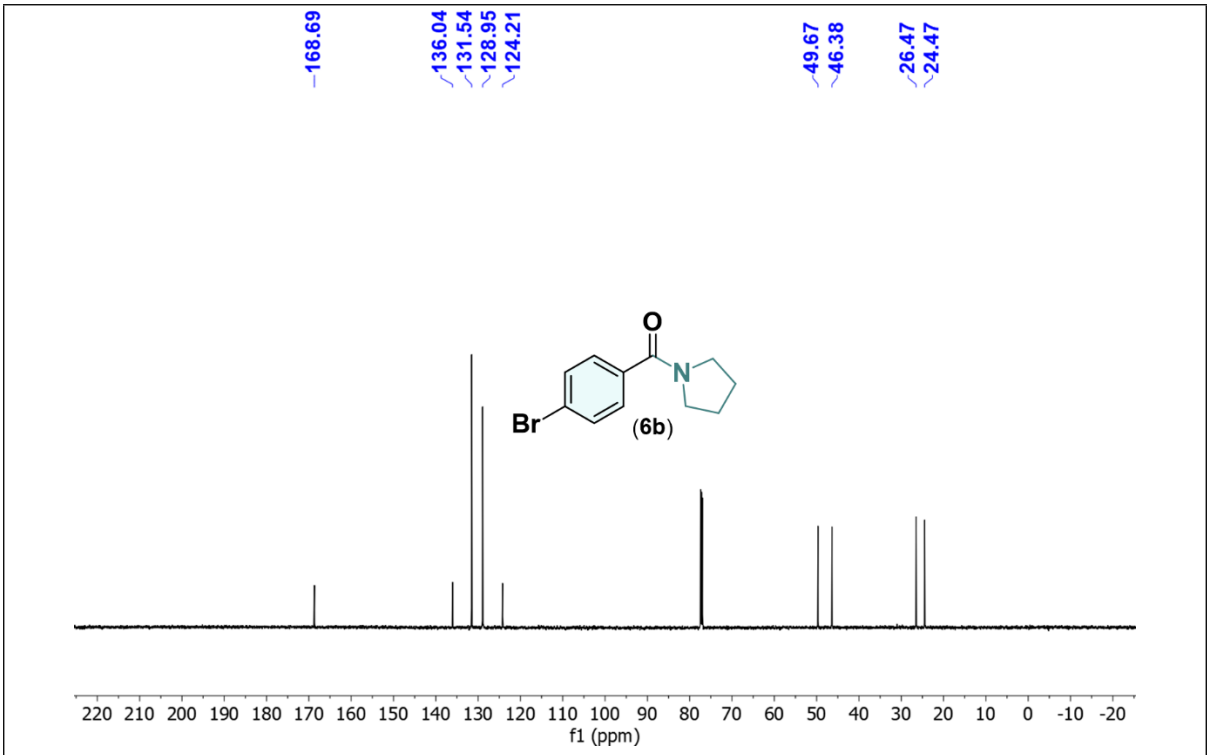


Fig. S14. ^{13}C–NMR of **6b** in $CDCl_3$ at 298K.

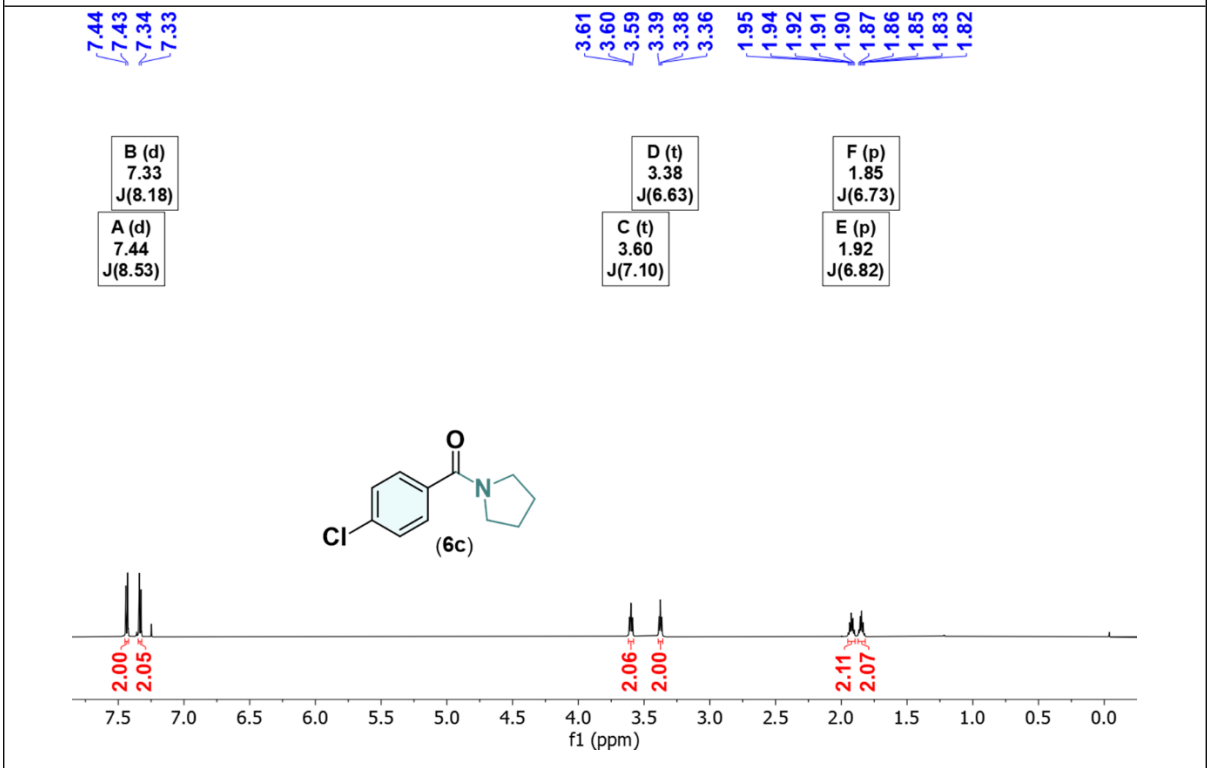


Fig. S15. ^{1}H–NMR of **6c** in $CDCl_3$ at 298K.

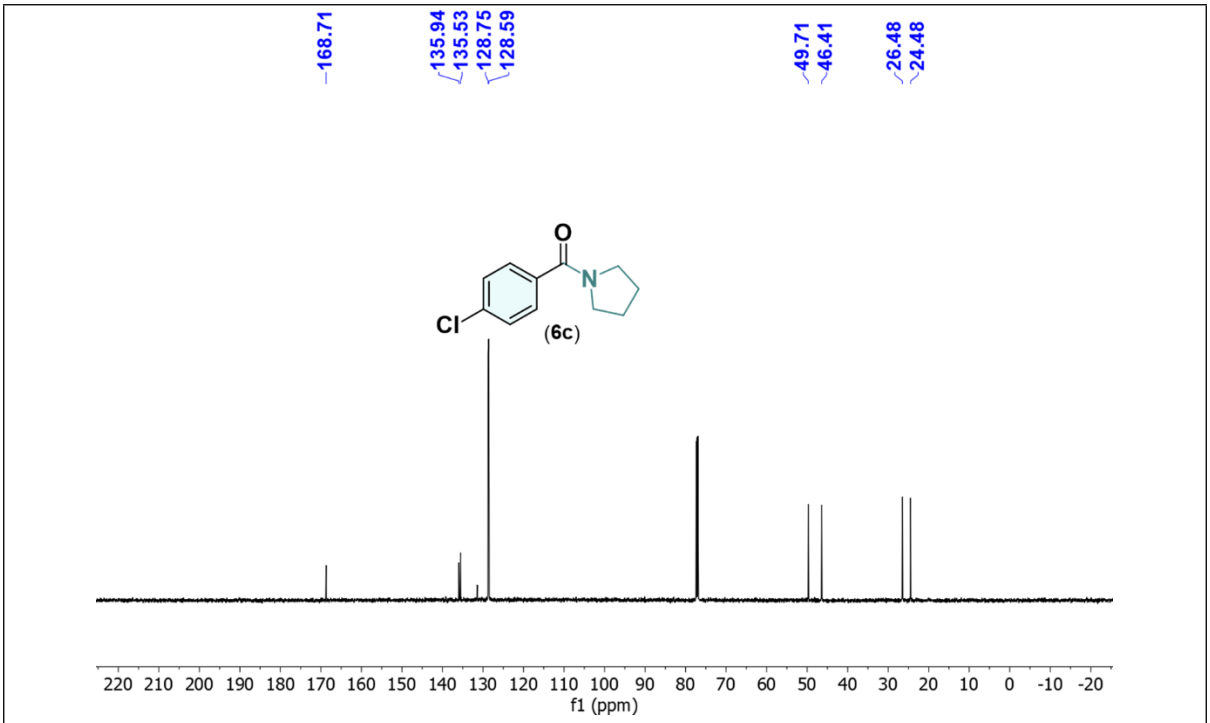


Fig. S16. ^{13}C–NMR of **6c** in $CDCl_3$ at 298K.

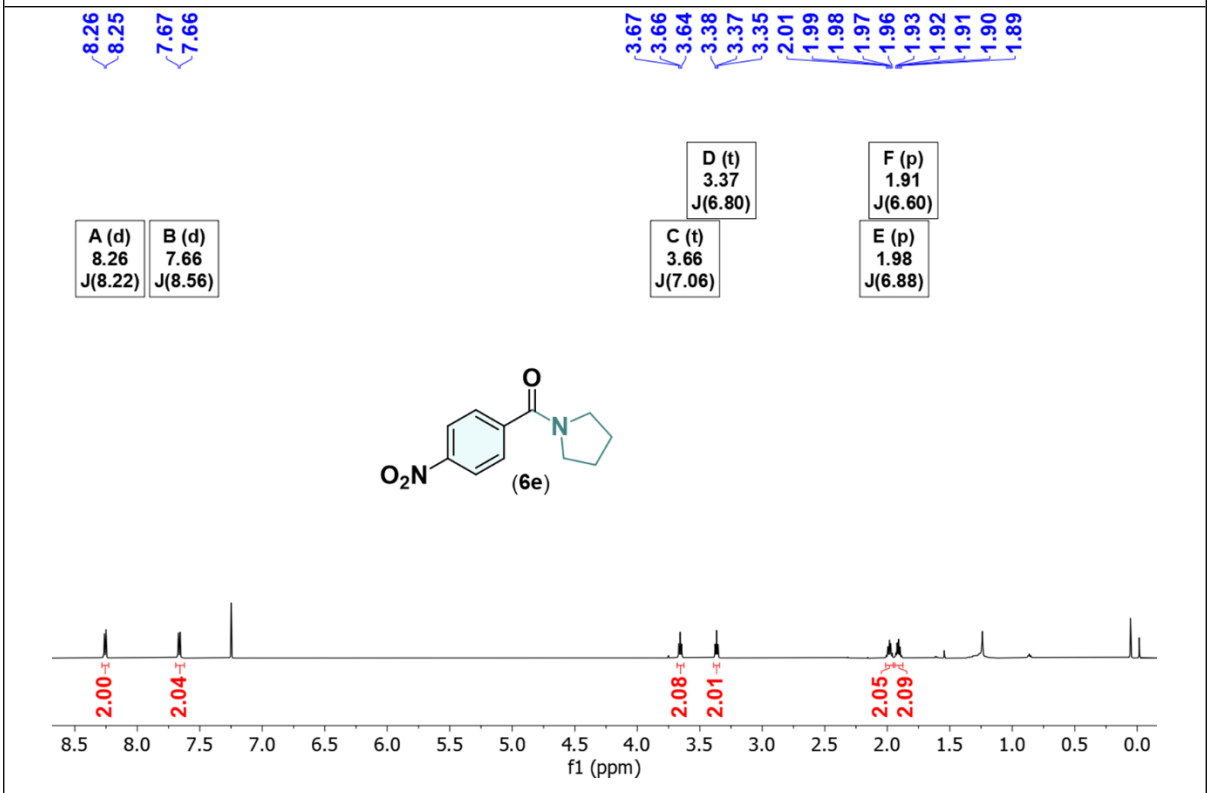


Fig. S17. ^{1}H–NMR of **6e** in $CDCl_3$ at 298K.

