# Iron and Base Catalyzed C(α)-Alkylation and One-pot Sequential Alkylation-Hydroxylation of Oxindoles with Secondary Alcohols

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### **General experimental**

All catalytic  $C(\alpha)$ -alkylation of oxindole were performed under dry nitrogen atmosphere using standard Schlenk or glovebox (MBraun) techniques. Catalytic  $\alpha$ -alkylation of oxindole were performed in Ace pressure tubes purchased from Sigma-Aldrich. Catalytic C-H hydroxylation of  $\alpha$ -alkylated oxindole were performed in air. Analysis and purification of the products of alkylations and hydroxylation were carried out in air. Solvents were purchased from Merck and Spectrochem. For the air-sensitive experiments, solvents (1,4 dioxane, toluene, *p*-xylene, *t*AmOH and benzene) were distilled, degassed and stored over 3 Å molecular sieves. Deuterated solvents (CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub>) were purchased from Sigma-Aldrich. TLC was performed on Merck Kiesel gel 60, F254 plates with the layer thickness of 0.25 mm. Column chromatography was performed using silica gel (100-200 mesh) as stationary phase. FeCl<sub>2</sub>, 1,10- phenanthroline, NaO*t*Bu, butylated hydroxytoluene (BHT), TEMPO, anisole(dry), all oxindole substrate and all secondary alcohols were purchased from Sigma Aldrich, Alfa Aesar and TCI Chemicals and used without further purification.

<sup>1</sup>H and <sup>13</sup>C {<sup>1</sup>H} NMR spectra were recorded at Bruker AV-400 and JEOL-400 (<sup>1</sup>H at 400 MHz and <sup>13</sup>C at 101 MHz). <sup>1</sup>H and <sup>13</sup>C {<sup>1</sup>H} NMR chemical shifts are referenced in parts per million (ppm) with respect to residual solvent peaks (CDCl<sub>3</sub>:  $\delta$  7.26 and 77.16 ppm; DMSO-d6: 2.50 and 39.52 ppm). The coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: s = singlet, brs = broad siglet, d = doublet, t = triplet, q = quadtrate, m = multiplate. GC was recorded using Shimadzu GC-2010 instrument. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-Q II Spectrometer. Gas chromatography (Thermo Scientific Trace 1110 GC) with a 60/80 Carboxen-1000 column, which was equipped with a thermal conductivity detector (TCD) was used to quantify gaseous products and high-purity Ar (99.999%) was used as carrier gas.

# General experimental procedure for the $C(\alpha)$ -alkylation of oxindole: General condition for reaction optimization:



**Procedure A**: In a 15 mL dried pressure tube fitted with a magnetic stir bar, an appropriate amount of 2-oxindole (S<sub>1</sub>) (0.04 g, 0.30 mmol), cyclohexanol (A<sub>1</sub>) (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (3 to 5 mol%), ligand (6 to 10 mol%), base (1 to 2 equivalent) and solvent (1 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature in a preheated oil bath for the appropriate time. Thereafter the reaction mixture was cooled down to r.t. *n*-dodecane (0.051 g, 0.3 mmol) was added to the resultant mixture, and the product mixture was analyzed by GC. Occasionally the crude product was purified by column chromatography using silica as stationary phase and hexane as eluent.

**Procedure B**: In a 15 mL dried pressure tube fitted with a magnetic stir bar, an appropriate amount of 2-oxindole (S<sub>1</sub>) (0.04 g, 0.30 mmol), cyclohexanol (A<sub>1</sub>) (0.09 g, 0.9 mmol), FeCl<sub>2</sub> (5 mol%), ligand (10 mol%) and NaO*t*Bu (1.5 equivalent) were added successively under a nitrogen atmosphere in absence of any added solvent. The reaction mixture was heated at 150 °C temperature in a preheated oil bath for the appropriate time. Thereafter the reaction mixture was cooled down to r.t. *n*-dodecane (0.051 g, 0.3 mmol) was added to the resultant mixture, and the product mixture was analyzed by GC. Occasionally the crude product was purified by column chromatography using silica as stationary phase and hexane as eluent.

