Supplementary Information

'Green' synthesis of amines from renewable resources? A detailed analysis of case studies using the CHEM21 Green Metrics Toolkit

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1. General remarks prior to the calculations

Due to the lack of detail in the experimental procedures, the following general considerations/assumptions have been made in order to properly follow the Green Metrics calculations (**Table S1**):

Table S1: Considerations for calculating Green Metrics using the CHEM21 Green Metrics Toolkit.

Experimental procedure	Assumption
Solvent filtration/extraction/washing	5 mL for 1 mmol limiting reactant
Recrystallization	1 mL for 1 mmol limiting reactant
Filtration over Celite/ silica plug	2 g for 1 mmol limiting reactant
Drying over $MgSO_4$ or Na_2SO_4	1 g for 1 mmol limiting reactant
Flash chromatography	100 mL solvent mixture (for example, EtOAc/petroleum ether: 20:80) and 8 g SiO_2 for 1 mmol limiting reactant
Washing with any inorganic solution (in case the quantity of the solvent is not mentioned)	5 mL for 1 mmol limiting reactant

2. Assumptions made for the classical synthesis of *N*-substituted tetrahydro-2-benzazepine

In *Step 1* of the classical synthesis of 2-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-ol from benzene with propylene, several assumptions were made. In one run, 13% of benzene to the desired product was converted. In order to obtain cumene with a yield of 91.3% according to the literature procedure, this step has to be repeated seven times, as such the amount of the propylene required in one run was multiplied by a factor of seven in the green metrics calculations. The zeolite catalyst used could be recycled several times therefore there was no need to multiply its amount.

For the oxidation of cumene to its hydroperoxide (*Step 2*), a similar assumption was made. According to the literature procedure, a 19.4% yield is obtained after a reaction time of one hour. Therefore, the amount of air required to get a 93.7% yield is 4.83 times more than what is reported in the procedure. For ease of calculations, the air was considered as a 20:80 mixture (mole ratio) of O_2 and N_2 gases.

For the hydroxylation of phenol (*Step 4*), more than 95% of the substrate is not converted in one single reaction under the given conditions. For this reason, the amount of phenol that is not converted (and therefore recycled in the next run) was not taken into account as a reactant.

The formation of co-products with specific industrial applications was also considered waste in the original CHEM21 Green Metrics. As these co-products were not the focus of our research, they were standardly treated as waste in our calculations.

3. Calculated quantitative and qualitative metrics for the synthesis of *N*-substituted tetrahydro-2-benzazepines

Table S2: Calculated discrete and cumulative quantitative metrics for the synthesis of *N*-substituted tetrahydro-2-benzazepines from benzene or dihydroconiferyl alcohol.

Step	Yield, %	AE, %	RME, %	PMI ($g \cdot g^{-1}$)			
				Tot	RRC	Rxn solv	WU
Literature-based approach for synthesis 2-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-ol							
1[1]	91.4	99.9	88.3	1.1	1.1	0	0
2[2]	93.7	99.9	99.3	1.5	1.0	0.5	0
3[3]	95.7	61.9	59.2	13.5	1.8	11.7	0
4[4]	54.0	85.9	46.0	2.7	2.3	0.4	0
5[5]	61.8	100.0	59.7	36.4	2.7	11.5	22.2
6[5]	96.0	75.0	72.0	117.6	9.1	108.5	0
7[5]	65.1	57.6	37.7	48.4	3.1	4.4	40.9
8[6]	96.7	42.8	38.6	435.7	2.6	22.2	410.9
9[6]	99.8	99.0	75.9	51.7	1.5	8.9	41.2
10[6]	98.3	93.3	91.7	43.5	1.2	11.9	30.4
11[6]	54.8	94.1	18.7	1050.5	6.4	0	1044.1
12[6]	92.9	83.9	69.7	776.4	1.4	31.3	743.7
13[6]	95.1	94.0	88.7	701.7	1.5	25.9	674.3
Overall (13 steps)	***7.8***	***31.3***	***5.1***	***3866.0***	***37.5***	***376.0***	***3452.5***
Bio-based approach for synthesis 2-(4-chlorophenyl)-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ol							
A[7]	97.0	94.2	81.8	381.9	1.3	15.2	365.4
B[7]	87.0	94.4	82.4	663.4	12.2	0	651.2
Overall (2 steps)	***84.4***	***89.4***	***68.6***	***1082.3***	***12.5***	***16.7***	***1053.1***

AE: Atom Economy; RME: Reaction Mass Efficiency; PMI: Process Mass Intensity; Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn solv: Reaction solvents; WU: Work-up.

Table S3: Qualitative appraisal of solvent use, inherent hazards of used chemicals, catalyst or reagent use, energy, and work-up methods for both approaches for the synthesis of *N*-substituted tetrahydro-2-benzazepines.

Step	Solvent Rxn	Flag	Solvent WU	Flag	Crit. el	Flag	Health & Safety	Flag	Reagent use	Flag	Energy Use	Flag	Work-up	Flag
Literature-based approach for synthesis 2-benzyl-8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-ol														
1[1]	-		-		Al		Benzene: H340, H350, H372, H410 Propylene: H220		Catalyst		150 °C		Distill.	
2[2]	-		-		-		Cumene: H411		Catalyst		118-126 °C		Distill.	
3[3]	HOAc		-		-		-		Catalyst		<22 °C		Filtr.	
4[4]	H_2O		H_2O		S		-		Catalyst		50 °C		Distill.	
5[5]	H_2O		H_2O EtOAc		Al		Catechol: H301, H311, H341, H401, H350		Stoich.		60 °C		Extr.	
6[5]	H_2O EtOAc		-		Cu		$CuCl_2$ $2H_2O$: H400, H410		Catalyst		60 °C		Filt.	
7[5]	H_2O		H_2O DCM		S		Me_2SO_4: H330, H350, H301, H341		Stoich.		55 °C		Extr.	
8[6]	DCM		EtOAc Hexane		P		-		Stoich.		RT to reflux		Chrom.	
9[6]	MeOH		DCM		Pd		-		Catalyst		RT		Filt.	
10[6]	H_2O THF		EtOAc		Li		Methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate: H351		Stoich.		RT		Extr.	
11[6]	-		H_2O, MeOH DCM		-		Benzyl amine: H301, H351, H361 H310, H340		Excess		150 °C		Chrom.	
12[6]	THF		H_2O, MeOH, EtOAc DCM		Li, Al		$LiAlH_4$: H301, H331 H310, H330, H340		Excess		RT to reflux		Chrom.	
13[6]	CH_3CN		H_2O, MeOH DCM		S		Paraformaldehyde: H341, H350		Stoich.		Reflux		Chrom.	
Bio-based approach for synthesis 2-(4-chlorophenyl)-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-ol														
A[7]	CPME		EtOAc pentane		Ru		*p*-Chloroaniline: H301, H311, H331, H412, H400, H350 Dihydroconiferyl alcohol: H351		Catalyst		130 °C		Chrom.	
B[7]	DES		H_2O, EtOAc pentane		-		Paraformaldehyde: H341, H350		Stoich.		70 °C		Chrom.	

Rxn: Reaction; WU: Work-up; Stoich.: Stoichiometric; Distill.: Distillation; Esxtr.: Extraction; Filtr.: Filtration; Chrom.: Chromatography.

4. Calculated quantitative and qualitative metrics for the synthesis of ranitidine

Table S4: Calculated discrete and cumulative quantitative metrics for the synthesis of ranitidine from furfuryl alcohol and 5-(chloromethyl)furfural (CMF).

Step	Yield, %	AE, %	RME, %	PMI ($g \cdot g^{-1}$)			
				Tot	RRC	Rxn solv	WU
Classical approach for synthesis of ranitidine							
1[8]	97.1	100	95.1	1.1	1.1	0	0
2[9]	43.4	74.0	24.9	39.1	4.0	4.5	30.6
3[10]	54.2	79.7	43.2	39.4	2.3	5.1	32.0
4[10]	80.7	86.7	69.0	6.7	1.5	1.1	4.2
Overall (4 steps)	***18.4***	***66.7***	***16.6***	***82.3***	***6.1***	***10.5***	***65.8***
Alternative approach for synthesis of ranitidine							
A[11]	91.2	86.2	78.6	522.4	1.4	37.5	483.5
B[11]	90.3	82.6	22.8	388.1	4.4	73.7	310.0
C[11]	93.5	83.6	78.2	717.4	5.4	51.7	660.3
D[11]	87.9	86.7	76.1	756.4	1.3	77.5	677.6
Overall (4 steps)	***67.7***	***63.5***	***19.4***	***2203.6***	***8.5***	***227.2***	***1967.9***

AE: Atom Economy; RME: Reaction Mass Efficiency; PMI: Process Mass Intensity; Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn solv: Reaction solvents; WU: Work-up.

Table S5: Qualitative appraisal of solvent use, inherent hazards of used chemicals, catalyst or reagent use, energy, and work-up methods for both approaches for the synthesis of ranitidine.

Step	Solvent Rxn	Flag	Solvent WU	Flag	Crit. el	Flag	Health & Safety	Flag	Reagent use	Flag	Energy Use	Flag	Work-up	Flag
Classical approach for synthesis of ranitidine														
1[8]	-		-		Cu, Cr		Furfural: H301, H330, H351, H412 Copper chromite: H410		Catalyst		180 °C		Filtr.	
							Hydrogen gas: H220							
2[9]	EtOH		Water		-		Paraformaldehyde: H341, H350		Excess		Reflux		Extr.	
			Et_2O				Furfuryl alcohol H331, H351, H373						Distill.	
3[10]	Water		Et_2O		S				Stoich.		0 °C		Quench.	
													Distill	
4[10]	Water		4-Methyl-2-pentanone		S				Stoich.		Reflux		Distill, Filter.	
Alternative approach for synthesis of ranitidine														
A[11]	THF		Water		S		THF: H351 5-Chloromethylfurfural: H351 DCM: H351		Stoich		RT		Extr.	
			DCM											
B[11]	MeOH		DCM		S, B		Dimethylamine: H220, H412 DCM: H351		Stoich		RT		Filtr.	
							$NaBH_4$: H301, H360FD MeOH: H301+H311+H331, H370							
C[11]	Water		DCM		S		DCM: H351		Stoich		Reflux		Extr.	
			Water											
D[11]	Water		$CHCl_3$		S		$CHCl_3$: H331, H351, H361, H412		Stoich		55 °C		Extr.	
			Water				$CHCl_3$: H372							

Rxn: Reaction; WU: Work-up; Stoich.: Stoichiometric; Quench.: quenching; Cryst.: Crystallization; Filtr.: Filtration; Distill.: Distillation; Extr.: Extraction.

5. Calculated quantitative and qualitative metrics for the synthesis of norfenefrine

Table S6: Calculated discrete and cumulative quantitative metrics for the synthesis of norfenefrine.

Step	Yield, %	AE, %	RME, %	PMI ($g \cdot g^{-1}$)			
				Tot	RRC	Rxn solv	WU
Literature-based approach for synthesis of norfenefrine							
1[12]	100	76.7	43.8	9177	5.6	432	8739
2[13]	92	62.8	54.1	195	1.8	63.6	129
3[14]	96	68.4	65.3	611	2.9	12.5	596
4[15]	89	72.7	64.8	85.1	1.6	4.7	78.9
5[16]	22	39.0	7.3	233	13.7	95.3	124
Overall (5 steps)	***17***	***22.2***	***5.4***	***47588***	***53.4***	***2643***	***44892***
Bio-based approach for synthesis of norfenefrine							
A[17]	94	66.1	5.5	399	18.4	25.1	355
B[17]	78	49	0.4	1165	247	75.7	843
C[17]	71	39.9	13.8	3707	7.5	26.7	3673
Overall (3 steps)	***52***	***24.6***	***0.22***	***6036***	***326***	***176***	***5534***

AE: Atom Economy; RME: Reaction Mass Efficiency; PMI: Process Mass Intensity; Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn solv: Reaction solvents; WU: Work-up.

Table S7: Qualitative appraisal of solvent use, inherent hazards of used chemicals, catalyst or reagent use, energy and work-up methods for both approaches for the synthesis of norfenefrine.

Step	Solvent Rxn	Flag	Solvent WU	Flag	Crit. el	Flag	Health & Safety	Flag	Reagent use	Flag	Energy Use	Flag	Work-up	Flag
Literature-based approach for synthesis norfenefrine														
1[12]	DCM		Water		Al		Benzene: H340, H350, H372, H410		Excess		0 °C to RT		Quench.	
			DCM				DCM: H351, H 373 Acetyl chloride: H412							
2[13]	$CFCl_3$, $CHCl_3$		Water		-		Br_2: H330, H400 $CFCl_3$: H420 $CHCl_3$: H372		Stoich.		-78 °C		Quench.	
	EtOH													
3[14]	Water		Hexane		Pd		$Pd_2(dba)_3$: H411 1,4-dioxane: H370, H372 Hexane: H411		Catalyst		80 °C		Chrom.	
	1,4-dioxane		EtOAc											
4[15]	EtOAc		EtOAc MeOH Water		Al		Br_2: H330, H400 Methanol: H370 Benzene: H340, H350, H372, H410		Catalyst		RT		Cryst.	
			Benzene											
5[16]	Chlorobenzene		EtOH		B		$NaBH_4$: H301, H311		Excess		50 °C		Cryst.	
	Methanol						Chlorobenzene: H411 Methanol: H370							
Bio-based approach for synthesis norfenefrine														
A[17]	2-Me-THF		EtOAc		Ru		Cardanol: H301, H311, H331 Petroleum ether: H411		Catalyst		RT		Chrom.	
			Petroleum ether											
B[17]	THF		EtOAc		Ru		Petroleum ether: H411 Bromo(tri-tert-butyl-phosphine)palladium(I) dimer: H250		Catalyst		50 °C		Chrom.	
			Petroleum ether		Pd									
C[17]	Water		DCM Et_3N		Fe		DCM: H351, H 373 Methanol: H370		Catalyst		RT		Chrom.	
	AcCN		MTBE				Et_3N: H311, H331, H401							
			MeOH Water											

Rxn: Reaction; WU: Work-up; Quench.: quenching, Cryst.: Crystalization, Chrom.: Chromatography.

6. Calculated quantitative and qualitative metrics for the synthesis of hexane-1,6-diamine (HMDA)

Table S8: Calculated discrete and cumulative quantitative metrics for the synthesis of HMDA.

Step	Yield, %	AE, %	RME, %	PMI ($g \cdot g^{-1}$)			
				Tot	RRC	Rxn solv	WU
Literature-based approach for synthesis of HMDA							
1[18]	39.0	100	43.5	4.3	2.9	1.4	0
2[19]	60.8	100	60.3	2.3	2.0	0.3	0
3[20]	97.8	91.4	50.3	2.1	2.1	0	0
Overall (3 steps)	***23.1***	***91.4***	***24.2***	***7.2***	***5.3***	***1.9***	***0***
*Bio-based approach **1** for synthesis of HMDA from HMF*							
I[21]	96.0	100	40.2	49.7	2.6	47.1	0
II[21]	88.9	88.1	12.2	33.8	8.7	25.2	0
III[22]	82.9	85.9	55.7	28.1	1.8	26.2	0
Overall (3 steps)	***70.7***	***79.0***	***7.8***	***143.5***	***13.7***	***129.8***	***0***
*Bio-based approach **2** for synthesis of HMDA from HMF*							
A[23]	99.9	98.4	98.3	102.7	73.3	29.4	0
B[24]	94.9	88.1	9.1	503.8	13.8	100.4	389.6
C[25]	88.5	100	65.7	36.6	2.6	34.1	0
D[26]	94.0	87.9	66.5	39.3	1.9	37.4	0
Overall (4 steps)	***78.9***	***77.9***	***6.6***	***875.5***	***118.3***	***248.8***	***508.4***

AE: Atom Economy; RME: Reaction Mass Efficiency; PMI: Process Mass Intensity; Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn solv: Reaction solvents; WU: Work-up.

Table S9: Qualitative appraisal of solvent use, inherent hazards of used chemicals, catalyst or reagent use, energy and work-up methods for both approaches for the synthesis of HMDA.