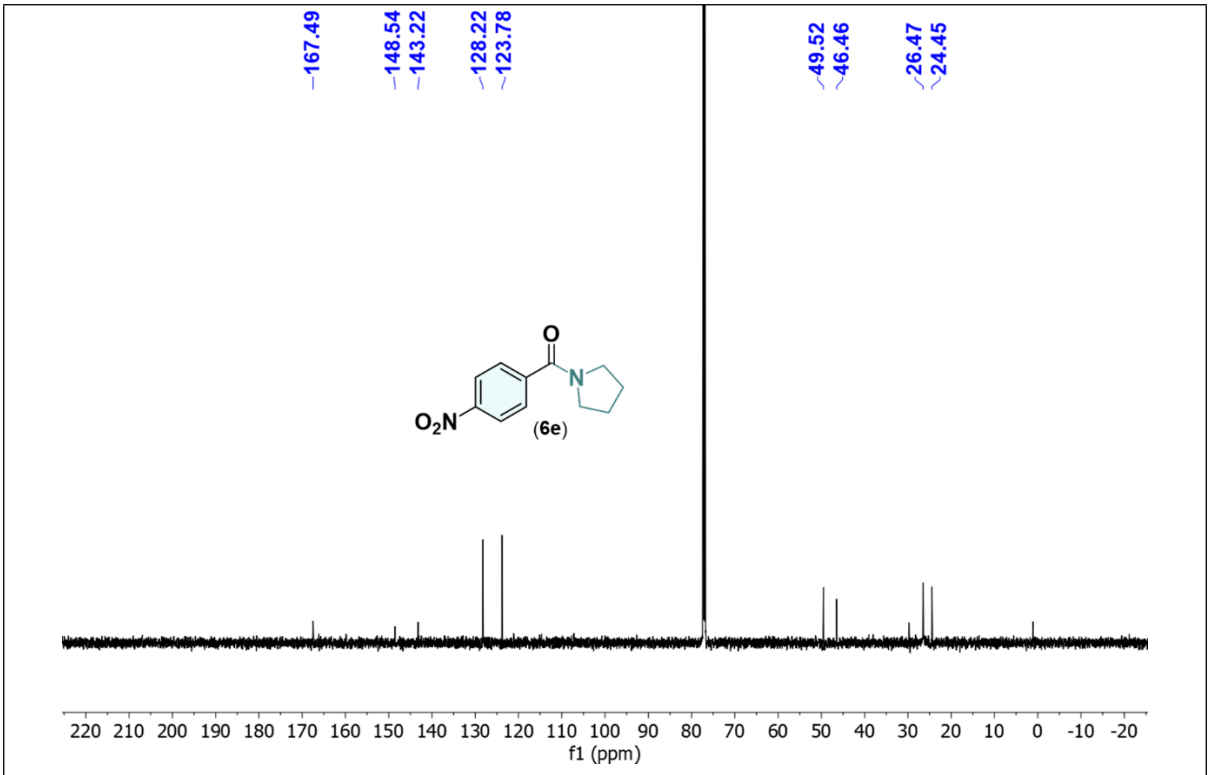


Fig. S18. ^{13}C–NMR of **6e** in $CDCl_3$ at 298K.

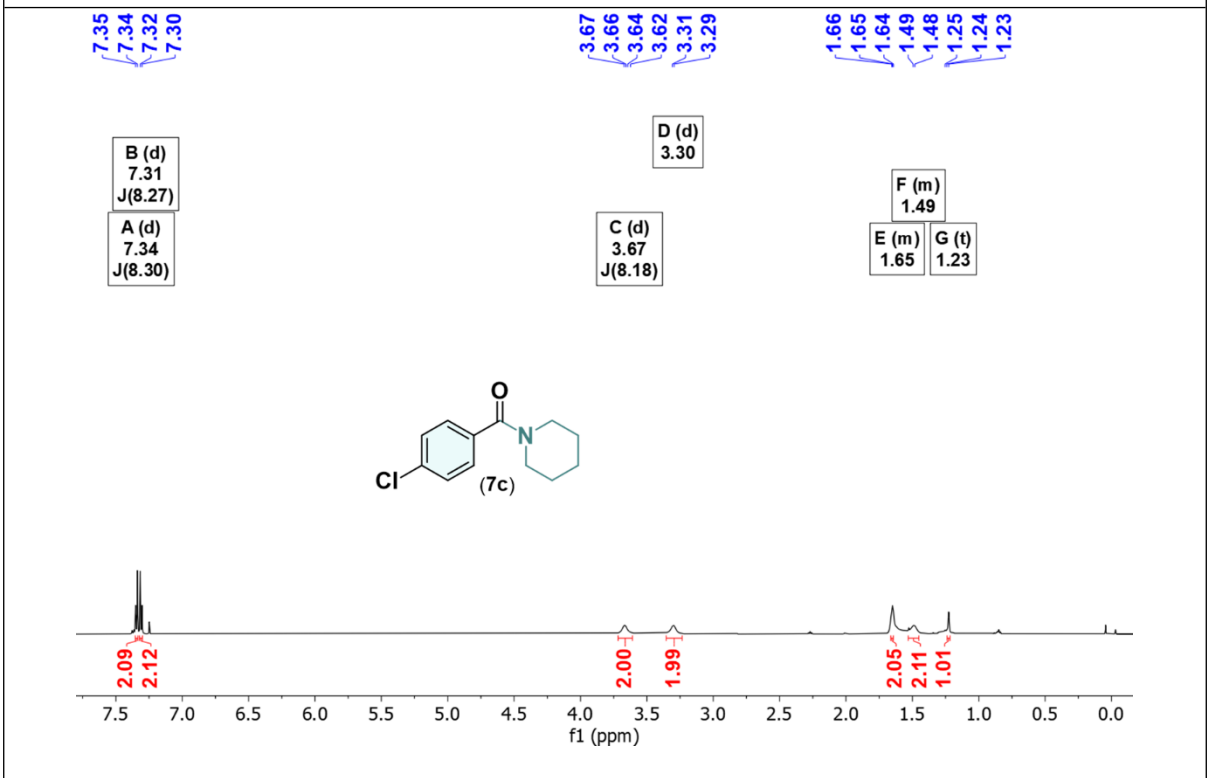


Fig. S19. ^{1}H–NMR of **7c** in $CDCl_3$ at 298K.

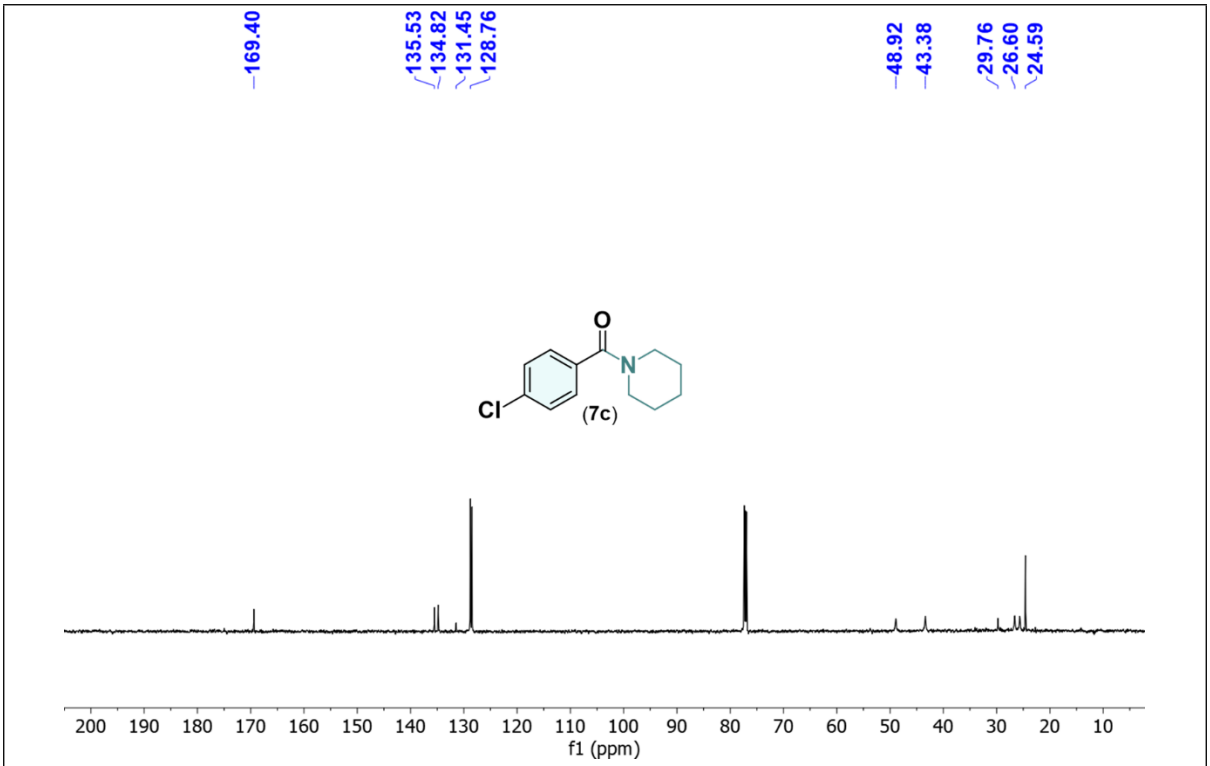


Fig. S20. ^{13}C–NMR of **7c** in $CDCl_3$ at 298K.