General condition for substrate screening:



**Procedure A**: In a 15 mL dried pressure tube fitted with a magnetic stir bar, a mixture of 2oxindole (S<sub>1</sub>) (0.3 mmol), secondary alcohols ( $A_x$ ) (0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10phenanthroline (0.054 g, 10 mol%), NaOtBu (0.45 mmol, 1.5 eq.), and anisole (1 mL) were successively added under a nitrogen atmosphere. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. Thereafter, the reaction mixture was cooled down to r.t, and the crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethyl acetate as eluent) to give a pure product.

**Procedure B**: In a 15 mL dried pressure tube fitted with a magnetic stir bar, a mixture of 2oxindole (S<sub>1</sub>) (0.3 mmol), secondary alcohols ( $A_x$ ) (0.9 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10phenanthroline (0.054 g, 10 mol%) and NaO*t*Bu (0.45 mmol, 1.5 eq.) were successively added under a nitrogen atmosphere in absence of any added solvent. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 8 h. Thereafter, the reaction mixture was cooled down to r.t, and the crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethyl acetate as eluent) to give a pure product.





**Procedure A:** In a 50 mL dried pressure tube fitted with a magnetic stir bar, a mixture of 2oxindole (1.065 g, 10.0 mmol), cyclohexanol (2.003 g, 20 mmol), FeCl<sub>2</sub> (0.063 g, 5 mol%), 1,10- phenanthroline (0.180 g, 10 mol%), NaO*t*Bu (1.440 g, 15 mmol) and anisole (10 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give a white solid as pure product (2.002 g, 93%).

**Procedure B:** In a 50 mL dried pressure tube fitted with a magnetic stir bar, a mixture of 2oxindole (1.065 g, 10.0 mmol), cyclohexanol (3.004 g, 30 mmol), FeCl<sub>2</sub> (0.063 g, 5 mol%), 1,10- phenanthroline (0.180 g, 10 mol%) and NaO*t*Bu (1.440 g, 15 mmol) were added successively under a nitrogen atmosphere in absence of any added solvent. The reaction mixture was heated at 150 °C in a preheated oil bath for 8 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give a white solid as pure product (1.937 g, 90%). General condition for one-pot alkylation-hydroxylation of oxindole:



In a 15 mL dried pressure tube fitted with a magnetic stir bar, a mixture of oxindole (0.3 mmol), secondary alcohols (0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10- phenanthroline (0.054 g, 10 mol%), NaO*t*Bu (1.5 eq.) and anisole (1 mL) were successively added under a nitrogen atmosphere. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. After cooling down to room temperature the reaction mixture was stirred under air for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 7:3) as eluent to give the desired product.

### General condition for gram scale synthesis of 3-cyclohexyl-3-hydroxyindolin-2-one (P<sub>30</sub>):



In a 100 mL dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (1.065 g, 10.0 mmol), cyclohexanol (2.003 g, 20 mmol), FeCl<sub>2</sub> (0.063 g, 5 mol%), 1,10-phenanthroline (0.180 g, 10 mol%), NaO*t*Bu (1.440 g, 15 mmol) and anisole (10 mL) were added successively under a nitrogen atmosphere. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. After cooling down to room temperature the reaction mixture was stirred under air for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 7:3) as eluent to give the desired product.

### **Preparative scale for the determination of Green Metrics:**

Analysis of optimized reactions with CHEM21 green metrics toolkit: In order to evaluate the advantages and shortcomings of our two optimized catalytic protocols for the C( $\alpha$ )alkylation of 2-oxindole with cyclohexanol (Method A and B), we analyzed them with the CHEM21 green metrics toolkit (Table S1). The results were also compared with the first report of base metal catalyzed 2-oxindole alkylation with secondary alcohol published by Sundararaju group (Method C).<sup>S1</sup> We also analyzed the optimized synthetic protocol for the one-pot alkylation-hydroxylation of 2-oxindole with cyclohexanol (Method D). In this context, we have employed green, amber, and red flags, representing acceptable, acceptable with concerns and unacceptable processes, respectively. All four methods A, B, C and D gave full conversion, excellent yield and complete selectivity and hence all methods received green flags for those metrics. Good atom economy and acceptable reaction mass efficiency were found in our optimized methods (Method A, B and D). In contrast, poor reaction mass efficiency was noted in Method C. We have used catalyst and green solvents (anisole or solvent-free) and thus, Method A, B and D earn green flags in solvent and catalyst metrics. However, Method C got amber flag for the use of hazardous toluene. Catalyst recovery is an important feature; however, catalysts could not be recovered in all the methods and they all received amber flags. We used most sustainable transition metal iron in these alkylations (Method A and B) and one-pot alkylation/hydroxylation (Method D) and they received green flags. In contrast, the alkylation method published by Sundararaju group (Method C) received amber flag for element metric due to use of cobalt. The reactions were performed in batches instead of continuous flow reactions. Thus, all methods earned amber flag. Our reaction conditions in terms of health & safety are in line with green metrics and received green flags. However, Method C got amber flag due to the use of toluene. So, we concluded that our optimized methods of alkylation have more green and sustainable features as compared to the past report.