Step	Solvent Rxn	Flag	Solvent WU	Flag	Crit. el	Flag	Health & Safety	Flag	Reagent use	Flag	Energy Use	Flag	Work-up	Flag
Literature-based approach for synthesis of HMDA														
1[18]	Benzene		-		Ni, P		1,3-Butadiene: H220, H340 HCN: H224, H330, H400, H410 Benzene: H361, H370, H372, H340, H350, H411		Catalyst		100 °C		Distill	
2[19]	-		-		Zn		HCN: H224, H330, H400, H410 $Zn(OAc)_2$: H411		Catalyst		115 °C		Filtr. Distill	
					Ni, P		3-Pentenenitrile H331							
3[20]	-		-		-		NH_3 gas: H331, H410		Catalyst		150 °C		Distill.	
							Hydrogen gas: H220 Adiponitrile: H301							
*Bio-based approach **1** for synthesis of HMDA from HMF*														
I[21]	EtOH		-		Ni		Raney Ni cat.: H351, H372, H412		Catalyst		100 °C		-	
							Hydrogen gas: H220							
II[21]	Water		-		Rh		Hydrogen gas: H220		Catalyst		80 °C		-	
					Re									
III[22]	Toluene		-		Ru		NH_3 gas: H331, H410		Catalyst		155 °C		Distill.	
					P		Toluene: H361d, H373, H412							
*Bio-based approach **2** for synthesis of HMDA from HMF*														
A[23]	Toluene		-		Mn		MnO_2 H373; Toluene H361d - H373 - H412		Catalyst		25 °C		Filtr	
B[24]	MeOH		Water		Co, Zr		MeOH H301, H311, H331, H370		Catalyst		100 °C		Centrifug., Distill., Recryst.	
			DCM				Hydrogen gas H220							
C[25]	MeOH		-		Ni		MeOH: H301, H311, H331, H370		Catalyst		60 °C		-	
							Hydrogen gas: H220							
D[26]	*o*-Xylene		-		Ni		Hydrogen gas: H220		Catalyst		140 °C		Centrifug.	

Rxn: Reaction; WU: Work-up; Distill.: Distillation; Recryst.: Recrystallization; Filtr.: Filtration; Evap.: Evaporation; Centifug.: Centrifugation.

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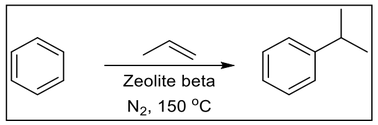
Classical approach: Step 1

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
benzene	352.00	78.11	4.51	Zeolite beta	0.40			N2			3.39						0.00
propylene	208.00	42.08	4.94								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	560.00	120.19			0.40		0.00				3.39		0.00				0.00



	Step	Cumulative
Yield	91.37	91.4
Conversion	100.0	/
Selectivity	91.37	/
AE	99.92	99.9
RME	88.30	88.30
PMI total	1.14	1.14
PMI Reaction	1.14	1.14
PMI reactants, reagents, catlyst	1.13	1.13
PMI reaction solvents	0.01	0.007
PMI Workup	0.00	0.000
PMI Workup chemical	0.00	0.000
PMI workup solvents	0.00	0.000

	Mass	MW	Mol
Product	494.49	120.09	4.12
	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	
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	

Experimental:
G. Spano, S. Ramello, G. Girotti, F. Rivetti, A. Carati *Polimeri Europa S.p.A., Italy; Enitecnologie S.p.A.* . **2006**, WO2006002805A1.

5 :Example nr. 5; 0.4 g of beta zeolite prepared according to what is described in example I, previously dried to 120°C for 16 hours, are charged into an electrically heated autoclave with an internal volume equal to 0.5 litres, equipped with a mechanical stirrer and with all the necessary devices forthe feeding of the benzene and propylene reagents.The autoclave is closed, put under vacuum by suction with a pump connected externally, and 352 g of benzene are .bul. then charged by suction. The autoclave is pressurized with nitrogen until a pressure of about 6 bar is reached and the heating is initiated to the programmed temperature of 150°C. When the temperature inside the autoclave has stably reached the pre-selected value, 26 g of propylene are rap-idly fed, by means of a pressure tank, and the mixture i s left to react for a time of exactly I hour, calculated starting from the end of the propylene feeding.At the end of the reaction, the product is discharged and analyzed by gas chromatography. The following products are present in the mixture at the end of the reaction: benzene, cumene, C_6 and C_9 ol'igomers of propylene, diisopropyl benzenes, other diisopropyl benzene isomers (C_6-phenyl = aromatic products generally indicated with the formula Ci_2Hi_8) / triisqpropyl benzenes, other triisopropyl benzene isomers (Cg-phenyl = aromatic products generally indicated with the formula Ci_5H_24) , polyalkylated products with a mo-lecular weight higher than triisopropyl benzene (heavy polyalkylated products).The propylene conversion proves to be higher than97.0percent, the selectivity to mono-alkylated product (cumene)with respect to the converted propylene is equal to 91.3percentand the selectivity to (cumene + diisopropyl benzenes + triisopropyl benzenes) with respect to the converted pro-pylene is equal to 97.5percent.The weight ratio, called R, between the sum of (diisopropyl benzenes + triisopropyl benzenes + C_6-phenyl + C_9-phenyl + heavy polyalkylated products) and the sum of (cumene + diisopropyl benzenes + triisopropyl benzenes + G_6-phenyl + C_9-phenyl + heavy polyalkylated products) proves to be equal to 0.052.This ratio R is a measurement of the total quantity ofthe polyalkylated by-products alone with respect to the to- tal products and alkylated by-products formed during thereaction.

With beta zeolite prepared from tetraethyl ammonium hydroxide, sodium aluminate, aluminum isopropylate and Ludox HS_{40}, Time= 1h, T= 150 °C , Product distribution / selectivity

Patent; **POLIMERI EUROPA S.P.A.**; **ENITECNOLOGIE S.P.A.**; WO2006/2805; (2006); (A1) English
View in Reaxys

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

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

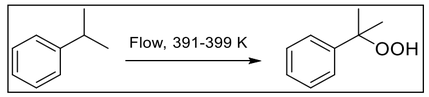
Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Propylene: H220	
Explosive thermal runaway	H230, H240,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

Classical approach: Step 2

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
cumene	2.68E+07	120.09	2.23E+05					N2 from air			1.57E+07						0.00
O2 from air	5.22E+06	31.99	1.63E+05								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	3.20E+07	152.08			0.00		0.00				1.57E+07		0.00				0.00



	Step	Cumulative
Yield	93.65	85.6
Conversion	100.0	/
Selectivity	93.65	/
AE	100.00	99.9
RME	99.31	89.33
PMI total	1.50	1.62
PMI Reaction	1.50	1.62
PMI reactants, reagents, catlyst	1.01	1.12
PMI reaction solvents	0.49	0.499
PMI Workup	0.00	0.000
PMI Workup chemical	0.00	0.000
PMI workup solvents	0.00	0.000
PMI workup solvents	0.00	0.000

	Mass	MW	Mol
Product	3.18E+07	152.08	2.09E+05
	mass		
Unreacted limiting reactant	0.00		

Experimental:

H. Bartkowiak, B. Haase, R. Hofmann, H. J. Naumann, B. Raue *VEB Leuna-Werke "Walter Ulbricht", Ger. Dem. Rep.* **1988**, DD258531A3.

Beispiel 1

Die Oxidation des Cumens zu Cumenhydroperoxid erfolgt in einem stehenden 62 m^3 großen Reaktor, der durch Siebbodenelemente in vier Reaktionsabschnitte geteilt ist, deren Reaktionsvolumen von oben nach unten 21, 21, 13 und 7 m^3 beinhalten. Dem Reaktor werden stündlich 26770 kg Cumen mit einer Temperatur von 388 K, das 1,8 Ma.-% Cumenhydroperoxid enthält, zugeführt. Unten werden 4330 kg/h Luft mit einer Temperatur von 298 K in den Reaktor eingeleitet. Oben verlassen den Reaktor 7100 kg/h Abgas, bestehend aus Stickstoff, Sauerstoff, Cumen und Cumenhydroperoxid mit einer Temperatur von 398 K. Mittels eines Kühlkreislaufes werden die Temperaturen in den einzelnen Reaktionsstufen zwischen 399 K oben und 391 K unten gehalten. Den Reaktor verlassen 24000 kg/h Oxidat mit einer Temperatur von 386 K und einem Gehalt an Cumenhydroperoxid von 19,4 Ma.-%. Das im Abgas enthaltene Cumen und Cumenhydroperoxid wird mittels Kühlwasser auskondensiert. Gleichfalls mittels Kühlwasser wird dem Kühlkreislauf die im Reaktor aufgenommene Wärme entzogen. Die Erwärmung des Cumens auf die Eintrittstemperatur von 388 K erfolgt zunächst in einem Wärmeaustauschapparat mittels des den Reaktor verlassenden Oxidats, wobei sich das Cumen von 303 K auf 349 K erwärmt und dann in einem weiteren Wärmeaustauscher mittels Heizdampf. Das Oxidat wird dabei innerhalb von 15 Minuten auf eine Temperatur von 346 K abgekühlt und gelangt danach in eine unterteilte, bei Drücken von 4 kPa und 1 kPa arbeitende Verdampferstufe, in der das Oxidat auf 89 Ma.-% Cumenhydroperoxid aufkonzentriert wird. Die Ausbeute an nutzbarem Cumenhydroperoxid beträgt bezüglich Cumen 93,7 Ma.-%. Der Verbrauch an Heizdampf zur Erzeugung des 89%igen Cumenhydroperoxids beträgt 4970 kg/h.

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	
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	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	X
Batch	Amber Flag	

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

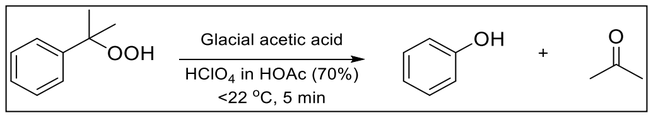
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, 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		Cumene (H411)		

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	

Classical approach: Step 3

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Cumene hydroperoxide	15.20	152.08	9.99E-02	HClO4	0.74			HOAc	100.00	1.05	105.00						0.00
								HOAc	0.10	1.05	0.11						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	15.20	152.08			0.74		0.00				105.11		0.00				0.00



	Step	Cumulative
Yield	95.65	81.8
Conversion	100.0	/
Selectivity	95.65	/
AE	61.88	61.8
RME	59.21	52.89
PMI total	13.45	14.49
PMI Reaction	13.45	14.49
PMI reactants, reagents, catlyst	1.77	1.97
PMI reaction solvents	11.68	12.522
PMI Workup	0.00	0.000
PMI Workup chemical	0.00	0.000
PMI workup solvents	0.00	0.000

	Mass	MW	Mol
Product	9.00	94.11	0.10
	mass		
Unreacted limiting reactant	0.00		

Experimental:
M. S. Kharasch, A. Fono, W. Nudenberg *J. Org. Chem.* **1950**, *15*, 748.

Decomposition of α-cumyl hydroperoxide in the presence of acetic acid and catalytic quantities of perchloric acid. α-Cumyl hydroperoxide (15.2 g., 0.1 mole), dissolved in 100 cc. of glacial acetic acid was treated with 0.1 cc. of a 5% solution of 70% perchloric acid in acetic acid. The temperature of the reaction mixture was kept below 22°. The peroxide titre of the mixture fell to zero after 5 minutes. *Phenol* (9 g., 95% yield) was isolated in crystalline form. *Acetone* was identified and estimated by means of its dinitrophenylhydrazone. An unidentified neutral oil (amounting to less than 3% of the starting material) was also obtained.

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	HOAc
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	

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}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

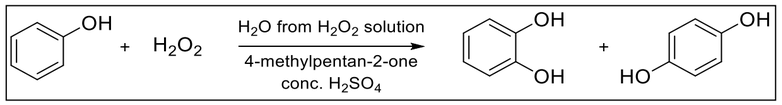
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				HClO4, HOAc
Toxic	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	

Classical approach: Step 4

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Phenol	90.00	94.11	0.96	H2SO4	0.10			H2O (H2O2)	22.32	1.00	22.32	NaOH	0.08	H2O (NaOH)	0.08	1.00	0.08
H2O2	33.48	34.01	0.98	MIBK	4.60			H2O (H2SO4)	0.00	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	123.48	128.12			4.70		0.00				22.32		0.08				0.08



	Step	Cumulative
Yield	53.95	44.2
Conversion	100.0	/
Selectivity	53.95	/
AE	85.94	59.1
RME	46.00	27.89
PMI total	2.65	24.03
PMI Reaction	2.65	24.03
PMI reactants, reagents, catlyst	2.26	3.80
PMI reaction solvents	0.39	20.234
PMI Workup	0.00	0.003
PMI Workup chemical	0.00	0.001
PMI workup solvents	0.00	0.001

	Mass	MW	Mol
Product	56.80	110.10	0.52
	mass		
Unreacted limiting reactant	0.00		

Experimental:
S. Umemura, N. Takamitsu, T. Hamamoto, N. Kuroda *Ube Industries Ltd* **1978**, US4078006A.

EXAMPLE 37

In the same reaction vessel as in Example 34, 1852 g. of phenol (19.68), 4.6 g. of 4-methyl-2-pentanone (0.046), 55.8 g. of 60 percent hydrogen peroxide (0.985 mole), and 0.10 g. of concentrated sulfuric acid were placed. The mixture was stirred at 50° C. in an oil bath for 10 minutes. After neutralization of sulfuric acid by adding 0.16 g. of 50 percent aqueous sodium hydroxide, the mixture was subjected to distillation under reduced perssure to fraction water, 3.7 g. of 4-methyl-2-pentanone, 1762 g. of phenol (18.72 moles), 56.8 g. of catechol (0.516 mole) and 38.5 g. of hydroquinone (0.350 mole). The total yield of the dihydric phenols based on hydrogen peroxide was 88.0 percent, and that based on phenol was 90.2 percent.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O
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	

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

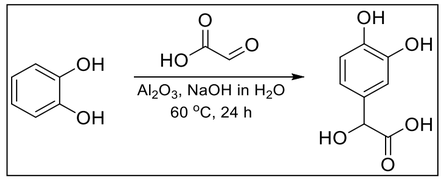
Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			H2O2, H2O, MIBK, KHSO4
Explosive thermal runaway	H230, 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	

Classical approach: Step 5

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Catechol	5.00	110.10	45.41	Al2O3	2.04	NaOH	3.21	H2O (NaOH)	55.00	1.00	55.00	NaOH	0.80	H2O (NaOH)	20.00	1.00	20.00
glyoxylic acid	3.55	74.04	47.95					H2O (glyoxylic acid)	3.55	1.00	3.55	HCl	3.50	H2O (HCl)	8.00	1.00	8.00
											0.00			EtOAc	90.00	0.90	81.18
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	8.55	184.14			2.04		3.21				58.55		4.30				109.18



	Step	Cumulative
Yield	61.83	27.3
Conversion	76.0	/
Selectivity	81.36	/
AE	100.00	70.8
RME	59.65	23.75
PMI total	36.44	59.02
PMI Reaction	14.19	36.77
PMI reactants, reagents, catlyst	2.71	5.45
PMI reaction solvents	11.48	31.318
PMI Workup	22.25	22.254
PMI Workup chemical	0.84	0.845
PMI workup solvents	21.41	21.409

	Mass	MW	Mol
Product	5.10	184.14	28.08
	mass		
Unreacted limiting reactant	1.20		

Experimental: *Org. Process Res. Dev.* **2000**, *4*, 534–543.

Catechol (5.00 g, 45.41 mmol) was dissolved in aqueous NaOH (3.21 g, 80.3 mmol in 55.0 mL of water) followed by addition of Al2O3 (2.04 g, 20 mmol). After 5 min glyoxylic acid (7.10 g of 50% aqueous solution, 48.0 mmol) was added to the reaction mixture, and the mixture was heated at 60 °C for 24 h under vigorous stirring. The reaction mixture was then allowed to precipitate for 10 min. and filtered to remove Al2O3. The obtained filter cake was washed with 1 M NaOH (20 mL). The basic washing water was combined with the water solution, and this was acidified to pH 3-4 with 6.0 mL of 37% HCl and extracted with ethyl acetate to recover the unreacted catechol (1.2 g). The aqueous solution was further acidified to pH 1 by 2 mL of concentrated HCl and extracted with ethyl acetate to isolate the mandelic acid derivative (5.1 g, 28.08 mmol).