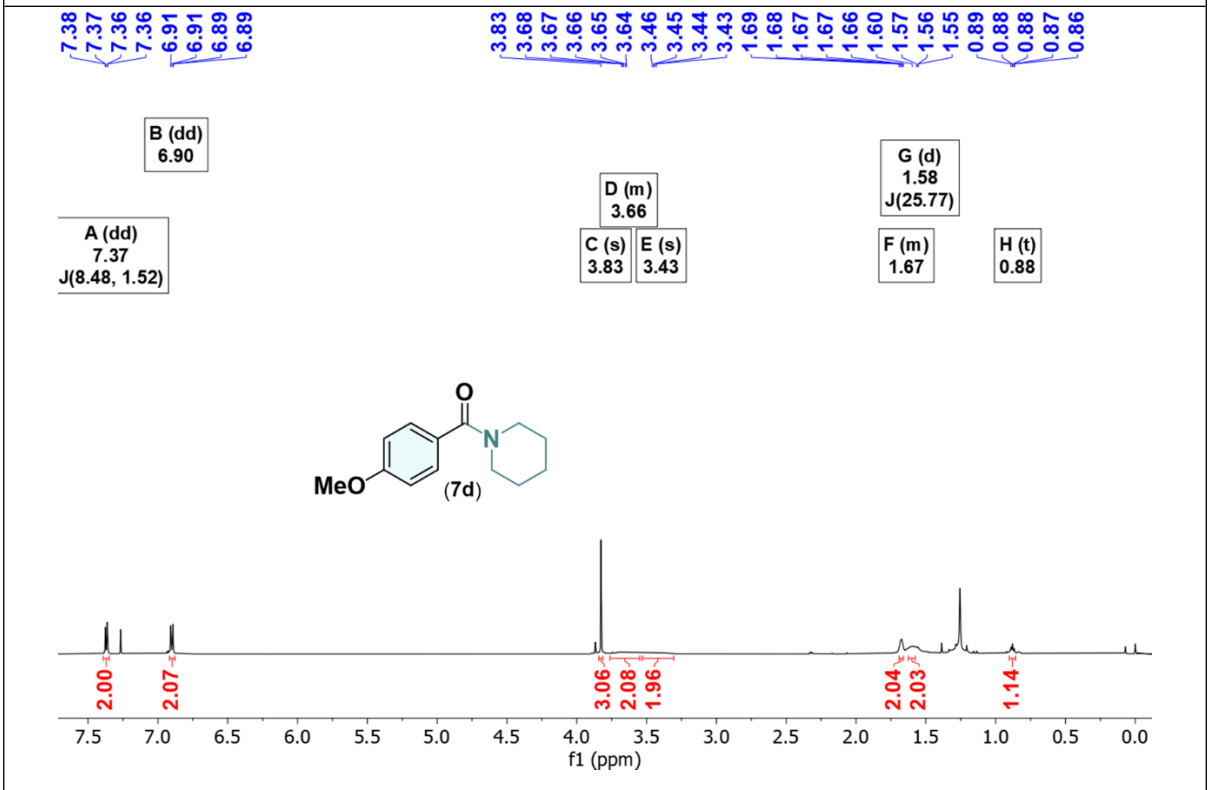


Fig. S21. ^{1}H–NMR of **7d** in $CDCl_3$ at 298K.

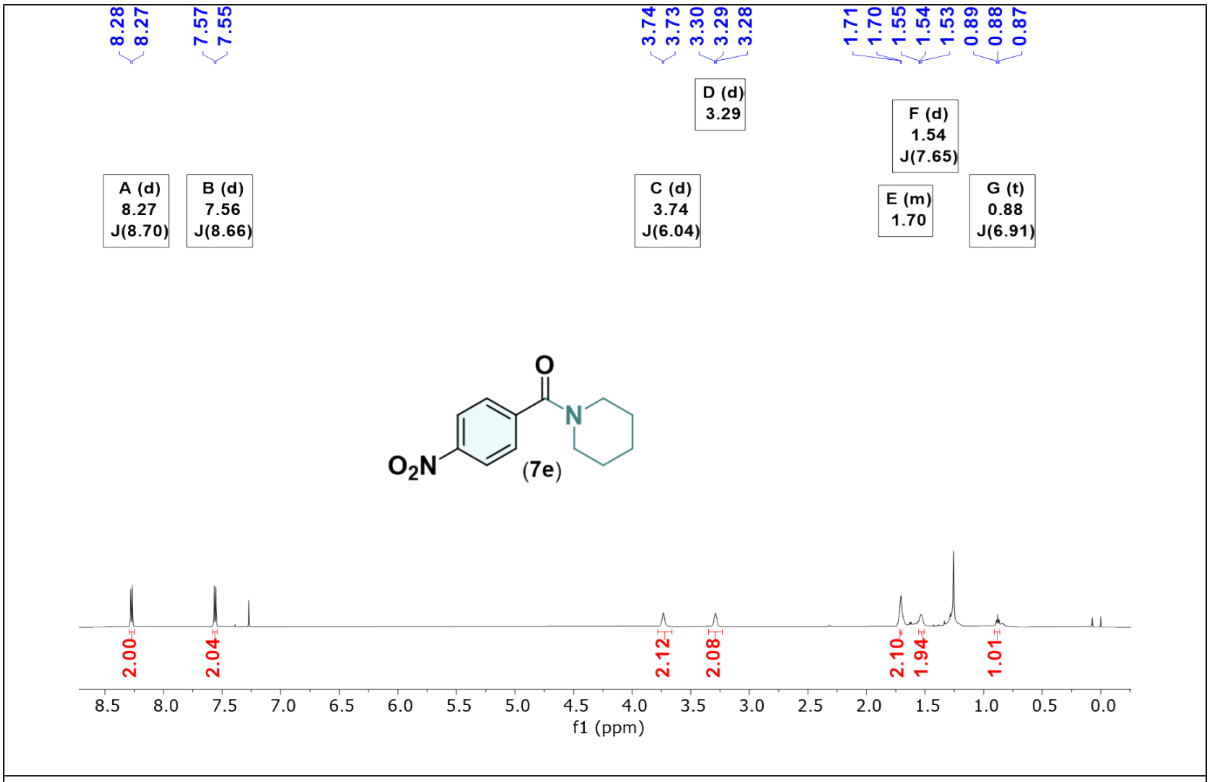


Fig. S22. ^{1}H–NMR of **7e** in $CDCl_3$ at 298K.

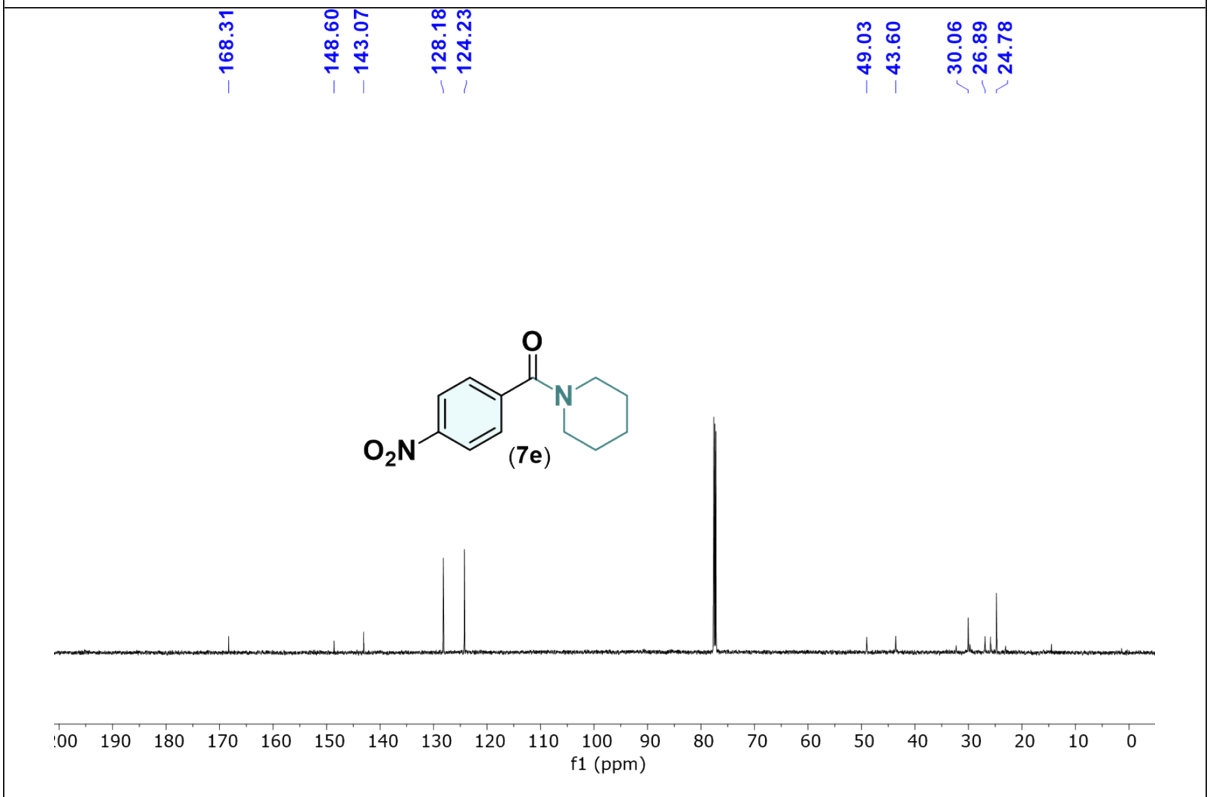


Fig. S23. ^{13}C–NMR of **7e** in $CDCl_3$ at 298K.

6. Synthesis and Characterization of Benzoate Side Product in the Oxidative Coupling of Benzaldehyde and Amine to Form Amide

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6.1 Procedure for the synthesis of benzoate:

Acyl chloride (17.8 mM) was diluted with anhydrous tetrahydrofuran (THF, 10 mL) and cooled in an ice bath under a nitrogen atmosphere. A solution of potassium tert-butoxide (4 g, 35.6 mM, 2 equivalents) in anhydrous THF (10 mL) was slowly added via a syringe. During the addition, a precipitate of potassium chloride was observed. The reaction mixture was allowed to stir for 4 hours at the ice bath temperature. After the completion of the reaction, it was quenched by the addition of aqueous saturated sodium bicarbonate ($NaHCO_3$) solution. The resulting mixture was diluted with ethyl acetate. The organic layer was separated and collected. The solvent was then evaporated under reduced pressure to afford a yellow oil product corresponding to the benzoate.