 

 Table S1: Comparison of optimized methods for the alkylation and one-pot alkylationhydroxylation of 2-oxindole.



E-factor for the synthesis of 3-cyclohexylindolin-2-one in presence of anisole as solvent	
(Method A, in anisole):	

Reagent 1:	Oxindole (10 mmol)	= 1.33 g
Reagent 2:	Cyclohexanol (20 mmol)	= 2.002 g
Base:	NaOtBu (15 mmol)	= 1.411  g
Catalyst:	FeCl <sub>2</sub> (5 mol %)	= 0.063  g
Ligand:	1,10-Phenantholine (10 mol %)	= 0.180  g
Reaction solvent:	anisole (10 mL, d= 0.995)	= 9.95 g
	[Solvent anisole (10 mL of reaction and 5 mL	
	of washing) was placed in a round bottom flask	
	and roughly 80 %; 11.94 g of anisole	
	was recovered via solvent distillation process;	
	waste = $(14.925 - 11.94) = 3.01 \text{ g}$ ]	
Product:	3-cyclohexylindolin-2-one (93% conversion; 2.0	02 g)
$E$ -factor = $\frac{mass (wast}{mass})$	<i>te)</i>	
mass (produ	uct)	
1.33 g (Oxin	dole) + 2.002 g (cyclohexanol) + 1.411 g (base) + 0.243 g	
	$(FeCl_2 + Ligand) + 3.01$ g (solvent anisole)	
=	2.002 g (product)	
= 7.996 g / 2.00	02 g	
= 3.99 kg wast	re / 1 kg of product	

E-factor for the synthesis of 3-cyclohexylindolin-2-one under neat reaction condition				
(Method B, neat):				
Reagent 1:	Oxindole (10 mmol)	= 1.33 g		
Reagent 2:	Cyclohexanol (40 mmol)	= 4.006 g		
Base:	NaOtBu (15 mmol)	= 1.411 g		
Catalyst:	FeCl <sub>2</sub> (5 mol %)	= 0.063 g		
Ligand:	1,10-Phenantholine (10 mol %)	= 0.180  g		
Reaction solvent:	Neat	= 00.00  g		
Workup solvent:	ethyl acetate (5 x 5 mL) x 0.902	= 22.55 g		
	[Combined EtOAc was placed in a round bottom			
	flask and roughly 95 %; 21.42 g of ethyl acetate			
	was recovered via solvent distillation process;			
	waste = $(22.55 - 21.42) = 1.13 \text{ g}$ ]			
Product:	3-cyclohexylindolin-2-one (90% conversion; 1.93	7 g)		
$E$ -factor = $\frac{mass (was)}{mass (was)}$	te)			
mass (produ	ict)			
1.33 g (Oxir	ndole) + 4.006 g (cyclohexanol) + 1.411 g (base) + 0.243 g			
$(FeCl_2 + Liga)$	and) + $1.13$ g (ethyl acetate during isolation of the product)			
=				
= 8.12  g / 1.937  g				
= 4.19 kg waste / 1 kg of product				

E footon for the sur	theorie of 2 avalable	wyl 2 hydrogyin	dolin 2 one (Meth	ad D in anicala)
L-factor for the syn	mesis of 5-cyclone	zyi-5-nyuroxyind	uomi-2-one (mieur	ou D, m amsole).