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc, H2O
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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}C at atmospheric	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	X
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

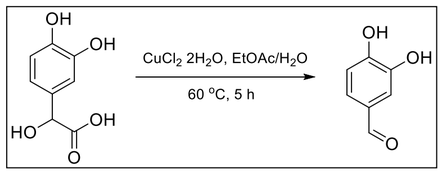
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241			Catechol H301, H311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

Classical approach: Step 6

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3,4-Dihydroxy mandelic acid	2.00	184.14	10.86	CuCl2 2H2O	11.11			EtOAc	140.00	0.90	126.28						0.00
								H2O	30.00	1.00	30.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	2.00	184.14			11.11		0.00				156.28		0.00				0.00



	Step	Cumulative
Yield	96.03	26.2
Conversion	100.0	/
Selectivity	96.03	/
AE	75.01	53.1
RME	72.00	17.10
PMI total	117.63	198.22
PMI Reaction	117.63	167.31
PMI reactants, reagents, catlyst	9.10	15.29
PMI reaction solvents	108.53	152.025
PMI Workup	0.00	30.908
PMI Workup chemical	0.00	1.173
PMI workup solvents	0.00	29.735

	Mass	MW	Mol
Product	1.44	138.12	10.43
	mass		
Unreacted limiting reactant			

Experimental: *Org. Process Res. Dev.* **2000**, *4*, 534–543.

3,4-Dihydroxy mandelic acid (2 g, 10.86 mmol) was dissolved in 140 mL of ethyl acetate, and 11.11 g of CuCl2 2H2O was dissolved in 30 mL of water. The two-phase system was vigorously stirred and heated at 60 °C for 5 h under nitrogen atmosphere. The organic phase was separated, and the solvent was removed. The HPLC analysis revealed a complete conversion of the mandelic acid derivative and the yield of protocatechualdehyde of 96%. The copper salt aqueous solution/suspension was recycled by oxidising Cu(I) to Cu(II) by air after the removal of the organic phase; the results were substantially unchanged.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O, EtOAc
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	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

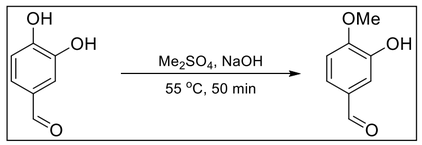
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, 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		CuCl2 2H2O H400, H410		

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	

Classical approach: Step 7

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Protocatechualdehyde	3.00	138.12	0.02			NaOH	0.88	DCM	3.30	1.33	4.39	Na2SO4	21.40	DCM	50.00	1.33	66.50
(Me)2SO4	2.70	126.13	0.02					H2O	5.00	1.00	5.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	5.70	264.25			0.00		0.88				9.39		21.40				66.50



	Step	Cumulative
Yield	65.06	17.1
Conversion	71.2	/
Selectivity	91.37	/
AE	57.58	39.4
RME	37.71	10.62
PMI total	48.35	323.54
PMI Reaction	7.43	239.49
PMI reactants, reagents, catlyst	3.06	23.00
PMI reaction solvents	4.37	216.501
PMI Workup	40.92	84.050
PMI Workup chemical	9.96	11.599
PMI workup solvents	30.96	72.450

	Mass	MW	Mol
Product	2.15	152.15	0.01
	mass		
Unreacted limiting reactant	0.86		

Experimental: *Org. Process Res. Dev.* **2000**, *4*, 534–543.

The reaction was carried out as in (A) at 55 °C by using 21.7 mmol of protocatechualdehyde and 4.5 mmol of NaOH and by simultaneously adding dropwise 21.4 mmol of dimethyl sulphate and 17.5 mmol of NaOH. The conversion was 70.8%, and the selectivity 93.2% in *iso*-vanillin, 4.0% of vanillin, and 2.8% of veratraldehyde.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O
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	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

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

Health & safety

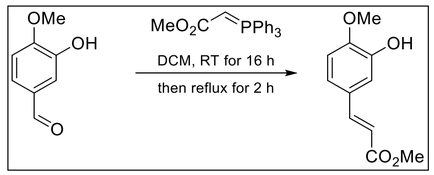
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,		Me2SO4 H330, H350	Me2SO4 H301, H341	
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	

Classical approach: Step 8

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Isovanillin	10.00	152.15	65.70					DCM	220.00	1.33	292.60	SiO2	525.60	Hexane	4161.00	0.66	2725.46
carbmethoxy methylene triphenyl phosphorane	24.20	334.35	72.30								0.00			EtOAc	2409.00	0.90	2172.92
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	34.20	486.50			0.00		0.00				292.60		525.60				4898.37



	Step	Cumulative
Yield	96.65	16.5
Conversion	100.0	/
Selectivity	96.65	/
AE	42.80	28.9
RME	38.60	11.15
PMI total	435.66	680.01
PMI Reaction	24.76	205.43
PMI reactants, reagents, catlyst	2.59	19.25
PMI reaction solvents	22.17	186.183
PMI Workup	410.91	474.581
PMI Workup chemical	39.82	48.606
PMI workup solvents	371.09	425.975

	Mass	MW	Mol
Product	13.20	208.21	63.50
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

Isovanillin (**6**; 10.0 g, 65.7 mmol, 1.0 equiv.) and carbmethoxy methylene triphenyl phosphorane (24.2 g, 72.3 mmol, 1.1 equiv.) were dissolved in DCM (220 mL) and stirred at room temperature for 16 h. The mixture was then heated to reflux for 2 h. After cooling, the solvent was removed *in vacuo* and the crude product was purified by flash silica gel column chromatography (hexanes/EtOAc, 2:1 → 3:2) to yield olefin **10** (13.2 g, 63.5 mmol, 97%) as a colorless solid.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc
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	DCM, 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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

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

Health & safety

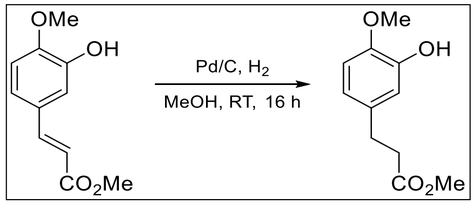
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, 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	

Classical approach: Step 9

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
methyl (E)-3-(3-hydroxy-4-methoxyphenyl)acrylate	13.20	208.21	0.06	Pd on charcoal	2.60			MeOH	150.00	0.79	118.80	Celite	126.80	DCM	317.00	1.33	421.61
hydrogen	4.32	2.02	20.73								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	17.52	210.23			2.60		0.00				118.80		126.80				421.61



	Step	Cumulative
Yield	99.84	16.5
Conversion	100.0	/
Selectivity	99.84	/
AE	99.04	28.8
RME	75.93	10.84
PMI total	51.68	725.59
PMI Reaction	10.44	213.34
PMI reactants, reagents, catlyst	1.51	19.63
PMI reaction solvents	8.93	193.715
PMI Workup	41.23	512.247
PMI Workup chemical	9.53	57.774
PMI workup solvents	31.70	454.473

	Mass	MW	Mol
Product	13.30	208.21	0.06
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

Olefin **10** (13.2 g, 63.4 mmol) was dissolved in MeOH (150 mL) and palladium on charcoal (2.60 g; 10%) was added. The reaction flask was evacuated and repurged with hydrogen (5x) and then stirred at room temperature under a hydrogen atmosphere for 16 h, filtered through Celite and washed thoroughly with DCM. The solvent was removed under reduced pressure, yielding compound **11** quantitatively (13.3 g, 63.3 mmol, 100%) as a colorless solid.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	MeOH
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	DCM
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	

		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^{o}C	Green Flag	X
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

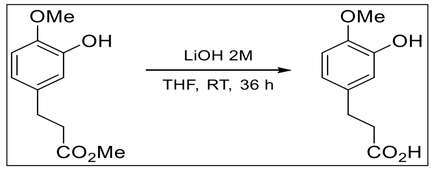
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, 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	

Classical approach: Step 10

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate	13.20	210.23	0.06			LiOH	1.68	THF	100.00	0.89	88.80	HCl	4.58	H2O (HCl)	62.80	1.00	62.80
								H2O (LiOH)	55.00	1.00	55.00	NaCl	26.93	EtOAc	150.00	0.90	135.30
											0.00	MgSO4	62.80	H2O(NaCl)	75.00	1.00	75.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	13.20	210.23			0.00		1.68				143.80		94.31				273.10



	Step	Cumulative
Yield	98.25	16.2
Conversion	100.0	/
Selectivity	98.25	/
AE	93.33	26.9
RME	91.67	9.94
PMI total	43.48	833.94
PMI Reaction	13.11	244.76
PMI reactants, reagents, catlyst	1.23	21.55
PMI reaction solvents	11.88	223.210
PMI Workup	30.36	589.179
PMI Workup chemical	7.79	70.820
PMI workup solvents	22.57	518.359

	Mass	MW	Mol
Product	12.10	196.20	0.06
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

Methyl ester **11** (13.2 g, 62.8 mmol) was dissolved in THF (100 mL) and a 2M solution of LiOH (35 mL) was added. The mixture was stirred for 16 h at room temperature. Since TLC indicated remaining starting material, another 20 mL of 2M LiOH was added and stirred for another 20 h. The mixture was acidified to pH 2-3 with 2M HCl and extracted with EtOAc (3x 50 mL). The combined organic phases were washed with brine (75 mL), dried over MgSO4, and concentrated under reduced pressure to yield free acid **12** (12.1 g, 61.7 mmol, 98%) as a colorless solid.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

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

Health & safety

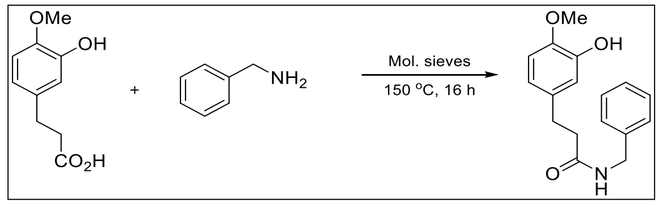
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate H351	
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	

Classical approach: Step 11

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3-(3-hydroxy-4-methoxyphenyl)propanoic acid	12.10	196.20	0.06			Mol sieves	10.00				0.00	HCl	16.41	DCM	300.00	1.33	399.00
benzyl amine	39.65	107.15	0.37								0.00	NaHCO3	28.80	H2O(HCl)	450.00	1.00	450.00
											0.00	NaCl	35.90	H2O(NaHCO3)	300.00	1.00	300.00
											0.00	MgSO4	61.70	H2O	100.00	1.00	100.00
											0.00	SiO2	493.60	H2O (NaCl)	100.00	1.00	100.00
											0.00			DCM	5954.05	1.33	7918.89
											0.00			MeOH	215.95	0.79	171.03
Total	51.75	303.35			0.00		10.00				0.00		636.41				9438.92



	Step	Cumulative
Yield	54.78	8.9
Conversion	100.0	/
Selectivity	54.78	/
AE	94.06	34.1
RME	18.65	5.98
PMI total	1050.47	2094.88
PMI Reaction	6.40	312.04
PMI reactants, reagents, catlyst	6.40	32.17
PMI reaction solvents	0.00	279.880
PMI Workup	1044.08	1782.838
PMI Workup chemical	65.95	154.749
PMI workup solvents	978.13	1628.089

	Mass	MW	Mol
Product	9.65	285.34	0.03
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

Carboxylic acid **12** (12.1 g, 61.7 mmol, 1.0 equiv.) was heated together with benzyl amine (40.0 mL, 370 mmol, 6.0 equiv.) and 3Å molecular sieves (10.0 g) to 150 °C for 16 h. The mixture was cooled, diluted with DCM (300 mL), washed with 1M HCl (3x 150 mL), a saturated solution of NaHCO3 (2x 150 mL), water (100 mL) and brine (100 mL). The organic phase was dried over MgSO4 and the solvent removed *in vacuo*. The crude product was purified by flash silica gel column chromatography (DCM/MeOH, 98:2 → 95:5) to give benzyl amide **13** (9.65 g, 33.8 mmol, 55%) as a colorless solid.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O, MeOH
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	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

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

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	
+500 years	Green Flag	C, N

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

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

Health & safety

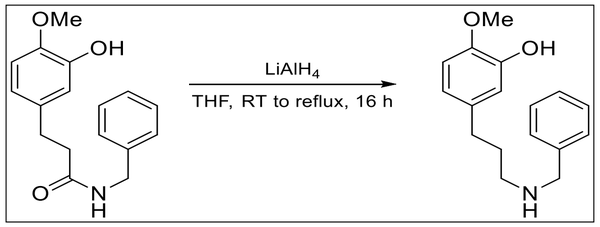
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241			benzyl amine H301,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

Classical approach: Step 12

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
N-benzyl-3-(3-hydroxy-4-methoxyphenyl)propanamide	9.65	285.34	0.03					THF	300.00	0.89	266.40	Rochelle's salt	330.00	H2O (Rochelle's salt)	500.00	1.00	500.00
LiAlH4	2.57	37.95	0.07								0.00	MgSO4	33.80	EtOAc	400.00	0.90	360.80
											0.00	SiO2	270.40	H2O	200.00	1.00	200.00
											0.00	NaCl	71.80	H2O (NaCl)	200.00	1.00	200.00
											0.00			DCM	3145.90	1.33	4184.05
											0.00			MeOH	234.10	0.79	185.41
											0.00						0.00
Total	12.22	323.29			0.00		0.00				266.40		706.00				5630.25



	Step	Cumulative
Yield	92.90	8.2
Conversion	100.0	/
Selectivity	92.90	/
AE	83.94	31.0
RME	69.72	5.20
PMI total	776.39	3147.99
PMI Reaction	32.70	385.00
PMI reactants, reagents, catlyst	1.43	36.74
PMI reaction solvents	31.27	348.268
PMI Workup	743.69	2762.986
PMI Workup chemical	82.86	258.137
PMI workup solvents	660.83	2504.849

	Mass	MW	Mol
Product	8.52	271.36	0.03
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

To a solution of amide **13** (9.65 g, 33.8 mmol, 1.0 equiv.) in THF (200 mL) was added slowly a suspension of LiAlH4 (2.57 g, 67.6 mmol, 2.0 equiv.) in THF (100 mL) at room temperature (gas evolution!). The reaction mixture was heated to reflux for 16 h. A sat. aqu. solution of Rochelle's salt (500 mL) was added and the mixture stirred vigorously for 1 h. The phases were separated and the aqueous layer was extracted with EtOAc (2x 200 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography (DCM/MeOH, 20:1, gradually increased to 10:1) to give secondary amine **14** (8.52 g, 31.4 mmol, 93%) as a colorless solid..

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc, H2O, MeOH
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	X

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

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	Li, Al
+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	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

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

Health & safety

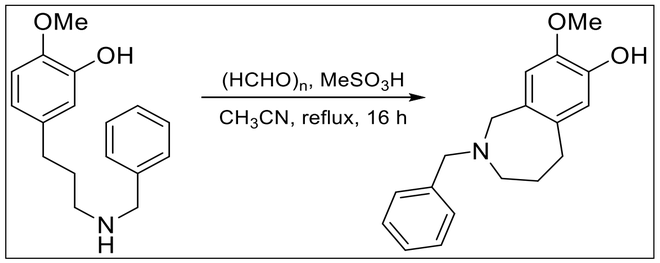
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310, H330	H301, H311, H331,			LiAlH4 H301, H331	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		LiAlH4 H310, H330, H340		
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	

Classical approach: Step 13

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
Amine	5.50	271.36	0.02			MeSO3H	2.14	CH3CN	180.00	0.79	141.48	NaHCO3	19.20	H2O (NaHCO3)	200.00	1.00	200.00
paraformaldehyde	0.67	30.03	0.07								0.00	NaCl	53.85	DCM	250.00	1.33	332.50
											0.00	MgSO4	20.30	H2O	150.00	1.00	150.00
											0.00	SiO2	162.40	H2O (NaCl)	150.00	1.00	150.00
											0.00			DCM	1845.00	1.33	2453.85
											0.00			MeOH	185.00	0.79	146.52
											0.00						0.00
Total	6.17	301.39			0.00		2.14				141.48		255.75				3432.87



	Step	Cumulative
Yield	95.07	7.8
Conversion	100.0	/
Selectivity	95.07	/
AE	94.02	31.3
RME	88.65	5.13
PMI total	701.72	3865.97
PMI Reaction	27.38	413.49
PMI reactants, reagents, catlyst	1.52	37.45
PMI reaction solvents	25.86	376.042
PMI Workup	674.34	3452.476
PMI Workup chemical	46.76	306.308
PMI workup solvents	627.58	3146.168

	Mass	MW	Mol
Product	5.47	283.37	0.02
	mass		
Unreacted limiting reactant			

Experimental: *Angew. Chem. Int. Ed.* **2013**, *52*, 9845 –9848.