6.2 ^{1}H and ^{13}C NMR Spectra of benzoate

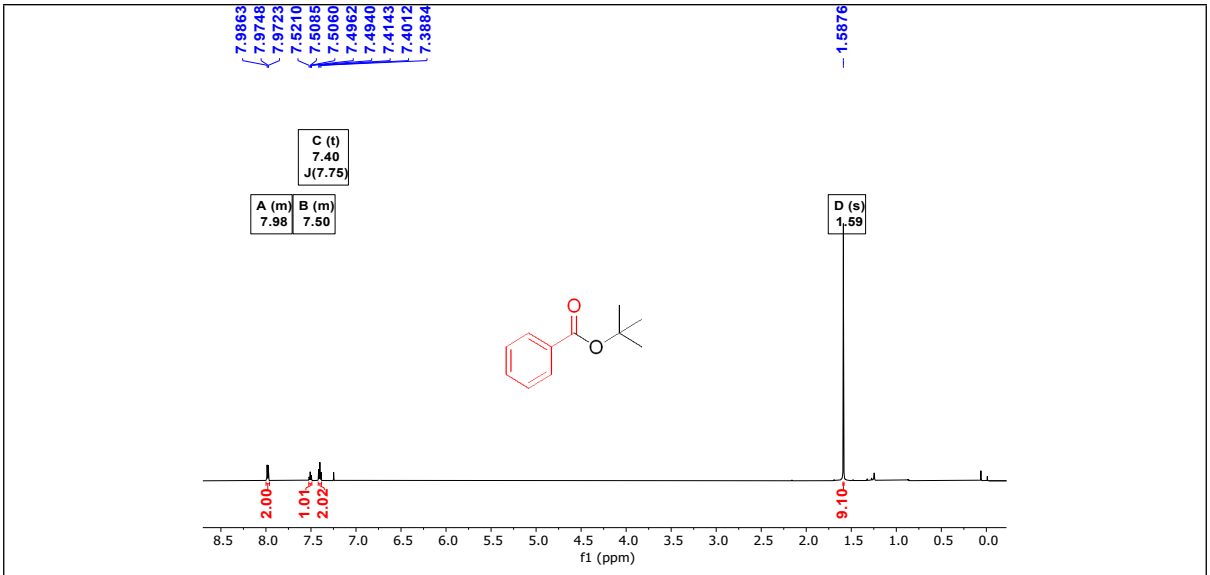


Fig. S24. ^{1}H–NMR of benzoate in $CDCl_3$ at 298K.

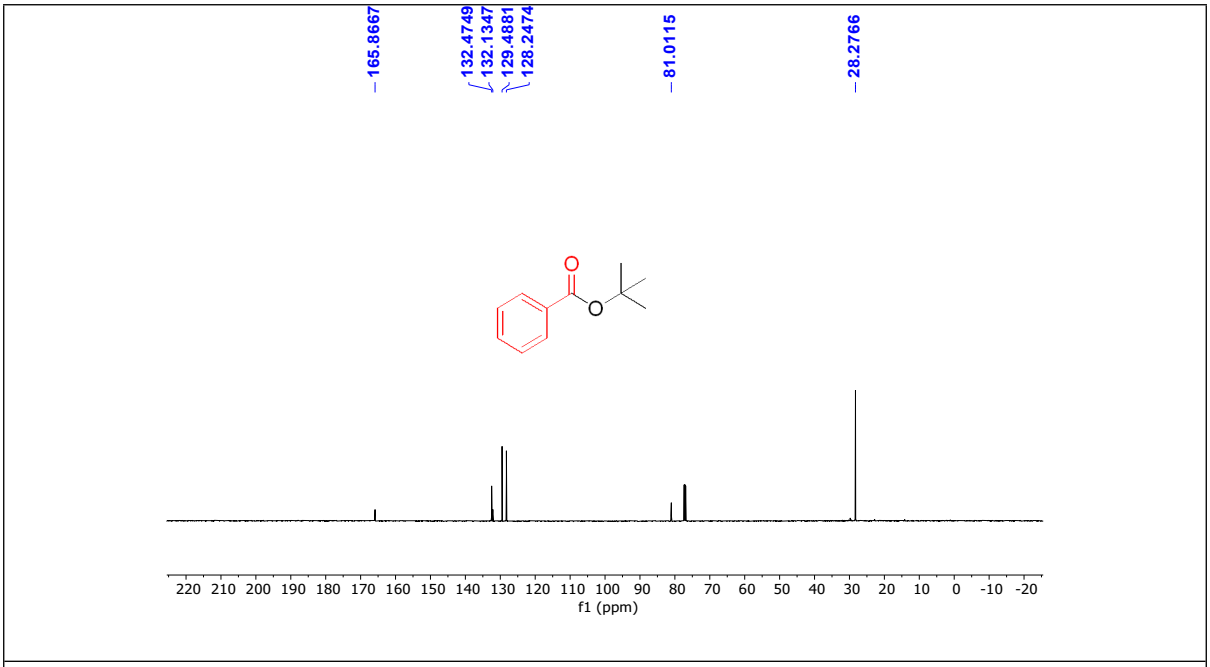


Fig. S25. ^{13}C–NMR of benzoate in $CDCl_3$ at 298K.

7. Reusability Study

Investigating material leaching, catalytic species involvement, and catalyst lifetime and durability through a series of experiments in the oxidative coupling of benzaldehyde and amine to form amide.

7.1 Recycling experiments for ZN–O–A–7 for oxidative amidation

The reaction was conducted in a pressure tube with simultaneous heating/cooling, stirring, and refluxing capabilities under an inert atmosphere using the Carousel 12 Plus reaction station, maintaining a dry and oxygen-free argon/nitrogen atmosphere. In the reaction vessel, 4-nitrobenzaldehyde (1a-5, 1 mM, 152 mg) and morpholine (2a, 1 mM, 86 µL) were combined with 5-6 M TBHP in dodecane (224 µL, ~1 mM) and **ZN-O-A-7** catalyst (36 mol%, 50 mg)

dissolved in 3 mL of THF. The mixture was then refluxed at 90°C for 2 hours. Upon completion of the reaction, the reaction mixture was centrifuged to recover the solid catalyst. The recovered catalyst was washed successively with water (20 mL × 2) and methanol (10 mL × 2), followed by drying at 60°C for up to 12 hours in a heating oven. Subsequently, 41 mg of solid **ZN-O-A-7** catalyst was collected and utilized for the next cycle. The THF solvent was evaporated, and water (50 mL) was added. The product was then extracted with ethyl acetate (50 mL × 3), washed with water (50 mL × 2) and brine (50 mL × 1), and dried over anhydrous Na_2SO_4 (5 g). After solvent removal under reduced pressure, the resulting crude product was analyzed by gas chromatography-mass spectrometry (GC-MS). The activity of the **ZN-O-A-7** catalyst was monitored up to the 4^{th} cycle. Additionally, the recovered **ZN-O-A-7** catalyst after the 2^{nd} and 4^{th} cycles was characterized using X-ray photoelectron spectroscopy (XPS) and powder X-ray diffraction (PXRD) techniques.

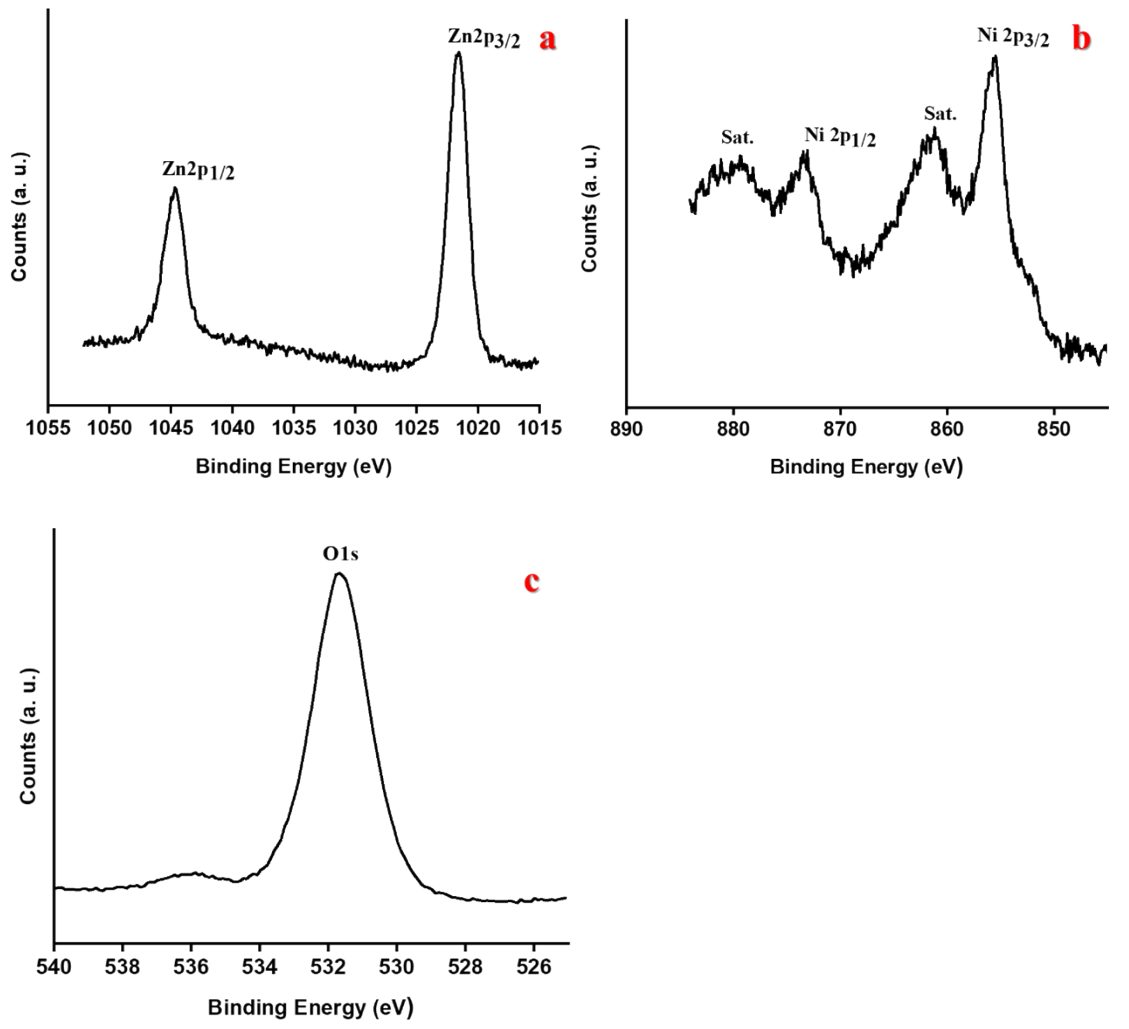


Fig. S26. XPS spectra of **ZN–O–A–7 (2nd Cycle)**,, survey scan (a), high-resolution XPS Zn2p (b), Ni2p (c), and O1s (d)