Reagent 1: Reagent 2: Base: Catalyst: Ligand: Reaction solvent:		Oxindole (10 mmol) Cyclohexanol (20 mmol) NaOtBu (15 mmol) FeCl <sub>2</sub> (5 mol %) 1,10-Phenantholine (10 mol %) anisole (10 mL, d= 0.995) [Solvent anisole (10 mL of reaction and 5 mL of washing) was placed in a round bottom flask and roughly 83 %; 12.39 g of anisole was recovered via solvent distillation process:	= 1.33 g = 2.002 g = 1.411 g = 0.063 g = 0.180 g = 9.95 g
		waste = $(14.925 - 12.39) = 2.54$ g]	
Product:		3-cyclohexyl-3-hydroxyindolin-2-one (90% conver	rsion; 2.081 g)
<i>E</i> -factor =	mass (wa mass (prod	uste)duct)	
	1.33 g (Ox	indole) + 2.002 g (cyclohexanol) + 1.411 g (base) + 0.243 g (FeCl <sub>2</sub> + Ligand) + 2.54 g (solvent anisole)	
—		2.081 g (product)	
=	7.526 g / 2.0	081 g	
=	3.61 kg wa	ste / 1 kg of product	

Table S2. Calculation of Eco Scale for the synthesis of 3-cyclohexylindolin-2-one (Method A in anisole)

Eco Scale = 100 – Sum of individuals penalties

Score on EcoScale: >75, Excellent; >50, Acceptable; <50, Inadequate

# A) Calculations of Penalty Points

Parameters Points	Pena	lty
1. Yield $(100 - \% \text{ yield})/2 = (100 - 93)/2 = 3.5$	=	3.5
2. Price of reaction components		
(To obtain 10 mmol of 3-cyclohexylindolin-2-one as end product)		
(a) Oxindole = 12.18 mmol = 1.691 g = USD 4.90		
(b) Cyclohexanol (24.36 mmol) = 2.536 mL = USD 0.08		
(c) NaOtBu (18.27 mmol) = $1.754 \text{ g} = 0.45 \text{ USD}$		
(d) $FeCl_2 = 5 \mod \% = 0.077 g = USD \ 0.085$		
(e) 1,10-Phenantholine (10 mol %) = $0.219 \text{ g} = 0.64 \text{ USD}$		
(f) solvent anisole $(10 \text{ mL}) = 1 \text{ USD}$		
Total cost for the synthesis of 3-cyclohexylindolin-2-one = USD $7.155$		
Thus, inexpensive since it is <usd 10<="" td=""><td>=</td><td>0</td></usd>	=	0
3. Safety		
1,10-Phenantholine (T)	=	5
4. Technical Setup		
Glove Box	=	3
5. Temperature and time		
Heating, >1 h	=	3
6. Workup and purification		
Removal of solvent with bp <150°C		0
Classical chromatography	=	10
Total Penalty Points	=	24.5

## **B)** EcoScale calculation:

EcoScale score = 100 - 24.5 = 75.5 (>75; it is an excellent synthetic process)

Table S3. Calculation of EcoScale for the synthesis of 3-cyclohexylindolin-2-one in presence of anisole as solvent (Method B, under neat)

Eco Scale = 100 – Sum of individuals penalties

Score on EcoScale: >75, Excellent; >50, Acceptable; <50, Inadequate

# A) Calculations of Penalty Points

Parameters Points	Pena	lty
1. Yield $(100 - \% \text{ yield})/2 = (100 - 90)/2 = 5$	=	5
2. Price of reaction components		
(To obtain 10 mmol of 3-cyclohexylindolin-2-one as end product)		
(a) Oxindole = 12.18 mmol = 1.691 g = USD 4.90		
(b) Cyclohexanol (48.72 mmol) = 5.072 mL = USD 0.16		
(c) NaOtBu (18.27 mmol) = 1.754 g = 0.45 USD		
(d) $FeCl_2 = 5 mol \% = 0.077 g = USD 0.085$		
(e) 1,10-Phenantholine (10 mol %) = 0.219 g = 0.64 USD		
Total cost for the synthesis of 3-cyclohexylindolin-2-one = USD $6.235$		
Thus, inexpensive since it is <usd 10<="" td=""><td>=</td><td>0</td></usd>	=	0
3. Safety		
1,10-Phenantholine (T)	=	5
4. Technical Setup		
Glove Box	=	3
5. Temperature and time		
Heating, >1 h	=	3
6. Workup and purification		
Removal of solvent with bp <150°C	=	0
Classical chromatography	=	10
Total Penalty Points	=	26