Amine **14** (5.50 g, 20.3 mmol, 1.0 equiv.) and paraformaldehyde (0.67 g, 22.3 mmol, 1.1 equiv.) were dissolved in acetonitrile (180 mL) and MeSO3H (1.45 mL, 22.3 mL, 1.1 equiv.) was added. The mixture was heated to reflux for 16 h. A saturated solution of NaHCO3 (200 mL) was added and the phases were separated. The aqueous phase was extracted with DCM (5 x 50 mL) and the combined organic layers were washed with water (150 mL) and brine (150 mL), dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography (DCM/MeOH, 10:1) to give benzazepine **15** (5.47 g, 19.3 mmol, 95%) as a pale yellow solid.

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O, MeOH
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	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

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

Health & safety

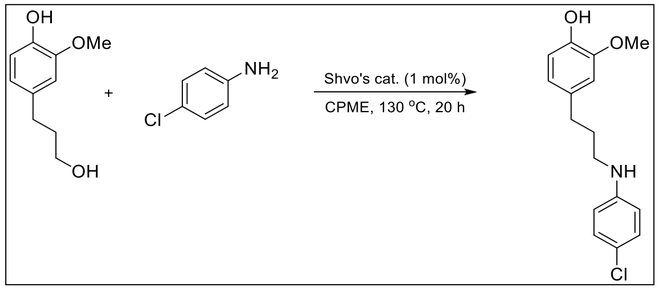
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310,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

Sustainable approach: Step 1

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
p-chloroaniline	0.05	127.57	4.00E-04	Shvo's catalyst	4.34E-03			CPME	2.00	0.86	1.72	SiO2 plug	0.80	EtOAc	10.00	0.90	9.02
Dihydroconiferyl alcohol	0.09	182.22	4.80E-04								0.00	SiO2 (column)	3.20	pentane	28.00	0.63	17.53
											0.00			EtOAc	12.00	0.90	10.82
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.14	309.79			0.00		0.00				1.72		4.00				37.37



	Step	Cumulative
Yield	97.00	97.00
Conversion	100.0	/
Selectivity	97.00	/
AE	94.18	94.18
RME	81.76	81.76
PMI total	381.90	381.90
PMI Reaction	16.45	16.45
PMI reactants, reagents, catlyst	1.26	1.26
PMI reaction solvents	15.19	15.19
PMI Workup	365.44	365.44
PMI Workup chemical	35.33	35.33
PMI workup solvents	330.11	330.11

	Mass	MW	Mol
Product	0.11	291.78	3.88E-04
	mass		
Unreacted limiting reactant			

Experimental: ACS Cent. Sci. 2019, 5, 1707−1716.

An oven-dried 20 mL Schlenk tube, equipped with a stirring bar, was charged with p-chloroaniline (0.4 mmol, 1 equiv.), **1G** (0.48 mmol, 1.2 equiv.), Shvo's catalyst (**C1**, 0.004 mmol, 1 mol%) and cyclopentyl methyl ether (CPME, 2 mL). The solid materials were weighed into the Schlenk tube under air and the Schlenk tube was subsequently connected to an argon line and vacuum-argon exchange was performed three times. Liquid starting materials and the solvent were charged under an argon stream. The Schlenk tube was capped and the mixture was rapidly stirred at room temperature for 1 min, then it was placed into a pre-heated oil bath at 130 °C and stirred for 20 h. The reaction mixture was cooled down to room temperature and the crude mixture was filtered through silica gel, eluted with ethyl acetate (10 mL), and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (70:30 = pentane : EtOAc) to provide the pure amine product (113 mg, 97% yield).

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc
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	CPME
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	pentane
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	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

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

Health & safety

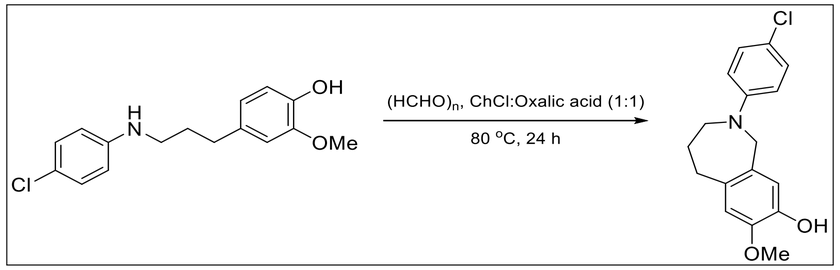
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241			dihydroconiferyl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

Sustainable approach: Step 2

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
aminoalkylphenol	0.10	291.78	3.43E-04			ChCl:Oxalic acid	1.00				0.00	NaHCO3	0.19	H2O	2.00	1.00	2.00
paraformaldehyde	0.01	30.03	3.43E-04								0.00	SiO2	2.74	H2O (NaHCO3)	2.00	1.00	2.00
											0.00			EtOAc	30.00	0.90	27.06
											0.00			EtOAc (column)	13.72	0.90	12.38
											0.00			pentane (column)	20.58	0.63	12.88
											0.00						0.00
											0.00						0.00
Total	0.11	321.81			0.00		1.00				0.00		2.94				56.32



	Step	Cumulative
Yield	87.00	84.4
Conversion	100.0	/
Selectivity	87.00	/
AE	94.40	89.4
RME	82.44	68.57
PMI total	663.35	1082.25
PMI Reaction	12.20	29.20
PMI reactants, reagents, catlyst	12.20	12.49
PMI reaction solvents	0.00	16.709
PMI Workup	651.15	1053.053
PMI Workup chemical	32.26	71.121
PMI workup solvents	618.88	981.932

	Mass	MW	Mol
Product	0.09	303.79	2.98E-04
	mass		
Unreacted limiting reactant			

Experimental: ACS Cent. Sci. 2019, 5, 1707−1716.

An oven-dried vial equipped with a stirring bar, was charged with aminoalkylphenol (0.343 mmol), paraformaldehyde (0.343 mmol) and ChCl/Oxalic acid (1:1 molar ratio, 1g) under air. Then the vial was capped and the mixture was rapidly stirred at room temperature for 1 min, then it was heated to 70 °C and stirred for 20 h. The reaction mixture was cooled down to room temperature, water (2 mL) and saturated solution of NaHCO3 (2 mL) was added and then the reaction mixture was stirred for one hour at room temperature. The crude mixture was extracted with ethyl acetate (3 × 10 mL) and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (pentane : ethyl acetate = 60:40) affording the target product (91 mg, 87% yield).

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	H2O, EtOAc
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	pentane
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	
Use of stoichiometric quantities of reagents	Amber Flag	X
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

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

Health & safety

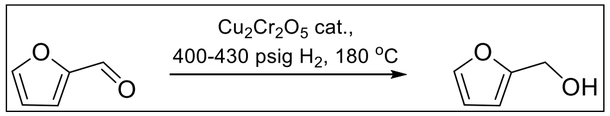
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	H300, H310,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

Classical pathway: Step 1

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
furfural	200.00	96.08	2.08	Cu2Cr2O5 cat.	1.50						0.00						0.00
hydrogen gas	8.48	2.01	4.22								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	208.48	98.09			1.50		0.00				0.00		0.00				0.00



	Step	Cumulative
Yield	97.1	97.1
Conversion	98.3	/
Selectivity	98.8	/
AE	100.0	100.0
RME	95.1	95.1
PMI total	1.1	1.1
PMI Reaction	1.1	1.1
PMI reactants, reagents, catlyst	1.1	1.1
PMI reaction solvents	0.0	0.0
PMI Workup	0.0	0.0
PMI Workup chemical	0.0	0.0
PMI workup solvents	0.0	0.0

	Mass	MW	Mol
Product	198.20	98.10	2.02
	mass		
Unreacted limiting reactant	3.45		

Experimental: Leo J. Frainier, Herman H. Fineberg, United States Pat. US4251396A, 1981

Furfuryl alcohol was prepared from furfural using the copper chromite catalyst of this invention. The copper chromite catalyst used was prepared as described in Examples 1 and 2. The furfuryl alcohol was prepared in a 300 milliliter AE autoclave. The autoclave was thoroughly cleaned and dried. It was then charged with 200 grams of furfural, 1.5 grams of a copper chromite catalyst prepared as described in Examples 1 and 2, and 1 gram of calcium oxide. The furfural (freshly distilled) was obtained from Profursa, a Spanish concern. Fisher technical calcium oxide was used. The autoclave was pressurized to 400 to 430 psig with hydrogen. The temperature was raised and maintained at 180° C. After five and a third hours, 98.3% of the furfural was converted. The selectivity of the converted furfural to furfuryl alcohol was 98.8%.

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	
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	

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

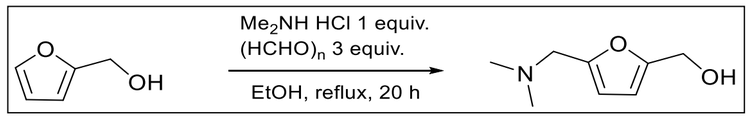
Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	furfural H226 - H301 - H312 - H315 - H319 - H330 - H335 - H351 - H412	Hydrogen gas H220 - H280	
Explosive thermal runaway	H230, H240, H250	H241		Copper chromite H272 - H335 - H410		
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	

Classical pathway: Step 2

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
furfuryl alcohol	153.00	98.10	1.56					ethanol	600.00	0.79	474.00	Na2CO3	86.00	water	500.00	1.00	500.00
dimethylamine hydrochloride	128.00	81.54	1.57								0.00	MgSO4	1560.00	diethyl-ether	1500.00	0.71	1065.00
paraformaldehyde	140.00	30.03	4.66								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	421.00	209.67			0.00		0.00				474.00		1646.00				1565.00



	Step	Cumulative
Yield	43.4	42.1
Conversion	100.0	/
Selectivity	43.4	/
AE	74.0	74.0
RME	24.9	24.48
PMI total	39.1	39.19
PMI Reaction	8.5	8.61
PMI reactants, reagents, catlyst	4.0	4.10
PMI reaction solvents	4.5	4.514
PMI Workup	30.6	30.581
PMI Workup chemical	15.7	15.676
PMI workup solvents	14.9	14.905

	Mass	MW	Mol
Product	105.00	155.19	0.68
	mass		
Unreacted limiting reactant	0.00		

Experimental: S. Hirai, H. Hirano, H. Arai, Y. Kiba, H. Shibata, Y. Kusayanagi, M. Yotsuji, K. Hashiba and K. Tanada, *US Patent* 4643849, 1987

With 600 ml of ethanol were mixed 153 g of furfuryl alcohol, 128 g of dimethylamine hydrochloride and 70 g of paraformaldehyde, and the resulting mixture was subjected to reaction under reflux for 2 hours. Thereafter, 70 g of paraformaldehyde was further added, and the mixture thus obtained was subjected to reaction under reflux for 18 hours. After completion of the reaction, the solvent was removed by distillation under reduced pressure, and 500 ml of water and 86 g of anhydrous sodium carbonate were added to the resulting residue. The oily substance separated was extracted with three 500-ml portions of diethyl ether, and the extracts were combined and then dried over anhydrous magnesium sulfate, after which the solvent was removed by distillation under reduced pressure. The oily substance thus obtained was distilled under reduced pressure to obtain 105 g (yield 43.4%) of 5-(dimethylamino)methyl-2-furfuryl alcohol having a boiling point of 128.degree.-133.degree. C./15 mmHg.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	ethanol, 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	diethyl-ether

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

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	X
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

Health & safety

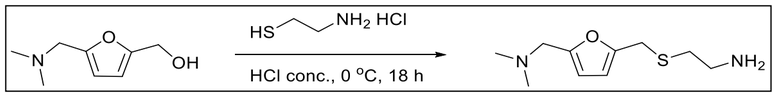
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	paraformaldehyde H228 - H302 + H332 - H315 - H317 - H318 - H335 - H341 - H350	furfuryl alcohol H302 + H312 - H319 - H331 - H335 - H351 - H373	dimethylamine hydrochloride H302 - H315 - H319
Explosive thermal runaway	H230, H240, H250	H241				ethanol H225 - H319
Toxic	H300, H310, H330	H301, H311, H331,				diethyl-ether H224, H302, H336
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	

Classical pathway: Step 3

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-(dimethylamino)methyl-2-furfuryl alcohol	15.50	155.19	0.0999					HCl	40.00	1.49	59.60	Na2CO3	16.00	diethyl-ether	500.00	0.71	355.00
cysteamine hydrochloride	11.36	113.61	0.1000								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	26.86	268.80			0.00		0.00				59.60		16.00				355.00



	Step	Cumulative
Yield	54.2	22.8
Conversion	100.0	/
Selectivity	54.2	/
AE	79.7	66.3
RME	43.2	15.53
PMI total	39.4	90.47
PMI Reaction	7.5	17.62
PMI reactants, reagents, catlyst	2.3	6.45
PMI reaction solvents	5.1	11.170
PMI Workup	32.0	72.845
PMI Workup chemical	1.4	22.326
PMI workup solvents	30.6	50.519

	Mass	MW	Mol
Product	11.60	214.32	0.05
	mass		
Unreacted limiting reactant	0.00		

Experimental:

B. J. Price, J. W. Clitherow and J. Bradshaw, US Patent 4128658, 1978

2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]thio]e-thanamine

5-(Dimethylamino)methyl-2-furanmethanol (15.5 g) was added dropwise to a stirred, ice-cold solution of cysteamine hydrochloride (11.36 g) in concentrated hydrochloric acid (40 ml). After standing at 0° for 18 hr, excess anhydrous sodium carbonate was added and the resultant solid extracted with diethyl ether. Removal of solvent followed by distillation of the residue gave 2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]e-thanamine (11.6 g) b.p. 104–106° (0.1 mm). Picrate salt m.p. 142–144°.

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-	
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	Et2O

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

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

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	x
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	x

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	x

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

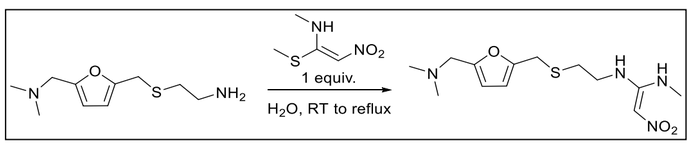
Health & safety	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			cysteamine hydrochloride H302, H317, H319, H335
Explosive thermal runaway	H230, H240, H250	H241				hydrochloric acid H290 - H314 - H335
Toxic	H300, H310, H330	H301, H311, H331,				Diethyl ether H224 - H302 - H336
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	

Classical pathway: Step 4

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
2-{[5-(dimethylamino)methyl-2-furyl]-methylthio}ethylamine	321.00	214.32	1.50					water	400.00	1.00	400.00	charcoal	10.00	4-Methyl-2-pentanone	2000.00	0.80	1600.00
N-Methyl-1-(methylthio)-2-nitroethenamine	230.00	148.18	1.55								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	551.00	362.50			0.00		0.00				400.00		10.00				1600.00



	Step	Cumulative
Yield	80.7	18.4
Conversion	100.0	/
Selectivity	80.7	/
AE	86.7	66.7
RME	69.0	16.55
PMI total	6.7	82.32
PMI Reaction	2.5	16.54
PMI reactants, reagents, catlyst	1.5	6.06
PMI reaction solvents	1.1	10.488
PMI Workup	4.2	65.772
PMI Workup chemical	0.0	18.886
PMI workup solvents	4.2	46.886

	Mass	MW	Mol
Product	380.00	314.40	1.21
	mass		
Unreacted limiting reactant	0.00		

Experimental:

B. J. Price, J. W. Clitherow and J. Bradshaw, US Patent 4128658, 1978.

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine

N-Methyl-1-(methylthio)-2-nitroetheneamine (230 g) in water (400 ml) was stirred and heated at 45°–50°. 2-[[[5-(Dimethylamino) methyl-2-furanyl[methyl]thio]ethanamine (321 g),was added dropwise over 4 hr and the resultant solution stirred for a further 3½ hr. The solution was then heated at reflux for ½ hr, cooled to 70° and 4-methylpentan-2-one (2 liters) added. The water was removed by azeotropic distillation under reduced pressure (260 torr) and the resultant solution treated with charcoal (10 g) at 50°. The solution was filtered and cooled to 10°. N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine (380 g) was filtered off and dried m.p. 69°–70°.