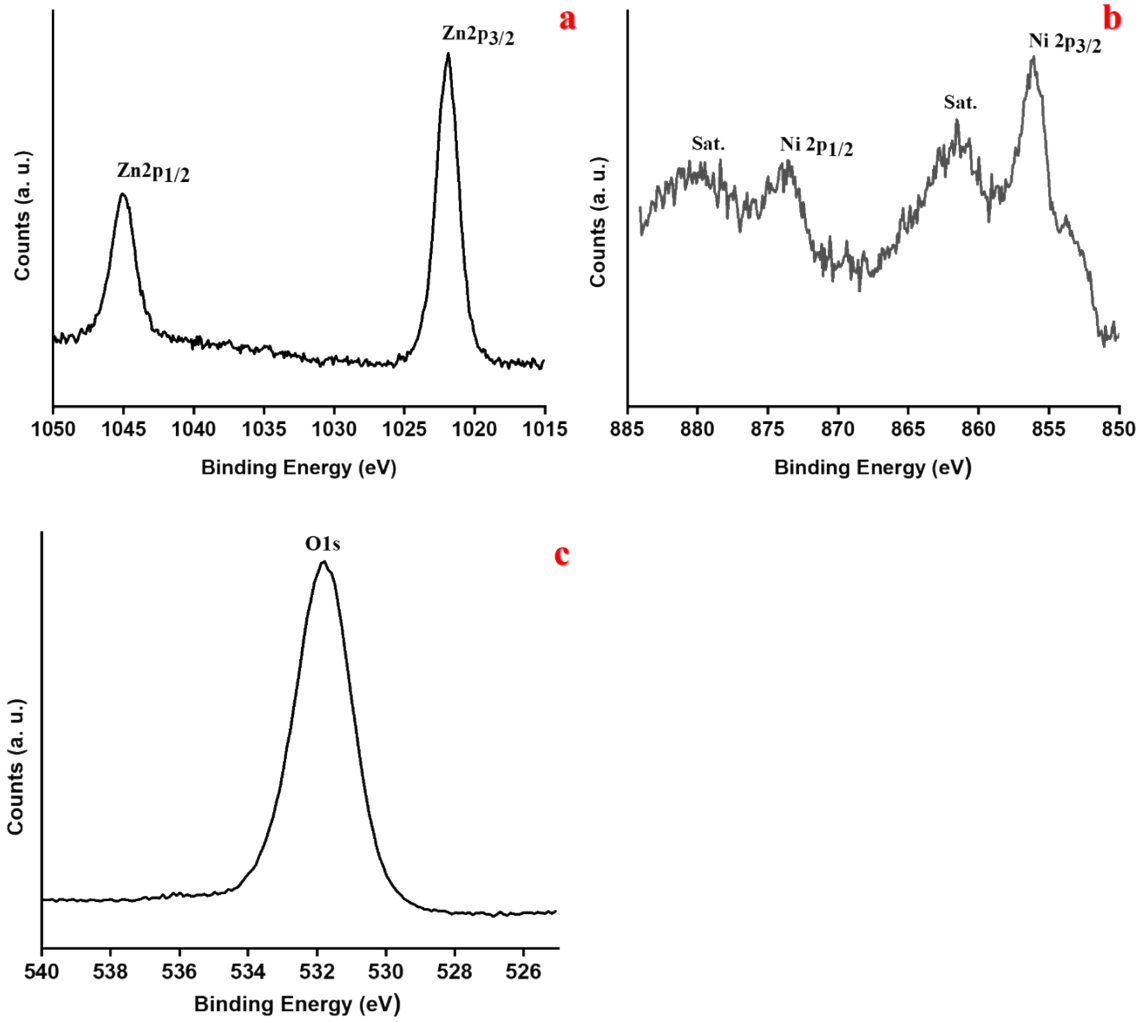
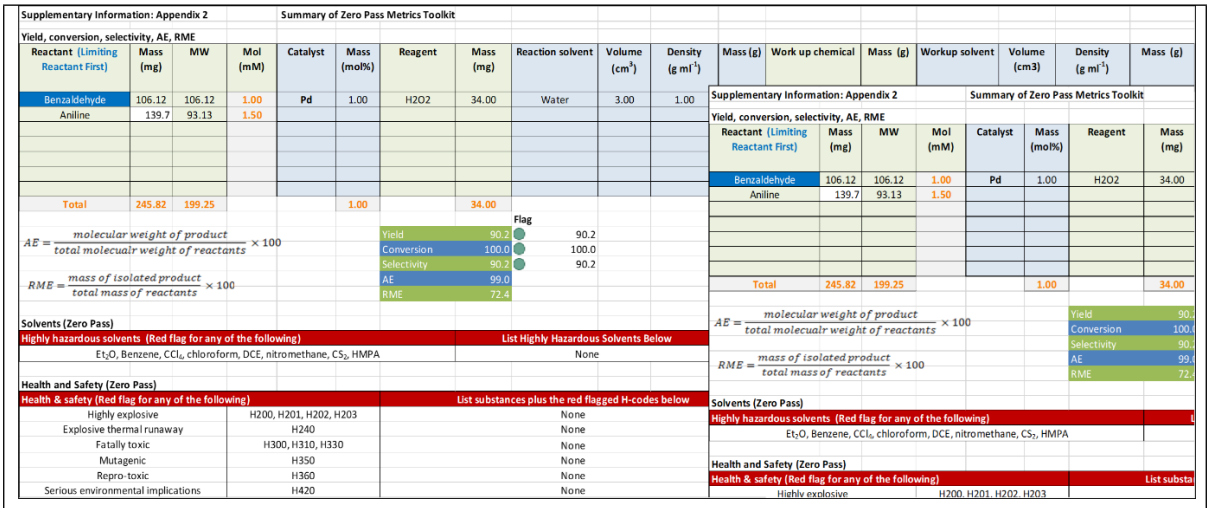


Fig. S27. XPS spectra of **ZN–O–A–7 (4th Cycle)**, survey scan (a), high-resolution XPS Zn2p (b), Ni2p (c), and O1s (d)

8. CHEM21 green matric toolkit



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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)
Benzaldehyde	106.12	106.12	1.00	Pd	1.00	H2O2	34.00	Water	3.00	1.00
Aniline	139.7	93.13	1.50							
Total	245.82	199.25			1.00		34.00			

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

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

		Flag
Yield	90.2	90.2
Conversion	100.0	100.0
Selectivity	90.2	90.2
AE	99.0	
RME	72.4	

Solvents (Zero Pass)

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

Health and Safety (Zero Pass)

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

Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)

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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)
Benzaldehyde	106.12	106.12	1.00	Pd	1.00	H2O2	34.00
Aniline	139.7	93.13	1.50				
Total	245.82	199.25			1.00		34.00

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

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

Yield	90.
Conversion	100.
Selectivity	90.
AE	99.
RME	72.

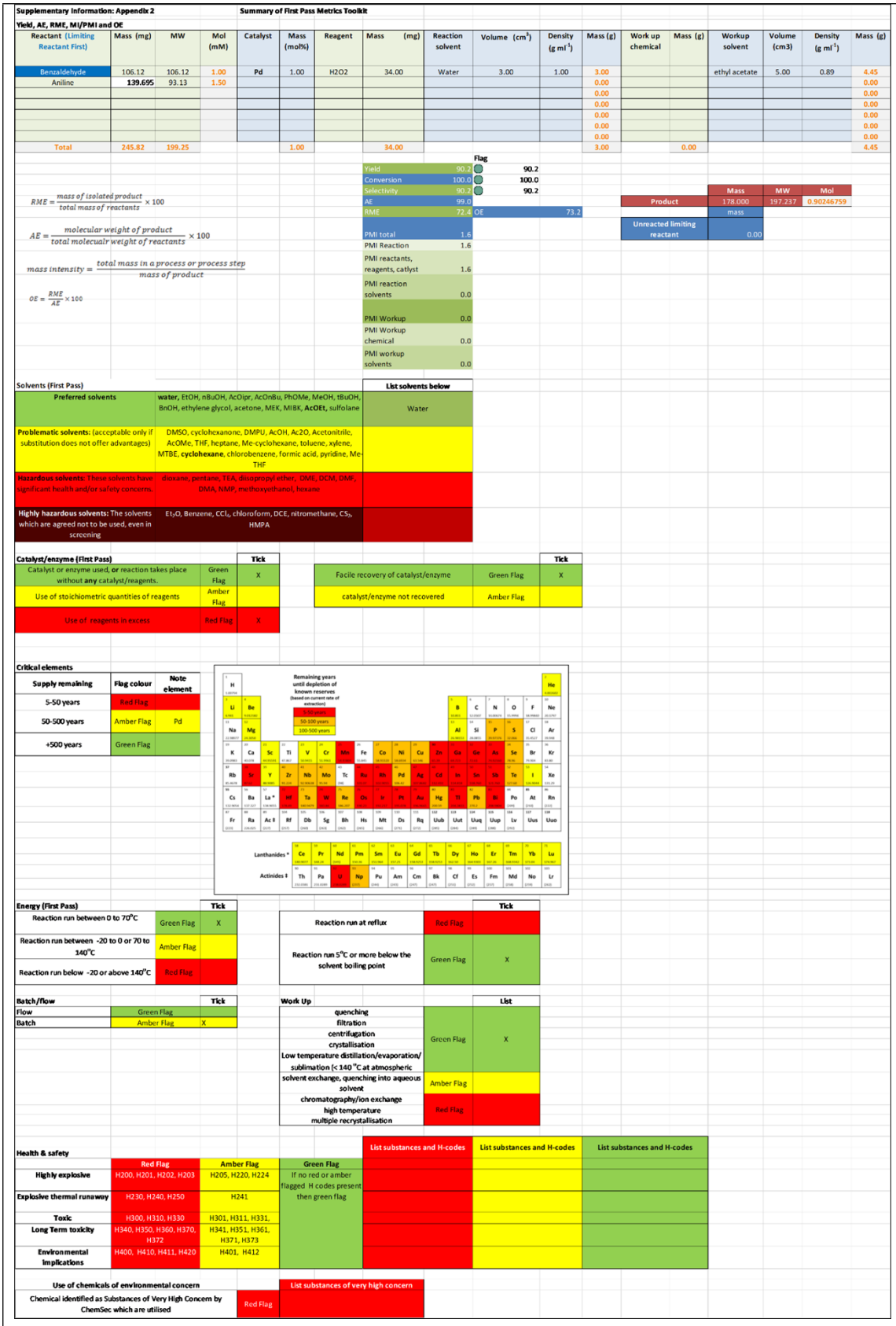
Solvents (Zero Pass)

Highly hazardous solvents (Red flag for any of the following)	
Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Health and Safety (Zero Pass)

Health & safety (Red flag for any of the following)		List substa
Highly explosive	H200, H201, H202, H203	

Fig. S28. Reference 27: Zero Pass CHEM21 green metrics toolkit.