### **B)** EcoScale calculation:

EcoScale score = 100 - 26 = 74 (>50; it is an acceptable synthetic process)

Table S4. Calculation of Eco Scale for the synthesis of 3-cyclohexyl-3-hydroxyindolin-2one (Method D, in anisole)

Eco Scale = 100 – Sum of individuals penalties

Score on EcoScale: >75, Excellent; >50, Acceptable; <50, Inadequate

# A) Calculations of Penalty Points

Parameters Points		lty
1. Yield $(100 - \% \text{ yield})/2 = (100 - 90)/2 = 5$	=	5
2. Price of reaction components		
(To obtain 10 mmol of 3-cyclohexylindolin-2-one as end product)		
(a) Oxindole = 12.18 mmol = 1.691 g = USD 4.90		
(b) Cyclohexanol (36.54 mmol) = 3.804 mL = USD 0.12		
(c) NaOtBu (18.27 mmol) = $1.754 \text{ g} = 0.45 \text{ USD}$		
(d) $FeCl_2 = 5 \mod \% = 0.077 g = USD \ 0.085$		
(e) 1,10-Phenantholine (10 mol %) = $0.219 \text{ g} = 0.64 \text{ USD}$		
(f) solvent anisole $(10 \text{ mL}) = 1 \text{ USD}$		
Total cost for the synthesis of 3-cyclohexylindolin-2-one = USD 7.195		
Thus, inexpensive since it is <usd 10<="" td=""><td>=</td><td>0</td></usd>	=	0
3. Safety		
1,10-Phenantholine (T)	=	5
4. Technical Setup		
Glove Box	=	3
5. Temperature and time		
Heating, >1 h	=	3
6. Workup and purification		
Removal of solvent with bp <150°C		0
Classical chromatography	=	10
Total Penalty Points	=	26

## **B)** EcoScale calculation:

EcoScale score = 100 - 26 = 74 (>50; it is an acceptable synthetic process)

# NMR data of pure alkylated products:

The following products are obtained by  $\alpha$ -alkylation of fluorene with primary and secondary alcohols using the standard catalytic protocol. Known compounds are characterized by <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopies and new compounds are characterized by <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopies and HRMS:



**3-cyclohexylindolin-2-one (P<sub>1</sub>):**<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product **P**<sub>1</sub> as a colourless solid (0.055 g, 93%).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.04 (brs, 1H), 7.30 – 7.26 (m, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 3.40 (d, *J* = 3.2 Hz, 1H), 2.21 – 2.15 (m, 1H), 1.83 – 1.43 (m, 6H), 1.35 – 1.10 (m, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.4, 142.1, 128.8, 127.8, 124.8, 122.1, 109.7, 52.2, 41.0, 30.5, 28.5, 26.8, 26.4, 26.2.



**3-cyclopentylindolin-2-one (P<sub>2</sub>):**<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product **P**<sub>2</sub> as a colourless solid (0.054 g, 90%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.30 (s, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.45 (d, *J* = 5.2 Hz, 1H), 2.46 – 2.33 (m, 1H), 1.90 – 1.70 (m, 1H), 1.73 – 1.63 (m, 1H), 1.62 – 1.38 (m, 5H), 1.30 – 1.16 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.9, 142.1, 129.2, 127.9, 124.8, 122.1, 109.9, 49.3, 42.0, 30.0, 28.4, 25.2, 25.1.



**3-cycloheptylindolin-2-one (P<sub>3</sub>):**<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product **P<sub>3</sub>** as a colourless solid (0.06 g, 87%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.89 (s, 1H), 7.20 (d, *J* = 9.7 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H),

6.93 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 3.38 (d, J = 2.8 Hz, 1H), 2.29 – 2.21 (m, 1H), 1.75 – 1.66 (m, 2H), 1.61 – 1.48 (m, 4H), 1.43 – 1.32 (m, 4H), 1.30 – 1.12 (m, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.4, 142.1, 128.9, 127.9, 124.6, 122.2, 109.7, 53.3, 42.4, 32.7, 30.5, 27.9, 27.6, 27.4, 27.1.