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, 4-Methyl-2-pentanone
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	
Use of stoichiometric quantities of reagents	Amber Flag	x
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

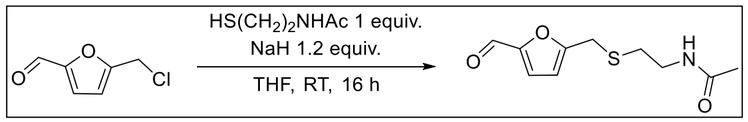
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			N-Methyl-1-methylthio-2-nitroethenamine H315 - H319
Explosive thermal runaway	H230, H240, H250	H241				4-Methyl-2-pentanone H225 - H319 - H332 - H335
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	

Alternative approach: Step A

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-(chloromethyl)furfural	0.4912	144.55	0.00340			NaH	0.10300	THF	30.00	0.88	26.40	NaCl	54.00	water (brine)	150.00	1.00	150.00
N-acetylcysteamine	0.4051	119.19	0.00340								0.00	Na2SO4	3.40	DCM	100.00	1.33	133.00
											0.00	charcoal	0.10				0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.8963	263.74			0.00		0.10				26.40		57.50				283.00



	Step	Cumulative
Yield	91.2	91.2
Conversion	100.0	100.0
Selectivity	91.2	91.2
AE	86.2	86.2
RME	78.6	78.6
PMI total	522.4	522.4
PMI Reaction	38.9	38.9
PMI reactants, reagents, catlyst	1.4	1.4
PMI reaction solvents	37.5	37.5
PMI Workup	483.5	483.5
PMI Workup chemical	81.7	81.7
PMI workup solvents	401.9	401.9

	Mass	MW	Mol
Product	0.70420	227.27	0.00310
	mass		
Unreacted limiting reactant	0.00		

Experimental:
Mark Mascal, Saikat Dutta, Green Chem., 2011, 13, 3101

Sodium hydride (95%) (103 mg, 4.08 mmol) was added to a solution of Nacetylcysteamine (0.4051 g, 3.40 mmol) in dry THF (20 mL) under argon. The resulting suspension was stirred at RT for 30 min and a solution of CMF **12** (0.4912 g, 3.40 mmol) in dry THF (10 mL) was added dropwise over a 10 min period. The resulting light yellow solution was allowed to stir overnight at RT. The solvent was evaporated and saturated brine (50 mL) was added. The mixture was extracted with CH2Cl2 (2 × 50 mL) and the organic layers were combined and washed with saturated brine (100 mL). The organic layer was dried over Na2SO4. Charcoal (100 mg) was added and the mixture was stirred for 20 min and filtered. The solvent was evaporated to give **14** as a yellow liquid (0.7042 g, 91 %).

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	THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	x
Use of reagents in excess	Red Flag	

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

Critical elements

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

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

Health & safety

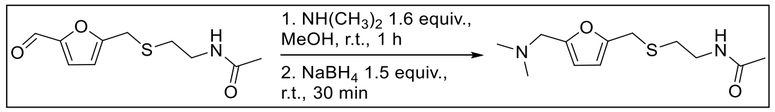
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		THF H225 - H302 - H319 - H335 - H336 - H351	NaH H228 - H260 - H290 - H314
Explosive thermal runaway	H230, H240, H250	H241			5-Chloromethylfurfural H227, H302, H314, H318, H351	N-Acetylcysteamine H315 - H319 - H335
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	

Alternative approach: Step B

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-[[(2-Acetamidoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine	0.2105	227.27	0.00093					MeOH	20.00	0.79	15.80			DCM	50.00	1.33	66.50
Dimethylamine	0.67	45.08	0.01486								0.00						0.00
NaBH4	0.06	37.83	0.00159								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.9405	310.18			0.00		0.00				15.80		0.00				66.50



	Step	Cumulative
Yield	90.3	82.4
Conversion	100.0	/
Selectivity	90.3	/
AE	82.6	74.0
RME	22.8	21.49
PMI total	388.1	899.78
PMI Reaction	78.0	115.25
PMI reactants, reagents, catlyst	4.4	4.80
PMI reaction solvents	73.7	110.450
PMI Workup	310.0	784.534
PMI Workup chemical	0.0	80.130
PMI workup solvents	310.0	704.404

	Mass	MW	Mol
Product	0.2145	256.36	0.00084
	mass		
Unreacted limiting reactant	0.00		

Experimental:
Mark Mascal, Saikat Dutta, Green Chem., 2011, 13, 3101

Me2NH (1.0 mL) was added to a solution of 14 (0.2105 g, 0.926 mmol) in dry methanol (20 mL) and the mixture was stirred at RT for 1 h. The resulting red solution was cooled to 0 °C and NaBH4 (98 %) (55 mg, 1.42 mmol) was added over a 5 min period. The mixture was allowed to come to RT and stirred for 30 min. The solvent was evaporated while keeping the bath temperature below 45 °C. The residue was dissolved in CH2Cl2 (50 mL) and filtered to remove inorganic impurities. The solvent was evaporated to give 15 (0.2145 g, 90 %) as a pale yellow oil.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	MeOH
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	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	x
Use of reagents in excess	Red Flag	

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

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	
50-500 years	Amber Flag	S, B
+500 years	Green Flag	

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	x
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}C at atmospheric	Green Flag	x
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

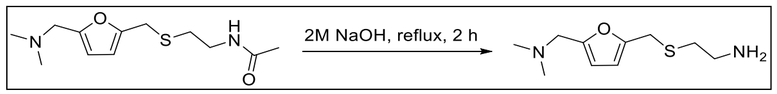
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	**Amber Flag**	**Green Flag**			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	DCM H225 - H301 + H311 + H331 - H370	Dimethylamine H220 - H280 - H315 - H318 - H332 - H335 -	
Explosive thermal runaway	H230, H240, H250	H241		NaBH4 H260 - H301 - H314 - H360FD		
Toxic	H300, H310, H330	H301, H311, H331,		x		
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	

Alternative approach: Step C

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine	0.2473	256.36	0.00096			NaOH	0.80	water	10.00	1.00	10.00	NaCl (brine)	2.00	DCM	90.00	1.33	119.70
											0.00	Na2SO4	1.00	water (brine)	5.00	1.00	5.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.2473	256.36			0.00		0.80				10.00		3.00				124.70



	Step	Cumulative
Yield	93.5	77.1
Conversion	100.0	/
Selectivity	93.5	/
AE	83.6	61.8
RME	78.2	16.81
PMI total	717.4	1866.68
PMI Reaction	57.1	203.21
PMI reactants, reagents, catlyst	5.4	10.27
PMI reaction solvents	51.7	192.938
PMI Workup	660.3	1663.471
PMI Workup chemical	15.5	117.974
PMI workup solvents	644.8	1545.496

	Mass	MW	Mol
Product	0.1934	214.32	0.00090
	mass		
Unreacted limiting reactant	0.00		

Experimental:
Mark Mascal, Saikat Dutta, Green Chem., 2011, 13, 3101

A solution of 15 (0.2473 g, 0.965 mmol) in freshly prepared 2N aq NaOH (10 mL) was heated at reflux for 2 h. The mixture was cooled to RT and extracted with CH2Cl2 (3×30 mL). The organic layers were combined and washed with saturated brine, dried over Na2SO4, and evaporated to give 5 (0.1934 g, 94 %) as a pale yellow oil.

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	DCM
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	
Use of stoichiometric quantities of reagents	Amber Flag	x
Use of reagents in excess	Red Flag	

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

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	x
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

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

Health & safety

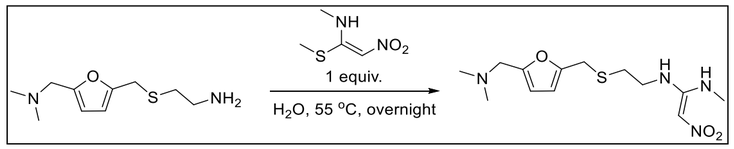
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		DCM: H351	
Explosive thermal runaway	H230, H240, H250	H241				
Toxic	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	

Alternative approach: Step D

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine	0.1501	214.32	0.00070					water	15.00	1.00	15.00	NaCl (brine)	11.00	CHCl3	60.00	1.49	89.40
N-Methyl-1-methylthio-2-nitroethenamine	0.1041	148.18	0.00070								0.00	Na2SO4	0.70	water (brine)	30.00	1.00	30.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.2542	362.50			0.00		0.00				15.00		11.70				119.40



	Step	Cumulative
Yield	87.9	67.7
Conversion	100.0	/
Selectivity	87.9	/
AE	86.7	63.5
RME	76.1	19.41
PMI total	756.4	2203.58
PMI Reaction	78.8	235.69
PMI reactants, reagents, catlyst	1.3	8.50
PMI reaction solvents	77.5	227.184
PMI Workup	677.5	1967.891
PMI Workup chemical	60.5	151.979
PMI workup solvents	617.1	1815.912

	Mass	MW	Mol
Product	0.1935	314.40	0.00062
	mass		
Unreacted limiting reactant	0.00		

Experimental:
Mark Mascal, Saikat Dutta, Green Chem., 2011, 13, 3101

A solution of 5 (0.1501 g, 0.700 mmol) in distilled water (10 mL) was added dropwise over a period of 10 min to a suspension of 1-methylthio-1-methylamino-2-nitroethylene 7 (0.1041 g, 0.703 mmol) in distilled water (5 mL) with stirring. The resulting light yellow solution was placed in an oil bath at 55 °C and the mixture was stirred at that temperature overnight. Saturated brine (30 mL) was added and the mixture was extracted with CHCl3 (3×20 mL). The combined organic layer was dried over Na2SO4. Evaporation of the solvent gave 1 as a pale yellow oil (0.1935 g, 88 %)

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	CHCl3

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

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

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	x
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}C at atmospheric	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	x
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

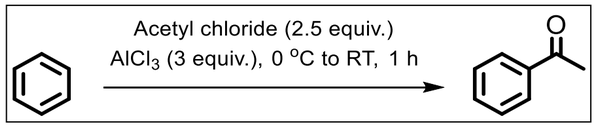
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	**Amber Flag**	**Green Flag**			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	H241		CHCl3: H372	CHCl3: H331, H351, H361, H412	
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	

Classical pathway: Step 1

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
benzene	0.01	78.11	0.00			AlCl3	0.05	DCM	5.00	1.33	6.65	MgSO4	0.13	water	30.00	1.00	30.00
AcCl	0.03	78.49	0.00								0.00	HCl 2M	4.38	DCM	30.00	1.33	39.90
											0.00			H2O (HCl 2 M)	60.00	1.00	60.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.04	156.60			0.00		0.05				6.65		4.51				129.90



	Step	Cumulative
Yield	100.0	100.0
Conversion	100.0	/
Selectivity	100.0	/
AE	76.7	76.7
RME	43.8	43.8
PMI total	9177.1	9177.1
PMI Reaction	438.0	438.0
PMI reactants, reagents, catlyst	5.6	5.6
PMI reaction solvents	432.4	432.4
PMI Workup	8739.1	8739.1
PMI Workup chemical	293.1	293.1
PMI workup solvents	8446.0	8446.0

	Mass	MW	Mol
Product	0.02	120.15	0.00
	mass		
Unreacted limiting reactant	0.00		

Experimental:
To a stirred suspension of aluminium(III) trichloride (51.2 mg, 384 µmol) and the respective aromatic starting material (128 µmol) in dichloromethane (5 mL) at 0 ºC was added acetyl chloride (22.8 µL, 320 µmol) using a micro-syringe under dynamic nitrogen. After coming to room temperature, the darkened reaction mixture was stirred for a further hour before being cooled back to 0 ºC. After careful quenching with water (30 mL) and further dilution with dichloromethane (30 mL), the lower organic layer was separated, was further washed with 2 M hydrochloric acid (2 x 30 mL) before being dried over magnesium sulfate. Filtration was followed by removal of the solvent under reduced pressure to yield the desired acylated species in quantitative yield as yellow solids. No attempt was made to separate regioisomers.

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	DCM
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	
Use of stoichiometric quantities of reagents	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	Al
+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	
solvent exchange, quenching into aqueous solvent	Amber Flag	X
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

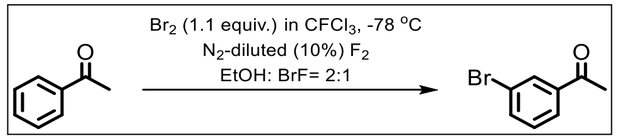
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				Benzene: H340, H350, H372, H410	DCM: H351, H373	
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Acetyl chloride: H412	
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	

Classical pathway: Step 2

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
acetophenone	3.24	120.15	0.03					CHCl3	5.00	1.49	7.45	MgSO4	27.00	water	100.00	1.00	100.00
Br2	4.76	158.81	0.03					CFCl3	100.00	1.49	149.00	NaHCO3	12.56	H2O (NaHCO3)	135.00	1.00	135.00
F2	1.14	38.00	0.03					EtOH	200.00	0.79	157.80	Na2S2O3	94.50	H2O (Na2S2O3)	135.00	1.00	135.00
											0.00			H2O(wash)	135.00	1.00	135.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	9.14	316.96			0.00		0.00				314.25		134.06				505.00



	Step	Cumulative
Yield	92.1	92.1
Conversion	100.0	/
Selectivity	92.1	/
AE	62.8	56.3
RME	54.1	37.16
PMI total	194.7	6209.41
PMI Reaction	65.4	351.86
PMI reactants, reagents, catlyst	1.8	4.87
PMI reaction solvents	63.6	346.988
PMI Workup	129.3	5857.551
PMI Workup chemical	27.1	219.244
PMI workup solvents	102.2	5638.307

	Mass	MW	Mol
Product	4.94	199.00	0.02
	mass		
Unreacted limiting reactant	0.00		

Experimental:
A suspension of 1.5 mL of Br_2 (about 30 mmol) in 100 mL of $CFCl_3$ was prepared at -78 °C. Nitrogen-diluted (10%) F_2 was bubbled through the suspension until the red color of Br_2 disappeared and was replaced by a pale-yellow suspension of BrF. From previous work and from independent experiments with olefins, it was concluded that the yield of BrF is practically quantitative in respect to both bromine and fluorine. The amount of ethanol which was then added depended on the substrate to be brominated or dibrominated. For best results with activated aromatic rings, the ratio of EtOH:BrF should be kept around 3, while for monobromination of deactivated compounds this ratio was lowered to 2. For dibromination of the latter type of compounds, it was further lowered to 1 to 1.5 and, with the most difficult case of 1,3-dinitrobenzene, this ratio was only 0.66. In all cases, the addition of the EtOH dissolved the BrF, forming a clear reddish solution. The aromatic substrate (26-27 mmol) was dissolved in a minimum amount of precooled $CHC1_3$ and added in one portion to the reaction vessel. The reaction mixture with the activated compounds was kept at -78 °C, while with the deactivated ones at -40 °C. The reactions were monitored by GC and stopped when practically full conversion was achieved. The mixture was then poured into dilute thiosulfate solution and the organic layer was washed with water and $NaHCO_3$ until neutral, dried over $MgSO_4$, and evaporated.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	Water, EtOH
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	CFCl3, CHCl3

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	X
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	
+500 years	Green Flag	X

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red 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 ^{o}C at atmospheric	Green Flag	
solvent exchange, quenching into aqueous solvent	Amber Flag	X
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	

Health & safety

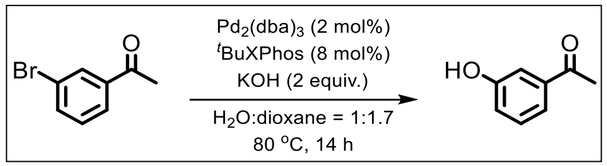
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				Br2: H330, H400		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	CFCl3: H420		
Explosive thermal runaway	H230, H240, H250	H241		CHCl3: H372		
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	

Classical pathway: Step 3

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3-bromoacetophenone	0.10	199.00	0.00	Pd2(dba)3	0.01	KOH	0.06	1,4-dioxane	0.50	1.03	0.52	SiO2	4.00	EtOAc	8.00	0.90	7.22
			#DIV/0!	L1	0.02			water	0.30	1.00	0.30			hexane	42.00	0.66	27.51
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
Total	0.10	199.00			0.03		0.06				0.82		4.00				34.73



	Step	Cumulative
Yield	95.5	88.0
Conversion	100.0	/
Selectivity	95.5	/
AE	68.4	38.5
RME	65.3	24.28
PMI total	611.2	10114.83
PMI Reaction	15.4	552.48
PMI reactants, reagents, catlyst	2.9	8.79
PMI reaction solvents	12.5	543.697
PMI Workup	595.8	9562.343
PMI Workup chemical	61.5	397.151
PMI workup solvents	534.2	9165.192

	Mass	MW	Mol
Product	0.07	136.15	0.00
	mass		
Unreacted limiting reactant	0.00		

Experimental:
Using the general procedure, 3'-bromoacetophenone (0.065 mL, 0.50 mmol), Pd2dba3 (9.20 mg, 0.01 mmol), L1 (17.0 mg, 0.040 mmol), KOH (60 mg, 1.0 mmol) in 1,4-dioxane (0.5 mL) and degassed water (0.3 mL) were allowed to react at 80 °C for 14 h. The crude material was purified by column chromatography (eluting with 5:1 hexanes:ethyl acetate) to give the title compound as a white solid (65 mg, 96%).