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

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Pd	1.00	H2O2	34.00	Water	3.00	1.00	3.00			ethyl acetate	5.00	0.89	4.45
Aniline	139.695	93.13	1.50								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	245.82	199.25			1.00		34.00				3.00		0.00				4.45

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

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

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

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

		Flag
Yield	90.2	90.2
Conversion	100.0	100.0
Selectivity	90.2	90.2
AE	99.0	
RME	72.4	OE 73.2
PMI total	1.6	
PMI Reaction	1.6	
PMI reactants, reagents, catlyst	1.6	
PMI reaction solvents	0.0	
PMI Workup	0.0	
PMI Workup chemical	0.0	
PMI workup solvents	0.0	

	Mass	MW	Mol
Product	178.000	197.237	0.90246759
	mass		
Unreacted limiting reactant	0.00		

Solvents (First Pass)

		List solvents below
Preferred solvents	**water**, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt**, sulfolane	Water
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)

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

		Tick
Facile recovery of catalyst/enzyme	Green Flag	X
catalyst/enzyme not recovered	Amber Flag	

Critical elements

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

Energy (First Pass)

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

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

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

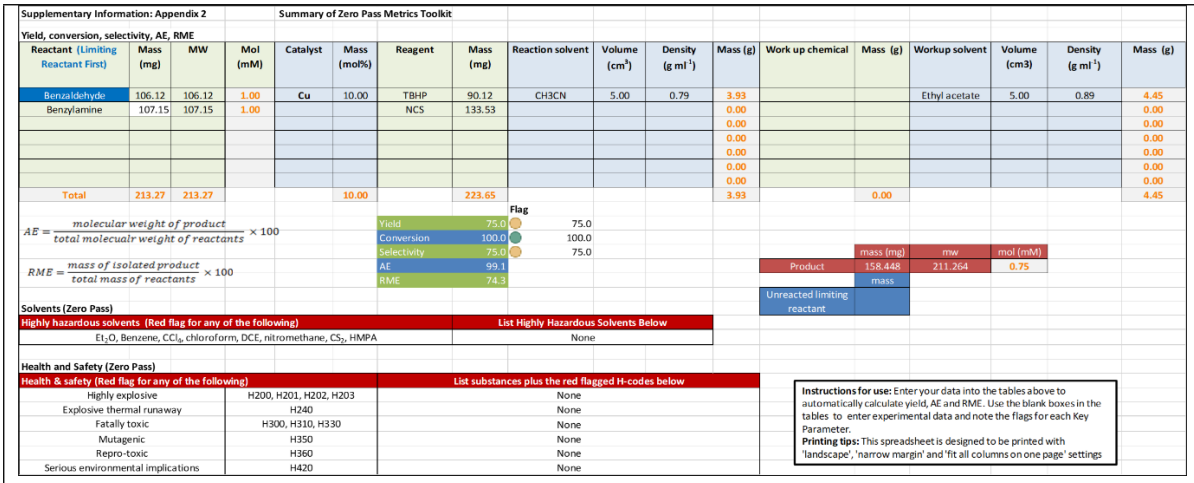
		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	X
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental Implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Fig. S29. Reference 27: First Pass CHEM21 green metrics toolkit.



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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Cu	10.00	TBHP	90.12	CH3CN	5.00	0.79	3.93			Ethyl acetate	5.00	0.89	4.45
Benzylamine	107.15	107.15	1.00			NCS	133.53				0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	213.27	213.27			10.00		223.65				3.93		0.00				4.45

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

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

		Flag
Yield	75.0	75.0
Conversion	100.0	100.0
Selectivity	75.0	75.0
AE	99.1	
RME	74.3	

	mass (mg)	mw	mol (mM)
Product	158.448	211.264	0.75
Unreacted limiting reactant	mass		

Solvents (Zero Pass)

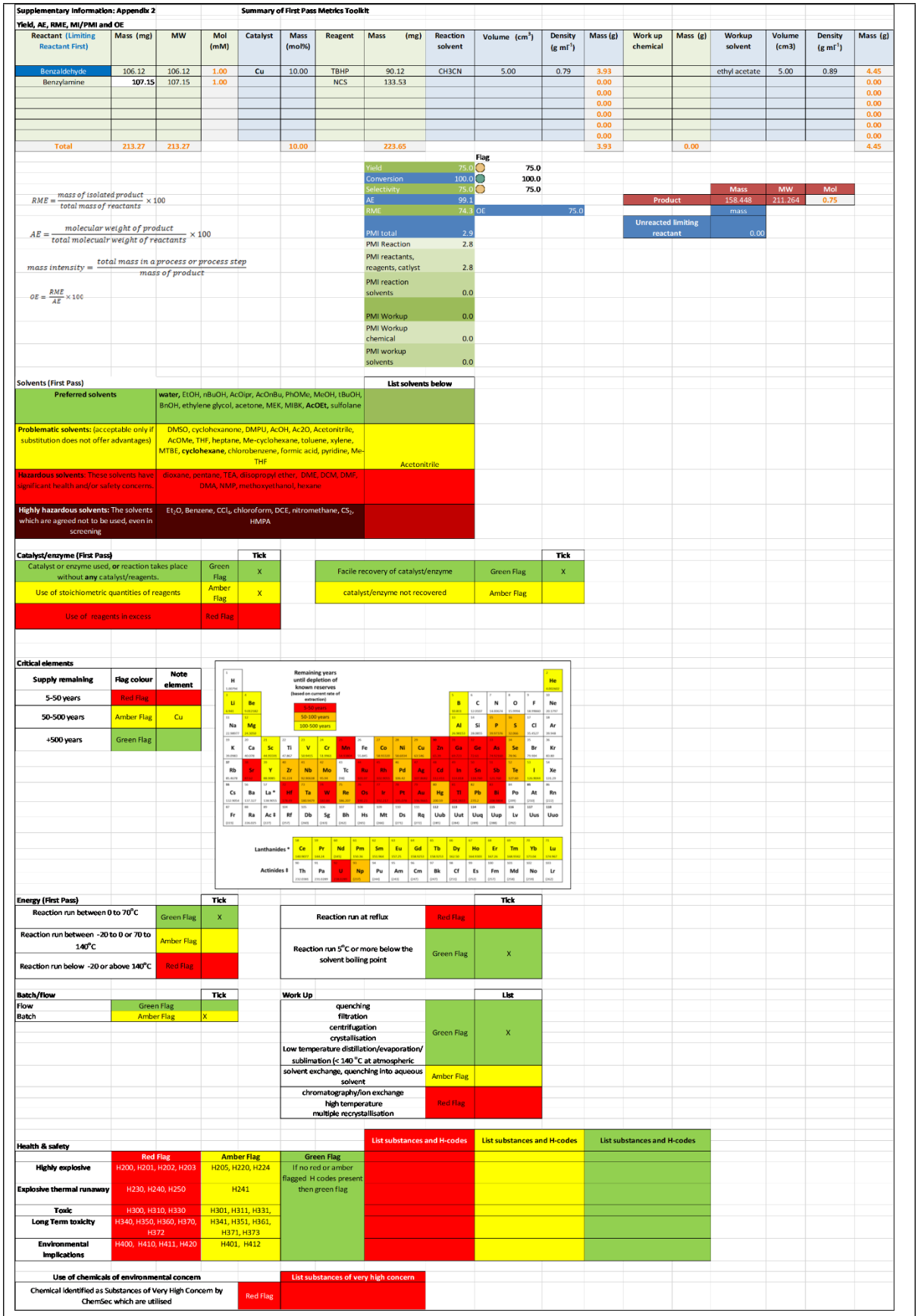
Highly hazardous solvents (Red flag for any of the following)	List Highly Hazardous Solvents Below
Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	None

Health and Safety (Zero Pass)

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

Instructions for use: Enter your data into the tables above to automatically calculate yield, AE and RME. Use the blank boxes in the tables to enter experimental data and note the flags for each Key Parameter.
Printing tips: This spreadsheet is designed to be printed with 'landscape', 'narrow margin' and 'fit all columns on one page' settings

Fig. S30. Reference 28: Zero Pass CHEM21 green metrics toolkit.



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

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Cu	10.00	TBHP	90.12	CH3CN	5.00	0.79	3.93			ethyl acetate	5.00	0.89	4.45
Benzylamine	107.15	107.15	1.00			NCS	133.53				0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	213.27	213.27			10.00		223.65				3.93		0.00				4.45

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

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

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

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

		Flag
Yield	75.0	75.0
Conversion	100.0	100.0
Selectivity	75.0	75.0
AE	99.1	
RME	74.3	OE 75.0
PMI total	2.9	
PMI Reaction	2.8	
PMI reactants, reagents, catlyst	2.8	
PMI reaction solvents	0.0	
PMI Workup	0.0	
PMI Workup chemical	0.0	
PMI workup solvents	0.0	

	Mass	MW	Mol
Product	158.448	211.264	0.75
	mass		
Unreacted limiting reactant	0.00		

Solvents (First Pass)

		List solvents below
Preferred solvents	**water**, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt**, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	Acetonitrile
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

Catalyst/enzyme (First Pass)

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

Critical elements

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

Energy (First Pass)

		Tick			Tick
Reaction run between 0 to 70°C	Green Flag	X	Reaction run at reflux	Red Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag		Reaction run 5°C or more below the solvent boiling point	Green Flag	X
Reaction run below -20 or above 140°C	Red Flag				

Batch/flow

		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up

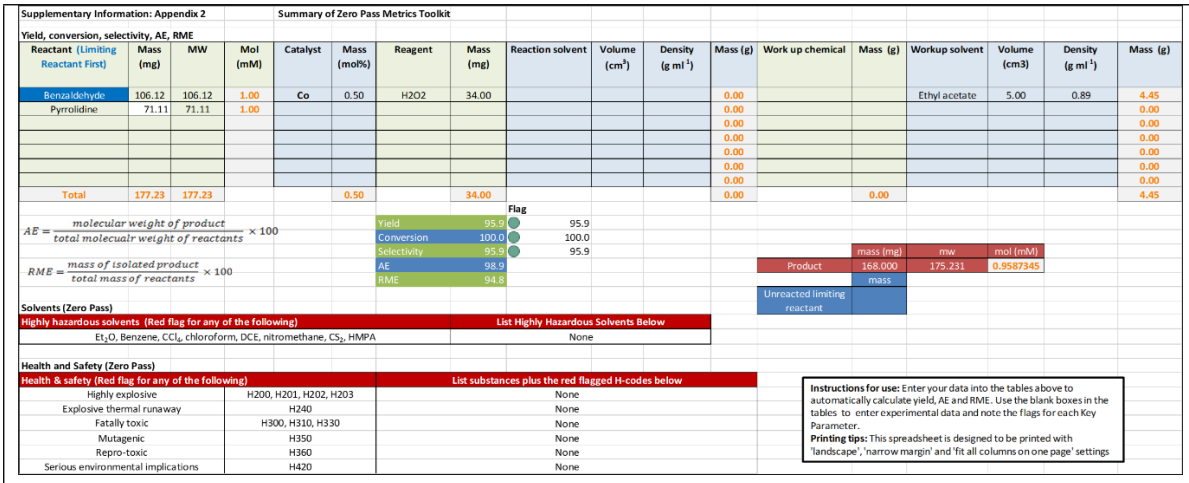
		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	X
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental Implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Fig. S31. Reference 28: First Pass CHEM21 green metrics toolkit.