**3-cyclododecylindolin-2-one** (P4):<sup>3</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product P4 as pale yellow oil (0.073 g, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.94 (s, 1H), 7.30 – 7.18 (m, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.52 (d, *J* = 2.7 Hz, 1H), 1.71 – 1.63 (m, 1H), 1.52 – 1.24 (m, 21H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.7, 142.1, 129.3, 127.7, 124.5, 122.1, 109.8, 49.3, 35.3, 27.7, 26.5, 24.3, 24.2, 24.1, 23.4, 23.2, 22.9, 22.7.



**3-isopropylindolin-2-one** (**P**<sub>5</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product **P**<sub>5</sub> as a pale yellow solid (0.039 g, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.98 (s, 1H), 7.28 (d, *J* = 6.1 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 3.43 (d, *J* = 3.4 Hz, 1H), 2.62 – 2.43 (m,1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.3, 142.2, 128.5, 127.92, 124.8, 122.2, 109.8, 52.3, 30.9, 20.0, 18.1.



**3-(pentan-3-yl)indolin-2-one** (**P**<sub>6</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product **P**<sub>6</sub> as a pale yellow oil (0.051 g, 84%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.93 (s, 1H), 7.22 (t, J = 7.2 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 3.63 (d, J = 2.6 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.72 – 1.62 (m, 1H), 1.53 – 1.35 (m, 2H), 1.30 – 1.17 (m, 1H), 1.05 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  181.0, 142.0, 128.8, 127.8, 124.6, 122.2, 109.8, 48.4, 44.3, 24.5, 23.6, 12.5, 12.3.



**3-(hexan-2-yl)indolin-2-one** (P<sub>7</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8.5:1.5 as eluent) to give pure product P<sub>7</sub> as a pale yellow oil (0.053 g, 81%). Two isomers ratio 1.45:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.20 (brs, 1H, m<sub>j</sub>), 9.09 (s, 1H, m<sub>n</sub>), 7.27 – 7.19 (m, 3H), 7.03 (t, *J* = 7.5 Hz, 2H), 6.93 (t, *J* = 7.0 Hz, 2H), 3.52 (d, *J* = 3.1 Hz, 1H, m<sub>j</sub>), 3.48 (d, *J* = 2.9 Hz, 1H, m<sub>n</sub>), 2.43 – 2.34 (m, 1H, m<sub>j</sub>), 2.33 – 2.23 (m, 1H, m<sub>n</sub>), 1.65 – 1.57 (m, 1H, m<sub>n</sub>), 1.55 – 1.48 (m, 1H, m<sub>j</sub>), 1.45 – 1.38 (m, 3H, m<sub>n</sub>), 1.32 – 1.25 (m, 5H, m<sub>j</sub>), 1.04 (d, *J* = 6.9 Hz, 2H, m<sub>n</sub>), 0.95 (t, *J* = 6.9 Hz, 3H, m<sub>j</sub>), 0.89 (t, *J* = 6.9 Hz, 2H, m<sub>n</sub>), 0.79 (d, *J* = 6.8 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  181.0, 180.3, 142.3, 142.1, 129.2, 128.1, 127.9, 127.8, 124.9, 124.4, 122.2, 122.1, 109.9, 109.8, 51.5, 51.0, 35.9, 35.5, 34.3, 32.5, 29.9, 29.8, 22.8, 17.0, 15.4, 14.2.



**3-(4-phenylbutan-2-yl)indolin-2-one (P8):** The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P8** as a pale yellow oil (0.065 g, 82%). Two isomers ratio 1.66:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.33 (m<sub>j</sub>), 9.21 (m<sub>n</sub>) (two s, 1H), 7.24 – 7.04 (m, 7H), 6.95 – 6.77 (m, 2H), 3.44 (m<sub>j</sub>), 3.41 (m<sub>n</sub>) (two d, J = 3 Hz, 1H), 2.77 – 2.45 (m, 2H), 2.39 – 2.19 (m, 1H), 1.89 – 1.47 (m, 2H), 0.98 (m<sub>j</sub>), 0.79 (m<sub>n</sub>) (two d, J = 6.8 Hz, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.8, 180.2, 142.3, 142.2, 142.1, 128.9, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 126.0, 125.8, 124.8, 124.3, 122.2, 122.1, 110.0, 109.9, 51.2, 51.1, 36.5, 35.4, 35.3, 34.7, 34.1, 33.9, 16.9, 15.3. HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>18</sub>H<sub>20</sub>NO] 266.1545; Found 266.1544.