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, EtOAc
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	1,4-dioxane, 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	

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	
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	X
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	
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	X

Health & safety

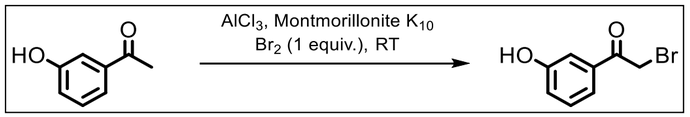
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Pd2(dba)3: H411		
Explosive thermal runaway	H230, H240, H250	H241		1,4-dioxane: H370, H372		
Toxic	H300, H310, H330	H301, H311, H331,		Hexane: H411		
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	

Classical pathway: Step 4

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3'-hydroxyacetophenone	13.62	136.15	0.10	AlCl3	0.01			EtOAc	100.00	0.90	90.20	Na2SO4	100.00	Water	100.00	1.00	100.00
Bromine	15.90	159.81	0.10	K10/KSF	0.50							NaCl	179.50	EtOAc	25.00	0.90	22.55
														Methanol	25.00	0.79	19.80
														Benzene (recryst)	100.00	0.88	87.60
														Water (wash)	500.00	1.00	500.00
														Water (brine)	500.00	1.00	500.00
																	0.00
Total	29.52	295.96			0.51		0.00				90.20		279.50				1229.95



	Step	Cumulative
Yield	89.0	78.3
Conversion	100.0	/
Selectivity	89.0	/
AE	72.7	41.9
RME	64.8	26.59
PMI total	85.1	7279.87
PMI Reaction	6.3	398.59
PMI reactants, reagents, catlyst	1.6	7.11
PMI reaction solvents	4.7	391.485
PMI Workup	78.9	6881.277
PMI Workup chemical	14.6	297.127
PMI workup solvents	64.3	6584.150

	Mass	MW	Mol
Product	19.14	215.05	0.09
	mass		
Unreacted limiting reactant	0.00		

Experimental:
The substrate (3'-hydroxyacetophenone) 0.1 mol in EtOAc (50 mL) and anhydrous $AlCl_3$ (0.010 g) were stirred at RT for 15 min. To this, K10/KSF (0.5 g) was added and stirring continued for further 15 min. Bromine (15.9 g, 5.13 mL, 0.1 mol) in EtOAc (50 mL) was added dropwise at a slow rate (addition time, 90 min). After the complete addition of bromine, stirring was continued for 30 min and the reaction mixture was poured to 100 mL of cold water. The solid K10/KSF catalyst was recovered by filtration and washed with fresh 25 mL of EtOAc followed by 25 mL MeOH. The methanol and EtOAc washings were combined with the filtrate. It was transferred to a separating funnel and the organic layer was separated from the aqueous layer. The organic layer was made neutral to pH by vigorous shaking with water and brine solution, dried with anhydrous sodium sulphate, and the solvent distilled off under reduced pressure. The crude product was purified by crystallization from benzene.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc, MeOH, 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	benzene (for recryst)

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

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

Critical elements

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

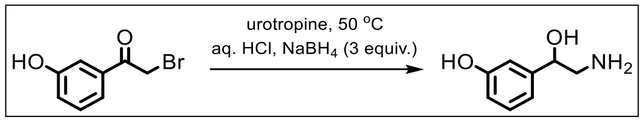
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Br2: H330, H400		
Explosive thermal runaway	H230, H240, H250	H241		Methanol: H370		
Toxic	H300, H310, H330	H301, H311, H331,		Benzene: H340, H350, H372, H410		
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	

Classical pathway: Step 5

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
Bromo-3-hydroxyacetophenone	13.00	215.05	0.06					C6H5Cl	29.00	1.11	32.19	HCl 1M	10.95	EtOH (HCl)	300.00	0.79	236.70
NaBH4	6.00	37.83	0.16					Methanol	200.00	0.79	158.40						
Urotropine	8.47	140.19	0.06														
Total	27.47	393.06			0.00		0.00				190.59		10.95				236.70



	Step	Cumulative
Yield	21.6	16.9
Conversion	100.0	/
Selectivity	21.6	/
AE	39.0	22.2
RME	7.3	3.16
PMI total	232.9	47545.50
PMI Reaction	109.0	2693.38
PMI reactants, reagents, catlyst	13.7	53.43
PMI reaction solvents	95.3	2639.947
PMI Workup	123.8	44852.124
PMI Workup chemical	5.5	1936.799
PMI workup solvents	118.4	42915.324

	Mass	MW	Mol
Product	2.00	153.18	0.01
	mass		
Unreacted limiting reactant	0.00		

Experimental:
ω-Bromo-3-hydroxyacetophenone (13 g) was converted into its hexamethylenetetramine derivative in dry monochlorobenzene (29 mL) at 50-52 °C This was decomposed with alcoholic hydrochloric acid into the ω -amino-ketone, isolated as its crystalline hydrochloride (5.3 g) which with sodium borohydride (6 g) in dry methanol (200 mL) afforded oily beta-hydroxy-3-methoxyethylamine (2 g).

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	Methanol, ethanol
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	Chlorobenzene
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	
Use of stoichiometric quantities of reagents	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	B
+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

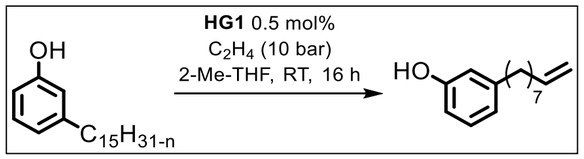
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				Chlorobenzene: H411	NaBH4: H301, H311	
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Methanol: H370		
Explosive 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	

Sustainable pathway: Step A

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
cardanol	1.00	302.49	0.00	HG1	0.02			2-Me-THF	20.00	0.85	17.08	SiO2	26.40	EtOAc	66.00	0.90	59.53
ethylene gas	11.47	28.05	0.41											petroleum ether	264.00	0.64	168.96
Total	12.46	330.54			0.02		0.00				17.08		26.40				228.49



	Step	Cumulative
Yield	94.4	94.4
Conversion	100.0	/
Selectivity	94.4	/
AE	66.1	66.1
RME	5.5	5.5
PMI total	418.3	398.9
PMI Reaction	43.5	43.5
PMI reactants, reagents, catlyst	18.4	18.4
PMI reaction solvents	25.1	25.1
PMI Workup	374.8	355.4
PMI Workup chemical	38.8	19.4
PMI workup solvents	336.0	336.0

	Mass	MW	Mol
Product	0.68	218.34	0.00
	mass		
Unreacted limiting reactant	0.00		

Experimental:
In the glove box, Hoveyda-Grubbs 1st generation catalyst (21.6 mg, 36 µmol, 0.5 mol%) was weighed into a 30 mL microwave vial fitted with a stirrer bar. The microwave vial was sealed and removed from the glove box. Under a flow of Ar, cardanol (3.3 mmol, 1 equiv.) and 2-methyl THF (20 mL) were introduced to the microwave vial by syringes. The microwave vial was introduced into a pre-purged 250 mL Hastelloy autoclave, and the cap of the microwave vial was removed under Ar flow. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (10 bar). The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was concentrated under reduced pressure. The product was obtained as a yellow oil (0.68 g, 94% yield) after purification by flash column chromatography (20% ethyl acetate/ petroleum ether).

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc
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	2-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	petroleum ether
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	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	Ru
50-500 years	Amber Flag	
+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	
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	X

Health & safety

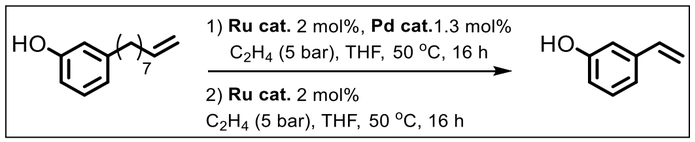
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				petroleum ether: H411		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag			
Explosive thermal runaway	H230, H240, H250	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	

Sustainable pathway: Step B

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3-(Non-8-en-1-yl)phenol	0.11	218.34	0.00	Pd dimer	0.01			THF	4.00	0.89	3.56	SiO2	4.00	EtOAc	10.00	0.90	9.02
ethylene gas	11.47	28.05	0.41	M1	0.01							SiO2 plug	1.00	petroleum ether	40.00	0.64	25.60
Total	11.57	246.39			0.02		0.00				3.56		5.00				34.62



	Step	Cumulative
Yield	78.4	74.0
Conversion	100.0	/
Selectivity	78.4	/
AE	48.8	33.5
RME	0.4	0.35
PMI total	1165.3	2088.09
PMI Reaction	322.3	420.81
PMI reactants, reagents, catlyst	246.6	286.90
PMI reaction solvents	75.7	133.911
PMI Workup	843.0	1667.272
PMI Workup chemical	106.4	151.402
PMI workup solvents	736.6	1515.871

	Mass	MW	Mol
Product	0.05	120.15	0.00
	mass		
Unreacted limiting reactant	0.00		

Experimental:
In the glove box, Bromo(tri-tertbutylphosphine)palladium(I) dimer (5 mg, 6.5 µmol, 1.3 mol%) and **M1** (6.6 mg, 10 µmol, 2 mol%) were weighed into a 10 mL microwave vial fitted with a stirrer bar. 3-(Non-8-en-1-yl)phenol (109 mg, 0.5 mmol) in anhydrous THF (2 mL) was also added into the microwave vial. The microwave vial was sealed, removed from the glove box, and introduced into a prepurged 250 mL Hastelloy autoclave. Two small needles were placed in the cap of the microwave vial to allow transfer of gas into the vial. The autoclave was sealed, purged 3 times with ethylene gas (~10 bar), and charged with ethylene (5 bar). The reaction mixture was stirred at 50 °C for 16 hours. After cooling to -78 °C, the pressure was slowly released. The reaction mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. Under inert atmosphere, **M1** (6.6 mg, 10 µmol, 2 mol%), crude product and THF (2 mL) were added into a microwave vial with two needles in an autoclave, the autoclave was charged with ethylene gas again (5 bar). The reaction mixture was stirred at 50 °C for another 16 hours. Purification by flash column chromatography (20% ethyl acetate/ petroleum ether) afforded the product as a pale-yellow oil (47 mg, 78% yield).

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF	THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	petroleum ether
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	

Critical elements

Supply remaining	Flag colour	Note element
5-50 years	Red Flag	Ru
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	
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	X

Health & safety

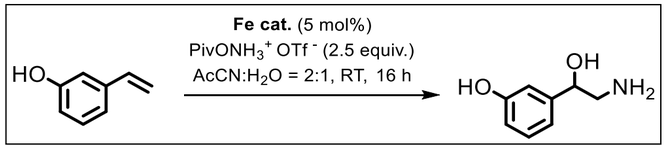
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				petroleum ether: H411		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Pd dimer: H250		
Explosive thermal runaway	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	

Sustainable pathway: Step C

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3-vinylphenol	0.06	120.15	0.00	Fe complex	0.01			AcCN	1.20	0.79	0.94	HCl 1M	1.64	MTBE	15.00	0.74	11.10
Opiv	0.33	264.00	0.00					Water	0.50	1.00	0.50	SiO2	4.00	H2O (HCl 1M)	45.00	1.01	45.45
														Et3N	1.00	0.73	0.73
														MeOH	43.00	0.79	34.06
														DCM	6.00	1.33	7.98
														Et3N (1 equiv.)	70.00	0.73	50.82
														DCM (1 equiv.)	32.00	1.33	42.56
Total	0.39	384.15			0.01		0.00				1.44		5.64				192.69



	Step	Cumulative
Yield	70.6	52.2
Conversion	100.0	/
Selectivity	70.6	/
AE	39.9	24.6
RME	13.8	0.31
PMI total	3707.1	6026.06
PMI Reaction	34.2	500.67
PMI reactants, reagents, catlyst	7.5	325.16
PMI reaction solvents	26.7	175.516
PMI Workup	3672.9	5525.386
PMI Workup chemical	104.5	272.715
PMI workup solvents	3568.4	5252.671

	Mass	MW	Mol
Product	0.05	153.18	0.00
	mass		
Unreacted limiting reactant	0.00		

Experimental:
A microwave vial fitted with a stirring bar was charged with iron (II) phthalocyanine (14.2 mg, 0.025 mmol), and degassed for 20 minutes with Ar. O-pivaloylhydroxylammonium triflate (0.33 g, 1.25 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL), and degassed for 5 minutes. 3-Vinylphenol (60 mg, 0.5 mmol) in degassed acetonitrile (0.2 mL) and the solution of O-pivaloylhydroxylammonium triflate were added to the microwave vial containing the iron catalyst simultaneously. The reaction mixture was stirred at room temperature for 16 hours. Afterwards, the reaction mixture was diluted with methyl *tert*-butyl ether (15 mL) and extracted with a HCl solution (1 M, 3 ×15 mL). The combined water phases were concentrated under reduced pressure to afford the amine salt. Dioxane was used as internal standard for an NMR yield in deuterated water (74% yield). The free amine was obtained by dissolving the chloride salt in triethyl amine (1 equiv. to the salt) and DCM, and purified by flash column chromatography (100: 15 :1.5 of DCM: MeOH: Et3N). The desired product was obtained as a pale yellow oil (54 mg, 71%).

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	MeOH, 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	MTBE, acetonitrile
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	DCM, TEA
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	

Critical elements

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

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	
solvent exchange, quenching into aqueous solvent	Amber Flag	
chromatography/ion exchange high temperature multiple recrystallisation	Red Flag	X

Health & safety

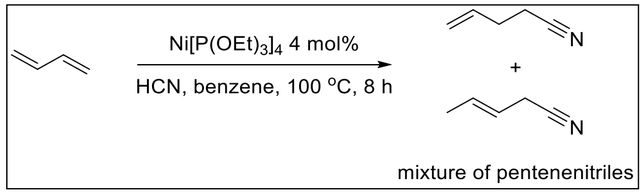
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
				DCM: H351, H373	Et3N: H331, H331, H401	
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Methanol: H370		
Explosive 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	

Classical approach: Step 1

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
1,3-butadiene	54.00	54.09	1.00	Ni[P(OEt)3]4	20.00			benzene	50.00	0.88	43.80						0.00
HCN	18.50	27.02	0.68								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	72.50	81.11			20.00		0.00				43.80		0.00				0.00



	Step	Cumulative
Yield	39.0	39.0
Conversion	100.0	/
Selectivity	39.0	/
AE	100.0	100.0
RME	43.5	43.5
PMI total	4.3	4.3
PMI Reaction	4.3	4.3
PMI reactants, reagents, catlyst	2.9	2.9
PMI reaction solvents	1.4	1.4
PMI Workup	0.0	0.0
PMI Workup chemical	0.0	0.0
PMI workup solvents	0.0	0.0

	Mass	MW	Mol
Product	31.55	81.12	0.39
	mass		
Unreacted limiting reactant	0.00		

Experimental:
William, C. D. & Richard, V. L., JR. Hydrocyanation of olefins using selected nickel phosphite catalysts. US3496215 (A) (1965).