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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Co	0.50	H2O2	34.00				0.00
Pyrrolidine	71.11	71.11	1.00								0.00
											0.00
											0.00
											0.00
											0.00
											0.00
											0.00
Total	177.23	177.23			0.50		34.00				0.00

Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
		Ethyl acetate	5.00	0.89	4.45
					0.00
					0.00
					0.00
					0.00
					0.00
					0.00
					0.00
	0.00				4.45

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

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

		Flag	
Yield	95.9		95.9
Conversion	100.0		100.0
Selectivity	95.9		95.9
AE	98.9		
RME	94.8		

	mass (mg)	mw	mol (mM)
Product	168.000	175.231	0.9587345
Unreacted limiting reactant	mass		

Solvents (Zero Pass)

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

Health and Safety (Zero Pass)

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

Instructions for use: Enter your data into the tables above to automatically calculate yield, AE and RME. Use the blank boxes in the tables to enter experimental data and note the flags for each Key Parameter.
Printing tips: This spreadsheet is designed to be printed with 'landscape', 'narrow margin' and 'fit all columns on one page' settings

Fig. S32. Reference 29: Zero Pass CHEM21 green metrics toolkit.

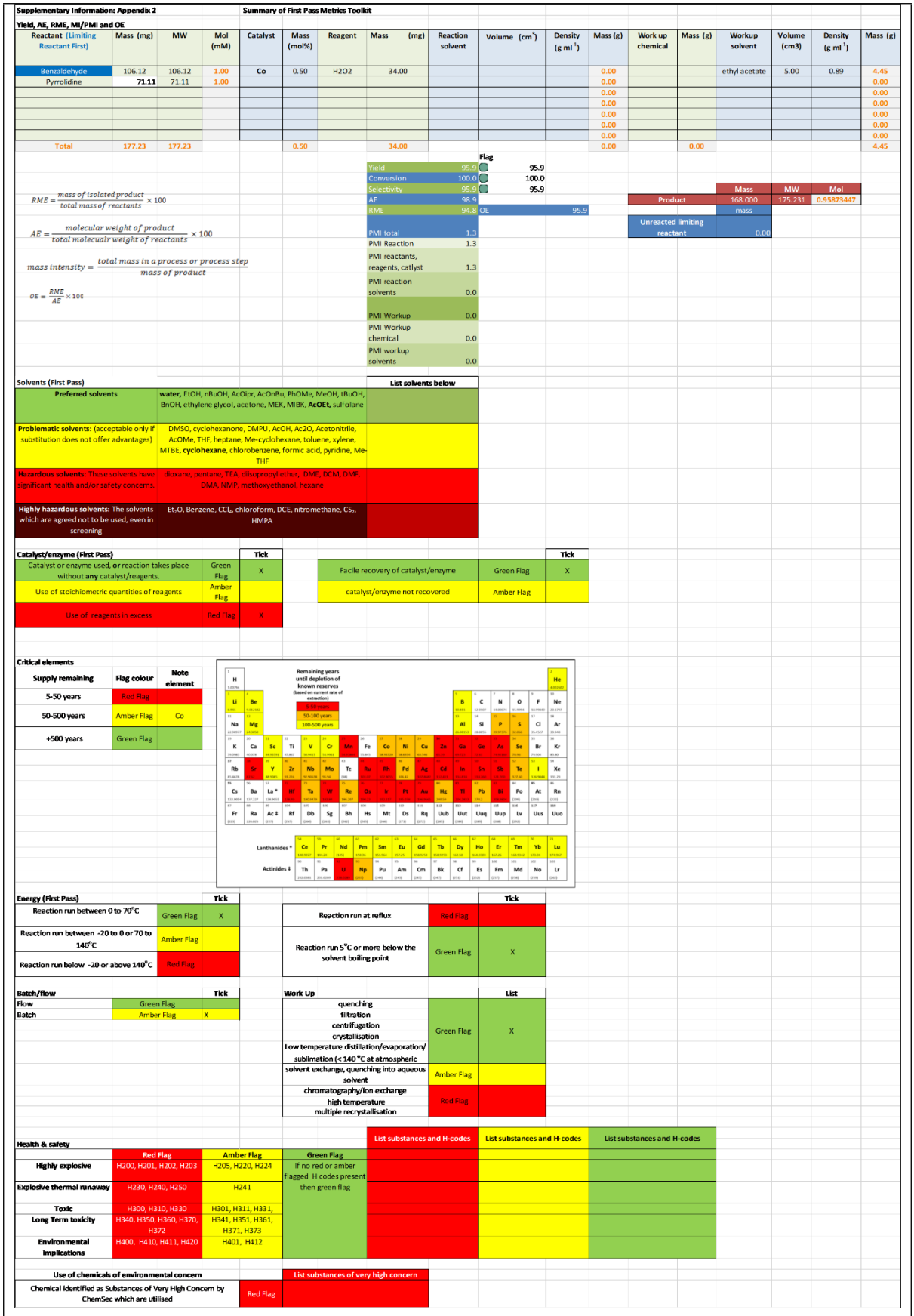
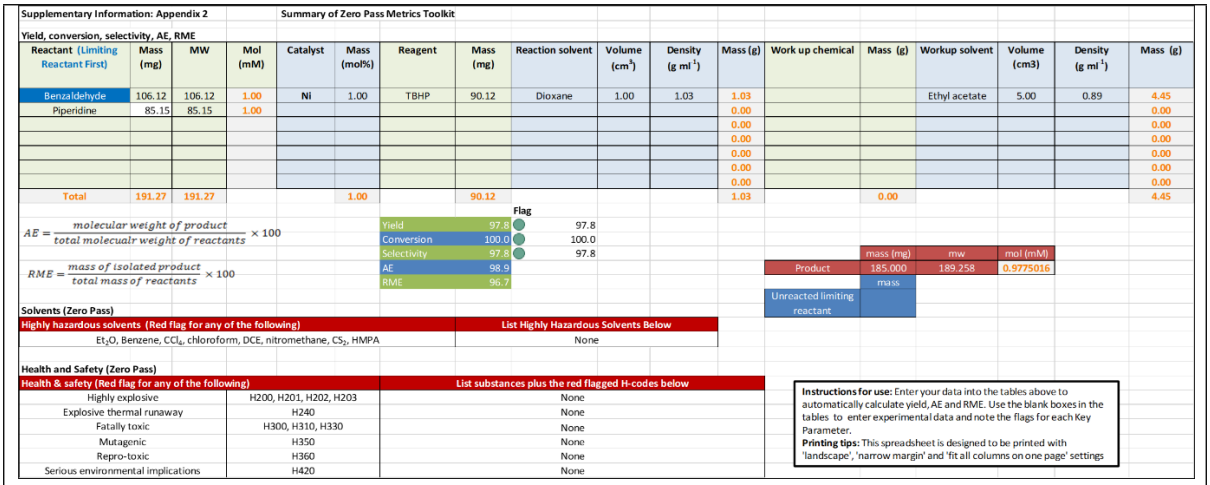


Fig. S33. Reference 29: First Pass CHEM21 green metrics toolkit.



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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Ni	1.00	TBHP	90.12	Dioxane	1.00	1.03	1.03			Ethyl acetate	5.00	0.89	4.45
Piperidine	85.15	85.15	1.00								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	191.27	191.27			1.00		90.12				1.03		0.00				4.45

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

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

		Flag	
Yield	97.8	●	97.8
Conversion	100.0	●	100.0
Selectivity	97.8	●	97.8
AE	98.9		
RME	96.7		

	mass (mg)	mw	mol (mM)
Product	185.000	189.258	0.9775016
Unreacted limiting reactant	mass		

Solvents (Zero Pass)

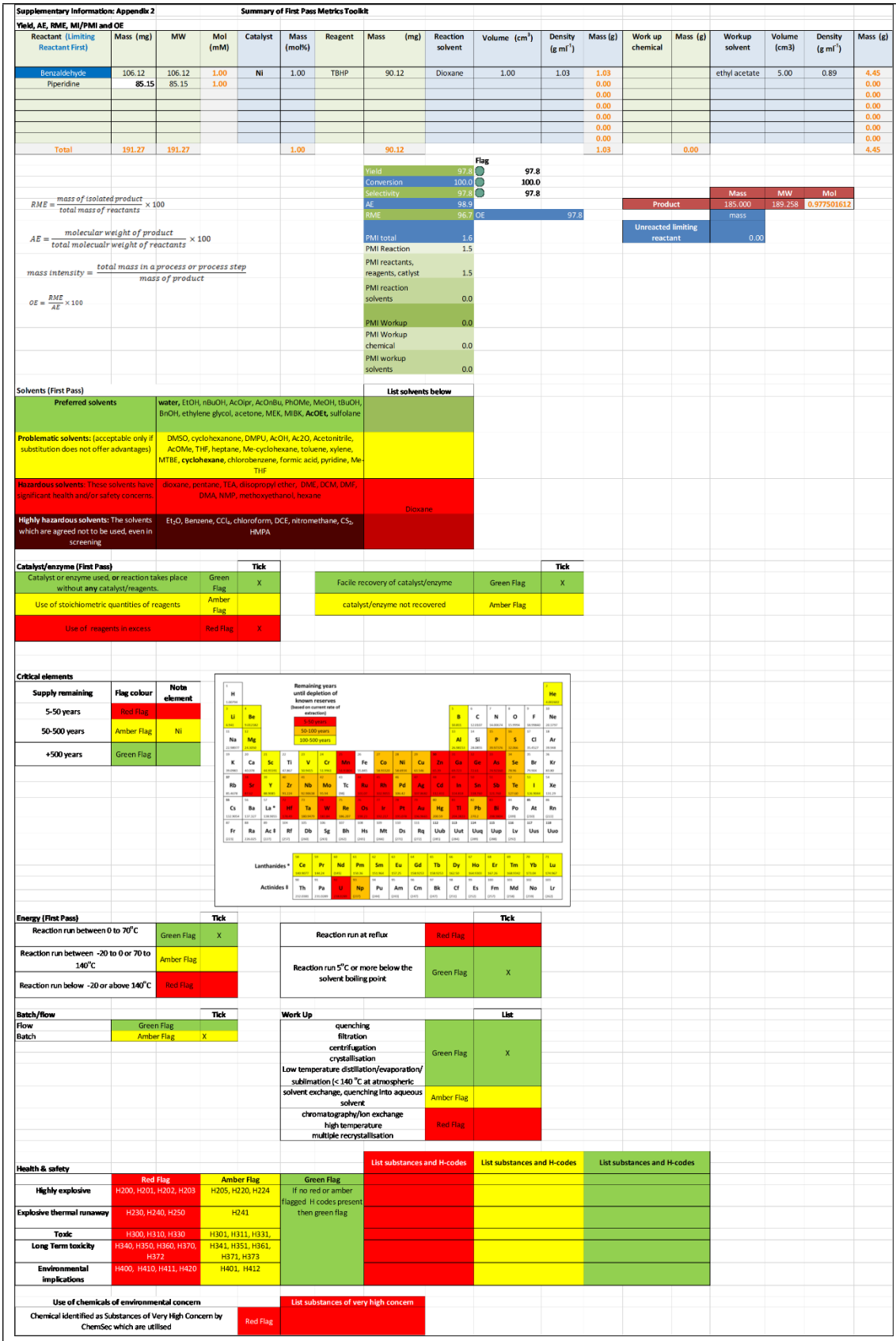
Highly hazardous solvents (Red flag for any of the following)	List Highly Hazardous Solvents Below
Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	None

Health and Safety (Zero Pass)

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

Instructions for use: Enter your data into the tables above to automatically calculate yield, AE and RME. Use the blank boxes in the tables to enter experimental data and note the flags for each Key Parameter.
Printing tips: This spreadsheet is designed to be printed with 'landscape', 'narrow margin' and 'fit all columns on one page' settings

Fig. S34. Reference 30: Zero Pass CHEM21 green metrics toolkit.



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

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Ni	1.00	TBHP	90.12	Dioxane	1.00	1.03	1.03			ethyl acetate	5.00	0.89	4.45
Piperidine	85.15	85.15	1.00								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	191.27	191.27			1.00		90.12				1.03		0.00				4.45

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

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

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

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

		Flag
Yield	97.8	97.8
Conversion	100.0	100.0
Selectivity	97.8	97.8
AE	98.9	
RME	96.7	OE 97.8
PMI total	1.6	
PMI Reaction	1.5	
PMI reactants, reagents, catlyst	1.5	
PMI reaction solvents	0.0	
PMI Workup	0.0	
PMI Workup chemical	0.0	
PMI workup solvents	0.0	

	Mass	MW	Mol
Product	185.000	189.258	0.977501612
	mass		
Unreacted limiting reactant	0.00		

Solvents (First Pass)

		List solvents below
Preferred solvents	**water**, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt**, sulfolane	
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	Dioxane
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA	

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

Critical elements

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

Energy (First Pass)		**Tick**			**Tick**
Reaction run between 0 to 70°C	Green Flag	X	Reaction run at reflux	Red Flag	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag		Reaction run 5°C or more below the solvent boiling point	Green Flag	X
Reaction run below -20 or above 140°C	Red Flag				

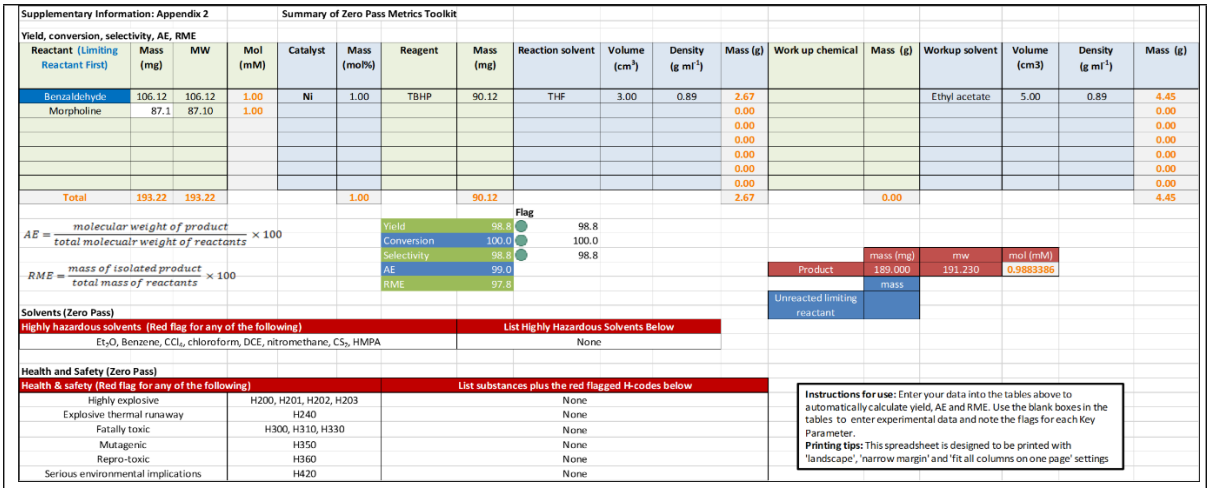
Batch/flow		**Tick**
Flow	Green Flag	
Batch	Amber Flag	X

Work Up		**List**
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 °C at atmospheric	Green Flag	X
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety	**Red Flag**	**Amber Flag**	**Green Flag**	**List substances and H-codes**	**List substances and H-codes**	**List substances and H-codes**
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,				
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

Use of chemicals of environmental concern		**List substances of very high concern**
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Fig. S35. Reference 30: First Pass CHEM21 green metrics toolkit.



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

Yield, conversion, selectivity, AE, RME

Reactant (Limiting Reactant First)	Mass (mg)	MW	Mol (mM)	Catalyst	Mass (mol%)	Reagent	Mass (mg)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Benzaldehyde	106.12	106.12	1.00	Ni	1.00	TBHP	90.12	THF	3.00	0.89	2.67			Ethyl acetate	5.00	0.89	4.45
Morpholine	87.1	87.10	1.00								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	193.22	193.22			1.00		90.12				2.67		0.00				4.45

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

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

		Flag	
Yield	98.8		98.8
Conversion	100.0		100.0
Selectivity	98.8		98.8
AE	99.0		
RME	97.8		

	mass (mg)	mw	mol (mM)
Product	189.000	191.230	0.9883386
	mass		
Unreacted limiting reactant			

Solvents (Zero Pass)

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

Health and Safety (Zero Pass)

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

Instructions for use: Enter your data into the tables above to automatically calculate yield, AE and RME. Use the blank boxes in the tables to enter experimental data and note the flags for each Key Parameter.
Printing tips: This spreadsheet is designed to be printed with 'landscape', 'narrow margin' and 'fit all columns on one page' settings

Fig. S36. This work: Zero Pass CHEM21 green metrics toolkit.

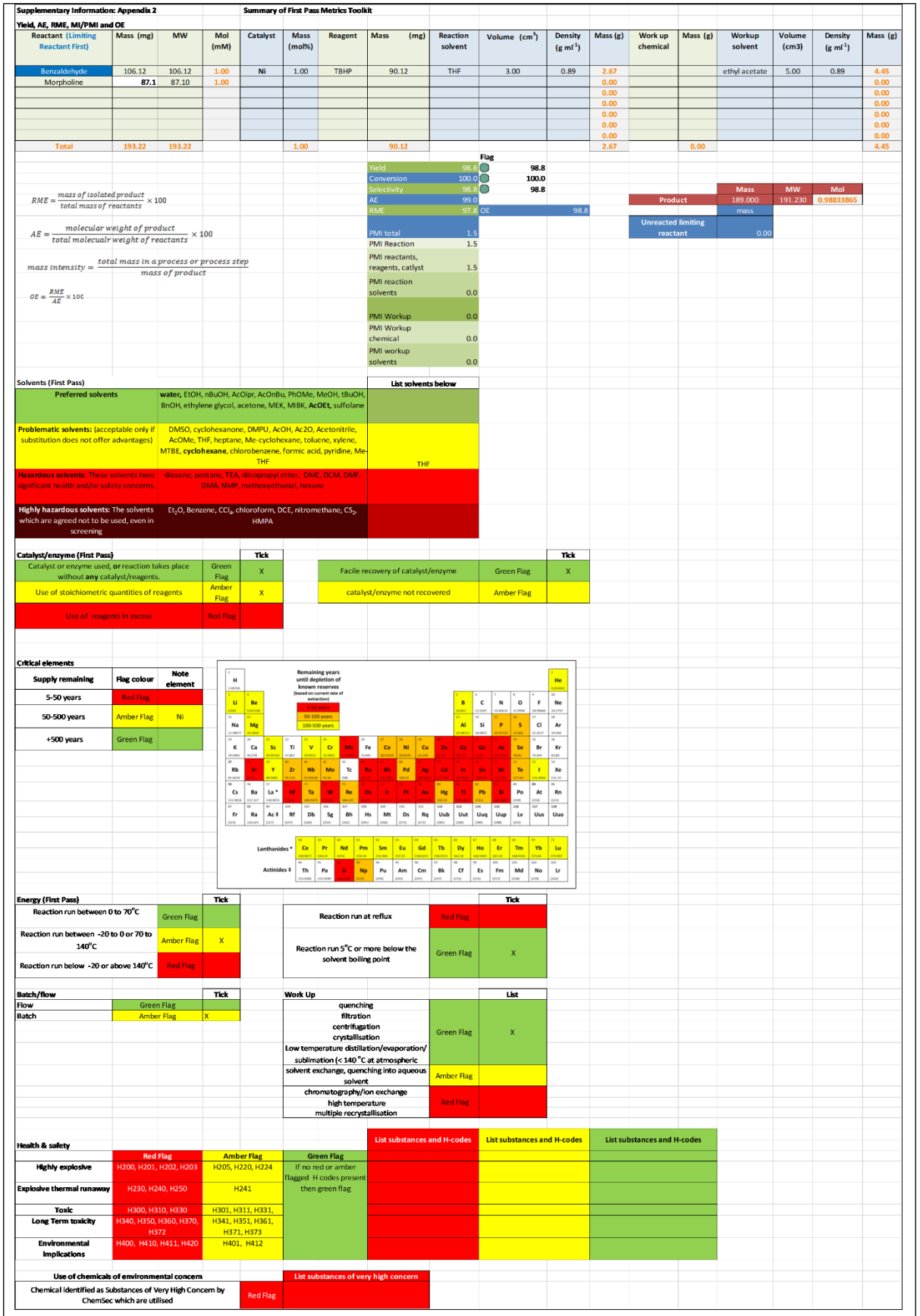


Fig. S37. This work: First Pass CHEM21 green metrics toolkit.

9. Reference

1. A. R. Shelte, R. D. Patil, S. Karan, G. R. Bhadu and S. Pratihar, *ACS Appl. Mater. Interfaces*, 2023, **15**, 24329-24345.

2. A. R. Shelte, R. N. Khatal and S. Pratihar, *Appl. Catal.*, 2023, **666**, 119417.