A mixture of 20 g. of $Ni[P(OEt)_3]_4$ 50 ml. benzene, 108 g. of liquid butadiene, and 54 ml. of liquid HCN is charged to a cooled, 400 ml., stainless steel pressure tube. The tube is heated at 100° C. for 8 hours, then cooled and vented. The dark red, crude liquid is distilled at 0.1 mm. at a pot temperature up to 100° C. to obtain a mixture of products composed of: 0.65 g. of trans-2-methyl-2-butenenitrile, 46.0 g. of 2-methyl - 3 - butenenitrile, 3.1 g. of cis-2-methyl-2-butenenitrile, 58.3 g. of trans-3-pentenenitrile, and 0.61 g. of cis-3-pentenenitrile. These products represent 49 cycles (moles of product/moles of catalyst) of the catalyst to produce nitrile products. Products are separated by gas chromatography and identified by gas chromatographic retention time, mass spectrometry, infrared spectrometry, nuclear magnetic resonance spectroscopy.

Table I reports the results obtained for the hydrocyanation of butadiene using a representative group of tetrakis (organophosphite)nickel(O) catalysts using the conditions described in Example I. In each case, a temperature of 100° C. for 8 hours is used. In Table I, Et stands for ethyl, Bu for butyl, iPr for isopropyl, ϕ for phenyl, and Me for methyl.

Products	$Ni[P(OEt)_3]_4$
Cis-3-pentenenitrile, g	.77
4-pentenenitrile, g	.34
Trans-3-pentenenitrile, g	30.1
Cis-2-methyl-2-butenenitrile, g	.34
2-methyl-3-butenenitrile, g	22.3
Trans-2-methyl-2-butenenitrile, g	.26
Reagents:	
HCN, ml	27
Butadiene, g	54
Catalyst, g	20

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	
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	Benzene

Catalyst/enzyme (First Pass)

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

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

Experimental:
Green Chem., 2015, 17, 4760–4772, DOI: 10.1039/c5gc01549a

The PEP yearbook 2012 gives the following process summary for the HMDA production from butadiene according to the Dupont process. It is worthwhile to note that this model is quite approximate and not fully representative of the new generations of HMDA processes. Butadiene and hydrogen cyanide react at 80 C and 7.8 atm using a Ni-tri-o-tolylphosphite (NTOTP) catalyst to form pentenenitriles (PNs) and unconverted reactants are recycled. PNs are distilled to remove methylbutenenitrile, which is isomerized into PNs over a Ni catalyst and distilled for PNs recovery. PNs from hydrocyanation and isomerization are hydrocyanated to adiponitrile (ADN) at 41-65 C and 1 atm using a NTOTP catalyst and triphenylborane (TPB) promoter. After PN separation, the reaction product is extracted with cyclohexane to separate NTOTP, which is recovered by evaporating the cyclohexane. The raffinate is distilled to recover PNs for recycling, to remove ADN isomers, and to recover ADN. The spent catalyst and TBP are recovered by a series of steps, including ammoniation, evaporation, calcination, and reaction with triotolylphosphite. Further hydrogenation of the ADN into HMDA can be carried out in the temperature range 90-200° C under hydrogen pressure of about (range 250-400 atm) in the presence of ammonia in an ammonia-to-ADN weight ratio of at least about 1.8/1. The product yield is about 85% based on butadiene and 88.7% based on HCN.

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	x
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

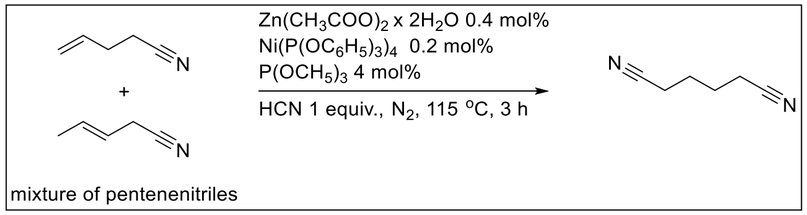
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	1,3-Butadiene H220 - H280 - H340		
Explosive thermal runaway	H230, H240, H250	H241		HCN H224, H330, H400, H410		
Toxic	H300, H310, H330	H301, H311, H331,		Benzene H302,H315, H319, H361, H370, H372, H340, H350, H336, H304, H411, H225		
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	

Classical approach: Step 2

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
3-pentenenitrile	20.00	81.12	0.25	Ni[P(OC6H5)3]4	0.65			N2	3620.00	1.25E-03	4.53						0.00
HCN	6.87	27.02	0.25	Zn(CH3COO)2x2H2O	2.19						0.00						0.00
				P(OC6H5)3	3.10						0.00						0.00
											0.00						0.00
Total	26.87	108.14			5.94		0.00				4.53		0.00				0.00



	Step	Cumulative
Yield	60.8	23.7
Conversion	75.7	/
Selectivity	80.3	/
AE	100.0	100.0
RME	60.3	30.67
PMI total	2.3	6.40
PMI Reaction	2.3	6.40
PMI reactants, reagents, catlyst	2.0	4.41
PMI reaction solvents	0.3	1.993
PMI Workup	0.0	0.000
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	0.000

	Mass	MW	Mol
Product	16.20	108.14	0.15
	mass		
Unreacted limiting reactant	4.87		

Experimental:
Yuan-tsan Chia, William Charles Drinkard, Edward Noonan Squire, Hydrocyanation of olefins, US3766237A, 1973

A 50 ml, three-necked, round bottom flask fitted with a reflux condenser connected to a Dry Ice trap, an inlet, and a magnetic stirrer, is set up in an oil bath maintained at 115° C. and purged with dry, deoxygenated nitrogen. The flask is charged with 2.19 g. (0.001 mole) of $Zn(CH_3COO)_2x2H_2O$ followed by 0.650 g. (0.0005 mole) of Ni(P(OCH5)3)4, 20 g. (0.25 mole) of 3-pentenenitrile, and 3.1 g (0.01mole) of P(OCH5)3. A stream of dry, deoxygenated nitrogen gas is bubbled through 10 ml. of liquid hydrogen cyanide contained in a 20 ml. receiver cooled in an ice bath. The nitrogen gas flow is adjusted to 20 ml. of nitrogen per minute to give a gaseous hydrogen cyanide feed rate equivalent to about 1.0 ml. measured at 0° C. of liquid hydrogen cyanide per hour. The resulting mixture of gases is passed through a bed of phosphorus pentoxide to eliminate traces of moisture and then is swept across the surface of the reaction mixture in the flask. After three hours, the reaction is shut down.
Gas chromatographic analysis indicates a yield of 16.2 g. of adiponitrile (79 percent as based on 3-pentenenitrile converted) and 4.4g. of 2-methylglutaronitrile. The number of cycles is 92.

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	
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	

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

Experimental:
Green Chem., 2015, 17, 4760–4772, DOI: 10.1039/c5gc01549a
The PEP yearbook 2012 gives the following process summary for the HMDA production from butadiene according to the Dupont process. It is worthwhile to note that this model is quite approximate and not fully representative of the new generations of HMDA processes. Butadiene and hydrogen cyanide react at 80 C and 7.8 atm using a Ni-tri-o-tolylphosphite (NTOTP) catalyst to form pentenenitriles (PNs) and unconverted reactants are recycled. PNs are distilled to remove methyl-butenenitrile, which is isomerized into PNs over a Ni catalyst and distilled for PNs recovery. PNs from hydrocyanation and isomerization are hydrocyanated to adiponitrile (ADN) at 41-65 C and 1 atm using a NTOTP catalyst and triphenylborane (TPB) promoter. After PN separation, the reaction product is extracted with cyclohexane to separate NTOTP, which is recovered by evaporating the cyclohexane. The raffinate is distilled to recover PNs for recycling, to remove ADN isomers, and to recover ADN. The spent catalyst and TBP are recovered by a series of steps, including ammoniation, evaporation, calcination, and reaction with triotolylphosphite. Further hydrogenation of the ADN into HMDA can be carried out in the temperature range 90-200° C under hydrogen pressure of about (range 250-400 atm) in the presence of ammonia in an ammonia-to-ADN weight ratio of at least about 1.8/1. The product yield is about 85% based on butadiene and 88.7% based on HCN.

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	x
Reaction run below -20 or above 140^{o}C	Red Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

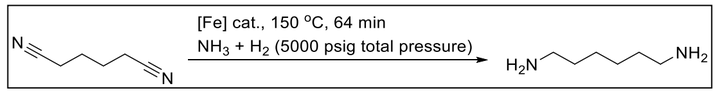
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	1,3-Butadiene H220 - H280 - H340	3-Pentenenitrile H226, H302, H331	
Explosive thermal runaway	H230, H240, H250	H241		HCN H224, H330, H400, H410		
Toxic	H300, H310, H330	H301, H311, H331,		Zn(OAc)2 H302, H318, H411		
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	

Classical approach: Step 3

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
adiponitrile	216.00	108.14	2.00	Fe catalyst	20.00						0.00						0.00
ammonia gas	216.00	17.03	12.68								0.00						0.00
hydrogen gas	19.66	2.02	9.73								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	451.66	127.19			20.00		0.00				0.00		0.00				0.00



	Step	Cumulative
Yield	97.8	23.1
Conversion	100.0	/
Selectivity	97.8	/
AE	91.4	91.4
RME	50.3	24.15
PMI total	2.1	7.22
PMI Reaction	2.1	7.22
PMI reactants, reagents, catlyst	2.1	5.32
PMI reaction solvents	0.0	1.897
PMI Workup	0.0	0.000
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	0.000

	Mass	MW	Mol
Product	227.00	116.21	1.95
	mass		
Unreacted limiting reactant			

Experimental:
Donald Bernard Bivens; Leo Wesley Patton; William Erbie Thomas, Hydrogenation of adiponitrile, US3758584A, 1970

A batch hydrogenation is conducted using 216 g. adiponitrile, 216 g ammonia, and 20 g of catalyst in a one liter stirred autoclave, at 150° C. and 5000 psig total pressure(pH, = 3500 psig; pNH + ADN = 1500 psig). The reaction is apparently complete in 64 minutes,having consumed the theoretical quantity of hydrogen based on ADN.

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	
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	

Experimental:
Green Chem., 2015, 17, 4760–4772, DOI: 10.1039/c5gc01549a
The PEP yearbook 2012 gives the following process summary for the HMDA production from butadiene according to the Dupont process. It is worthwhile to note that this model is quite approximate and not fully representative of the new generations of HMDA processes. Butadiene and hydrogen cyanide react at 80 C and 7.8 atm using a Ni-tri-o-tolylphosphite (NTOTP) catalyst to form pentenenitriles (PNs) and unconverted reactants are recycled. PNs are distilled to remove methyl-butenenitrile, which is isomerized into PNs over a Ni catalyst and distilled for PNs recovery. PNs from hydrocyanation and isomerization are hydrocyanated to adiponitrile (ADN) at 41-65 C and 1 atm using a NTOTP catalyst and triphenylborane (TPB) promoter. After PN separation, the reaction product is extracted with cyclohexane to separate NTOTP, which is recovered by evaporating the cyclohexane. The raffinate is distilled to recover PNs for recycling, to remove ADN isomers, and to recover ADN. The spent catalyst and TBP are recovered by a series of steps, including ammoniation, evaporation, calcination, and reaction with triotolylphosphite. Further hydrogenation of the ADN into HMDA can be carried out in the temperature range 90-200° C under hydrogen pressure of about (range 250-400 atm) in the presence of ammonia in an ammonia-to-ADN weight ratio of at least about 1.8/1. The product yield is about 85% based on butadiene and 88.7% based on HCN.

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

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

Critical elements

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

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

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

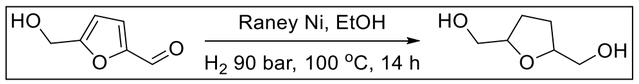
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	NH3 gas H280, H314, H331, H410	Adiponitrile H301, H332	
Explosive thermal runaway	H230, H240, H250	H241			Hydrogen gas H220 - H280	
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	

Bio-based approach: Step I

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
5-HMF	0.500	126.11	0.0040	Raney nickel catalyst	0.050			ethanol	30.00	0.79	23.70						0.00
hydrogen gas	0.75	2.02	0.37129								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	1.25	128.13			0.05		0.00				23.70		0.00				0.00



	Step	Cumulative
Yield	96.0	99.0
Conversion	100.0	/
Selectivity	96.0	/
AE	103.1	100.0
RME	40.2	40.2
PMI total	49.7	49.7
PMI Reaction	49.7	49.7
PMI reactants, reagents, catlyst	2.6	2.6
PMI reaction solvents	47.1	47.1
PMI Workup	0.0	0.0
PMI Workup chemical	0.0	0.0
PMI workup solvents	0.0	0.0

	Mass	MW	Mol
Product	0.50300	132.16	0.00381
	mass		
Unreacted limiting reactant			

Experimental:
Angew. Chem. Int. Ed. 2011, 50, 7083 –7087, DOI: 10.1002/anie.201102156

HMF (500 mg, 4 mmol) dissolved in ethanol (30 mL) and Raney nickel catalyst (50 mg) were added to a 100 mL stainless steel autoclave (Parr). The reactor was
flushed three times with nitrogen and subsequently with hydrogen. After flushing, the reactor was pressurized to 90 bar, and the reaction mixture was stirred and heated to 100 C for 14 h. GC analysis showed 100% conversion and 99% selectivity to THFDM.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	EtOH
Problematic solvents: (acceptable only if substitution does not offer	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene,	
Hazardous solvents: These solvents have significant health and/or safety	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	

		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	Ni
+500 years	Green Flag	

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	x
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	x

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

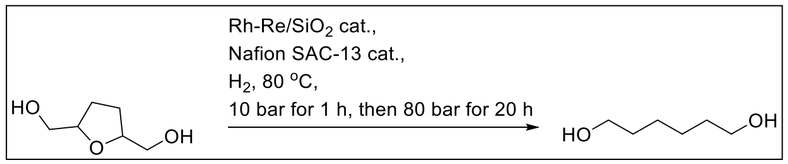
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	Raney nickel cat. H251, H317, H351, H372, H412	Hydrogen gas H220 - H280	Ethanol H225, H319
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	

Bio-based approach: Step II

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
THFDM	0.100	132.16	0.0008	Rh-Re/SiO2 catalyst	0.025			water	2.00	1.00	2.00						0.00
hydrogen gas	0.55	2.02	0.27228	Nafion SAC-13 catalyst	0.02						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	0.65	134.18			0.04		0.00				2.00		0.00				0.00



	Step	Cumulative
Yield	88.9	88.0
Conversion	100.0	/
Selectivity	88.9	/
AE	88.1	88.1
RME	12.2	9.96
PMI total	33.8	95.10
PMI Reaction	33.8	95.10
PMI reactants, reagents, catlyst	8.7	10.67
PMI reaction solvents	25.2	84.424
PMI Workup	0.0	0.000
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	0.000

	Mass	MW	Mol
Product	0.07950	118.17	0.00067
	mass		
Unreacted limiting reactant			

Experimental:
Angew. Chem. Int. Ed. 2011, 50, 7083 –7087, DOI: 10.1002/anie.201102156

The same procedure was used as described above for the hydrogenation of THFDM to 1,2,6-HT, but with an additional 15 mg of acid catalyst added.
THFDM (100 mg, 0.8 mmol), Rh-Re/SiO2 catalyst (25 mg), water (2 mL), and a Teflon stirring bar were added to a 8 mL glass vial capped with a septum. The vial was then pierced with a small needle and placed in a stainless steel autoclave. The lid of the autoclave was closed and stirring was started at 1000 rpm. After pressurizing three times with first nitrogen and then hydrogen, the autoclave was pressurized to 10 bar and the temperature was raised to 80 C. After 1 h, the pressure was raised to 80 bar and the reactions were continued for 20 h. The autoclave was then allowed to cool to ambient temperature and the pressure was released.

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	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane,**	
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	

		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	Rh
50-500 years	Amber Flag	Re
+500 years	Green Flag	

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	x
Reaction run below -20 or above 140^{o}C	Red Flag	

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	x

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	X

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

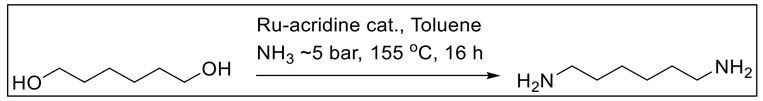
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		Hydrogen gas H220 - H280	
Explosive thermal runaway	H230, H240, H250	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	

Bio-based approach: Step III

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
1,6-hexanediol	0.8100	118.17	0.0069	Ru-acridine cat.	0.0310			toluene	20.00	0.87	17.30						0.00
ammonia gas	0.3747	17.03	0.0220								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	1.1847	135.20			0.0310		0.00				17.30		0.00				0.00



	Step	Cumulative
Yield	82.9	70.7
Conversion	100.0	/
Selectivity	82.9	/
AE	85.9	79.0
RME	55.7	7.76
PMI total	28.1	143.54
PMI Reaction	28.1	143.54
PMI reactants, reagents, catlyst	1.8	13.71
PMI reaction solvents	26.2	129.824
PMI Workup	0.0	0.000
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	0.000

	Mass	MW	Mol
Product	0.66	116.20	0.0057
	mass		
Unreacted limiting reactant	0.00		

Experimental: ACS Catal. 2016, 6, 2802-2810 DOI: 10.1021/acscatal.6b00189

An 810 mg portion (6.9 mmol) of 1,6-hexanediol was mixed in a Premex steel autoclave with 31 mg of chlorocarbonylhydrido[4,5-bis(dicyclohexylphosphinomethyl)-acridine]ruthenium(II) and 20 mL of toluene. The autoclave was closed, cooled to 0 °C, and pressurized for 1 h with ammonia gas (~5 bar). The autoclave was heated to 155 °C and stirred for 16 h. After the mixture was cooled, the solvent was removed in vacuo and the product mixture analyzed by NMR spectroscopy with naphthalene as internal standard. The amount of 1,6-hexanediamine in the crude mixture was 88% on the basis of used 1,6-hexanediol. After Kugelrohr distillation 660 mg of the product was obtained as colorless crystals.

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	toluene
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	

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

Critical elements

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

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	x

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	X

		Tick
Reaction run at reflux	Red Flag	x
Reaction run 5^{o}C or more below the solvent boiling point	Green Flag	

Work Up		List
quenching filtration centrifugation crystallisation Low temperature distillation/evaporation/ sublimation (< 140 ^{o}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

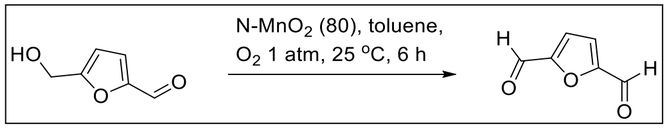
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	NH3 gas H280, H314, H331, H410	Toluene H225 - H304 - H315 - H336 - H361d - H373 - H412	Ru complex H315, H319, H335
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	

Bio-based approach: Step A

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
5-HMF	0.060	126.11	0.0005	N-MnO2(80)	0.150	oxygen gas	4.12	toluene	2.00	0.87	1.73						0.00
											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	0.06	126.11			0.15		4.12				1.73		0.00				0.00



	Step	Cumulative
Yield	99.9	99.9
Conversion	100.0	/
Selectivity	99.9	/
AE	98.4	98.4
RME	98.3	98.3
PMI total	102.7	102.7
PMI Reaction	102.7	102.7
PMI reactants, reagents, catlyst	73.3	73.3
PMI reaction solvents	29.4	29.4
PMI Workup	0.0	0.0
PMI Workup chemical	0.0	0.0
PMI workup solvents	0.0	0.0

	Mass	MW	Mol
Product	0.059	124.09	0.00048
	mass		
Unreacted limiting reactant			

Experimental:
Qingping Ke, Yangxin Jin, Fei Ruan, Minh Ngoc Ha, Dandan Li, Peixin Cui, Yali Cao, Hao Wang, Tongtong Wang, Van Noi Nguyen, Xinya Han, Xi Wang, Ping Cui, Boosting the activity of catalytic oxidation of 5-hydroxymethylfurfural to 2,5-diformylfuran over nitrogen-doped manganese oxide catalysts, Green Chem., 2019,21, 4313-4318, https://doi.org/10.1039/C9GC01041F

The mixtures of HMF (60 mg, 0.5 mmol), N-MnO2 (80) catalyst (150 mg), and toluene (2 mL) were added in a 10 mL Schlenk tube at 25±2 °C for 6 h, the oxygen with flux of 8 mL/min was bubbled in the tube by Internal pipeline. Afterwards, the catalyst was separated from the mixture by filtration. The crude products without further purification, and their reactant conversions and product selectivities were determined by a chromatograph-mass spectrometer (Agilent 7890B, USA), and 1H NMR spectra recorded on a BrukerALX400 spectrometer operating at 400 MHz.

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	toluene
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	

		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	Mn
50-500 years	Amber Flag	
+500 years	Green Flag	

Energy (First Pass)		Tick
Reaction run between 0 to 70^{o}C	Green Flag	x
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}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

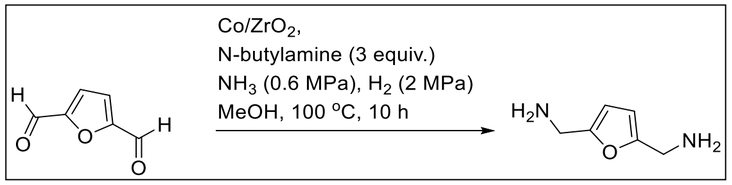
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag		MnO2 H302 + H332, H373	Oxygen gas H270 - H280
Explosive thermal runaway	H230, H240, H250	H241			Toluene H225 - H304 - H315 - H336 - H361d - H373 - H412	
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	

Bio-based approach: Step B

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
DFF	0.031	124.09	0.00025	Co/ZrO2	0.030	N-butylamine	0.055	MeOH	3.80	0.79	3.00			DCM	5.00	1.33	6.65
ammonia gas	0.2	17.03	0.01251								0.00			water	5.00	1.00	5.00
hydrogen gas	0.08	2.02	0.04								0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
											0.00						0.00
Total	0.33	143.14			0.03		0.055				3.00		0.00				11.65



	Step	Cumulative
Yield	94.9	94.8
Conversion	100.0	/
Selectivity	94.9	/
AE	88.1	86.9
RME	9.1	9.10
PMI total	503.8	609.28
PMI Reaction	114.2	219.65
PMI reactants, reagents, catlyst	13.8	88.78
PMI reaction solvents	100.4	130.872
PMI Workup	389.6	389.632
PMI Workup chemical	0.0	0.000
PMI workup solvents	389.6	389.632

	Mass	MW	Mol
Product	0.030	126.15	0.00024
	mass		
Unreacted limiting reactant			

Experimental:
Haifeng Qi, Fei Liu, Leilei Zhang, Lin Li, Yang Su, Jingyi Yang, Rui Hao, Aiqin Wang, Tao Zhang, Modulating trans-imination and hydrogenation towards the highly selective production of primary diamines from dialdehydes, Green Chem., 2020,22, 6897-6901, DOI https://doi.org/10.1039/D0GC02280B

In the typical reaction for reductive amination of dialdehydes, 0.25 mmol 2,5-diformylfuran (DFF) (Bidepharm), 0.75 mmol butylamine, 30 mg catalyst, and 3 g methanol were put into an autoclave (Parr reactor with a volume of 50 mL). The autoclave was purged with NH3 for three times, and charged with 0.6 MPa NH3 and 2 MPa H2 at room temperature. After sealing the autoclave, the reaction mixture was stirred at a rate of 800 r/min and heated at 373 K for 10 h with continuous stirring. After the reaction, the liquid-phase products were analyzed with a GC system (Agilent 7890A) equipped with a HP-5 column (30 m × 0.25 um × 0.25 mm i.d) and a FID detector by using dodecane as an internal standard.
After the typical reaction, the Co/ZrO2 catalyst was removed by centrifugation, and the upper liquid was distilled by rotatory evaporator. Then, 5 ml CH2Cl2 and 5 ml H2O were add to the residue, and the BAMF was extracted in H2O phase. The pure BAMF solid was obtained by recrystallization

Solvents (First Pass)

		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	MeOH, 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	DCM
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	

		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	Co, Zr
+500 years	Green Flag	

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

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	x

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

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

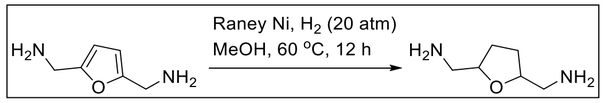
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	NH3 gas H280, H314, H331, H410	Hydrogen gas H220 - H280	
Explosive thermal runaway	H230, H240, H250	H241		MeOH H225 - H301 + H311 + H331 - H370		
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	

Bio-based approach: Step C

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
FDA	0.127	126.16	0.0010	Raney Ni	0.120			MeOH	5.00	0.79	3.95						0.00
hydrogen gas	0.050	2.02	0.02450								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	0.18	128.18			0.12		0.00				3.95		0.00				0.00



	Step	Cumulative
Yield	88.5	83.9
Conversion	100.0	/
Selectivity	88.5	/
AE	101.6	88.4
RME	65.7	8.03
PMI total	36.6	702.57
PMI Reaction	36.6	275.99
PMI reactants, reagents, catlyst	2.6	98.66
PMI reaction solvents	34.1	177.334
PMI Workup	0.0	426.580
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	426.580
PMI workup solvents	0.0	426.580

	Mass	MW	Mol
Product	0.116	130.19	0.00089
	mass		
Unreacted limiting reactant			

Experimental:
Peng Li, Armin T. Liebens, A process for producing a tetrahydrofuran compound comprising at least two amine functional groups, WO2018113599A1, 2017

Into a 30ml autoclave, 2,5-bis(aminomethyl)furan (127 mg, 1.01 mmol) and doped Raney Ni (120 mg) from Ningbo HanYi were added and dissolved in methanol (5 ml). The mixture was stirred at 60°C under 20 atms H_2 atmosphere for 12 h. The reaction mixture, after completion of the reaction, was analysed by GC and 2,5-bis(aminomethyl) tetrahydrofuran was obtained in 89% yield.

Experimental:
Green Chem., 2015, 17, 4760–4772, DOI: 10.1039/c5gc01549a

The first step involves the oxidation of HMF into DFF. The second step involves the amination of DFF into AM-THF, which is similar to 1,6 HDO amination into HMDA previously described. The last step from AM-THF to HMDA has also been described previously. Dealing with the first step, DFF may be produced industrially from the oxidation of pure HMF in an oxygenated solvent. Another option could start from a HMF mixture issued from the dehydration of HFS. The main advantage is that HMF is not extracted from the reaction mixture and the solvent used for the dehydration is also used for the oxygenation step. However, this one-pot reaction is more complicated. In our case, our choice was to model the first case starting from pure HMF. The oxidation (50 °C; atmospheric pressure; 8 h, MnO2 catalyst) was assumed to be realized in a batch reactor (dichloromethane : HMF weight ratio of 8 : 1), achieving a yield to DFF of 80%. The catalyst might be then filtered, regenerated and recycled. The solvent might be further recovered by distillation and recycled with a 99.9% yield. The separation of unreacted HMF would be performed by a precipitation step. After the reaction, the dissolved mixture would be cooled to precipitate DFF. The HMF is expected to remain soluble in the liquid phase. The recovered HMF might be dried for water removal and recycled.

The third step consists of an opening of the AM-THF molecular ring by reaction over a hydrodeoxygenation catalyst in the presence of a halogenated solvent. Such a reaction has been recently addressed by Rennovia patent. The patent claims the possibility of converting tetrahydrofuran 2,5-dicarboxilic acid (THFDCA) into linear adipic acid molecule with a yield of 99% over a Pd catalyst supported on silica beads. The reaction was realized at 160 C for 3 h under hydrogen iodide: THFDCA equimolar ratio. The reactor was pressurized with hydrogen until 48 atm. Here we have assumed that such reactions conditions and yield could be attained for the conversion of AM-THF into HMDA due to the very similar reaction mechanism. Finally, even if the Rennovia's patent does not tackle the separation step, we can reasonably propose that hydrogen iodide and H2 gas could be recovered after reaction by reactor depressurization, recompression and recycling into reactor. A recovery rate of 99.9% was assumed for hydrogen iodide as base case. After the reaction, the crude HMDA would be purified in a distillation column, crystallized and dried.

Solvents (First Pass)		List solvents below
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane	MeOH
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	

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

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
Reaction run between 0 to 70^{o}C	Green Flag	x
Reaction run between -20 to 0 or 70 to 140^{o}C	Amber Flag	
Reaction run below -20 or above 140^{o}C	Red Flag	

		Tick
Reaction run at reflux	Red Flag	
Reaction run 5^{o}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 ^{o}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

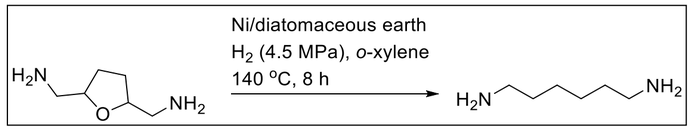
	Red Flag	Amber Flag	Green Flag	List substances and H-codes	List substances and H-codes	List substances and H-codes
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag	MeOH H225 - H301 + H311 + H331 - H370	Hydrogen gas H220 - H280	
Explosive 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	

Bio-based approach: Step D

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density (g ml^{-1})	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml^{-1})	Mass (g)
2,5-diaminomethyltetrahydrofuran	0.140	130.19	0.0011	Ni/diatomaceous earth	0.050			o-xylene	5.00	0.88	4.40						0.00
hydrogen gas	0.037	2.02	0.01812								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	0.18	132.21			0.05		0.00				4.40		0.00				0.00



	Step	Cumulative
Yield	94.0	78.9
Conversion	98.0	/
Selectivity	95.9	/
AE	87.9	77.9
RME	66.5	6.60
PMI total	39.3	875.55
PMI Reaction	39.3	367.11
PMI reactants, reagents, catlyst	1.9	118.33
PMI reaction solvents	37.4	248.781
PMI Workup	0.0	508.439
PMI Workup chemical	0.0	0.000
PMI workup solvents	0.0	508.439

	Mass	MW	Mol
Product	0.117	116.21	0.001
	mass		
Unreacted limiting reactant	0.003		

Experimental:
Xu, Jie; Xu, Yongming; Ma, Jiping; Jia, Xiuquan; Gao, Jin; Miao, Hong; Xia, Fei, Method for preparing aliphatic amine compound from furfurylamine compound by catalytic hydrogenolysis, From Faming Zhuanli Shenqing, 111100015, 05 May 2020.

Into a 10 mL reactor 0.14 g of 2,5-diaminomethyltetrahydrofuran, 0.05 g Ni/diatomaceous earth, 5 mL o-xylene were added; the reactor was filled with hydrogen to 4.5M Pa, under constant stirring. The reaction was carried out at 140 °C for 8.0 h. After the reaction was completed, it was cooled to room temperature. The reaction solution was centrifuged, and the supernatant was taken for gas chromatography analysis. The conversion rate of 2,5-diaminomethyltetrahydrofuran was 98%. The selectivity to 1,6-hexanediamine was 94%.

Solvents (First Pass)

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Catalyst/enzyme (First Pass)

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

		Tick
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catalyst/enzyme not recovered	Amber Flag	

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Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	x

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

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