**3-(1-butoxypropan-2-yl)indolin-2-one (P9):** The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P9** as a pale yellow oil (0.058 g, 79%). Two isomers ratio 1:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.13 (m<sub>j</sub>), 9.00 (m<sub>n</sub>) (two brs, 1H), 7.13 (dt, J = 7.8, 5.7 Hz, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.83 (t, J = 8.5 Hz, 1H), 3.70 (m<sub>j</sub>), 3.56 (m<sub>n</sub>) (two d, J = 2.8 Hz, 1H), 3.53 – 3.20 (m, 4H), 2.73 – 2.46 (m, 1H), 1.58 – 1.38 (m, 2H), 1.37 – 1.17 (m, 2H), 0.87 (m<sub>j</sub>), 0.84 (m<sub>j</sub>)

(one d, J = 7.1 Hz, one t, J = 8 Hz, 3H), 0.80 (m<sub>n</sub>), 0.62 (m<sub>n</sub>) (one d, J = 7.1 Hz, one t, J = 8 Hz 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  181.0, 180.0, 142.4, 142.3, 128.8, 127.9, 127.8, 127.5, 125.3, 124.1, 122.1, 109.9, 109.7, 73.1, 72.7, 71.0, 70.9, 48.2, 47.9, 36.2, 35.2, 32.0, 31.8, 19.5, 19.4, 14.1, 14.0, 13.7, 12.0. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub>] 248.1651; Found 248.1674.



**3-(1-phenylethyl)indolin-2-one** (P<sub>10</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>10</sub> as a colourless oil (0.055 g, 78%). Two isomers ratio 1.79:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer):  $\delta$  8.93 (brs, 1H, m<sub>j</sub>), 8.56 (brs, 1H, m<sub>n</sub>), 7.41 – 7.33 (m, 4H, m<sub>j</sub>), 7.32 – 7.26 (m, 1H, m<sub>n</sub>), 7.22 – 7.15 (m, 3H, m<sub>j</sub>), 7.13 – 7.05 (m, 2H, m<sub>n</sub>), 6.97 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.92 – 6.85 (m, 2H, m<sub>j</sub>), 6.78 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.53 (d, *J* = 7.4 Hz, 1H, m<sub>j</sub>), 3.87 – 3.82 (m, 1H, m<sub>j</sub>), 3.81 (d, *J* = 3.7 Hz, 1H, m<sub>j</sub>), 3.69 (d, *J* = 5.5 Hz, 1H, m<sub>n</sub>), 3.62 – 3.44 (m, 1H, m<sub>n</sub>), 1.66 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.21 (d, *J* = 7.0 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.7, 179.3, 142.9, 142.2, 142.1, 141.8, 128.5, 128.2, 128.1, 128.0, 127.9, 127.0, 126.9, 126.8, 125.2, 122.0, 109.7, 53.1, 52.5, 41.9, 39.6, 19.4, 13.6.



**3-(1-(p-tolyl)ethyl)indolin-2-one** (**P**<sub>11</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>11</sub> as a pale yellow oil (0.056 g, 75%). Two isomers ratio 2.22:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.48 (s, 1H, m<sub>j</sub>), 8.12 (s, 1H, m<sub>n</sub>), 7.21 – 7.14 (m, 5H), 7.08 (d, *J* = 7.4 Hz, 1H, m<sub>n</sub>), 6.96 (s, 2H), 6.86 (t, *J* = 7.9 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 1H, m<sub>n</sub>), 6.54 (d, *J* = 7.4 Hz, 1H, m<sub>j</sub>), 3.79 – 3.70 (m, 2H), 3.64 (d, *J* = 5.4 Hz, 1H, m<sub>n</sub>), 3.55 – 3.42 (m, 1H, m<sub>n</sub>), 2.36 (s, 3H, m<sub>j</sub>), 2.24 (s, 3H, m<sub>n</sub>), 1.60 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.16 (d, *J* = 6.9 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.4, 179.0, 142.0, 141.7, 139.8, 139.2, 136.3, 129.2, 128.8, 128.3, 128.1, 128.0, 127.9, 127.8, 127.2, 125.3, 122.0, 109.6, 53.1, 52.5, 41.6, 39.2, 21.2, 21.1, 19.5, 13.7.



**3-(1-(4-methoxyphenyl)ethyl)indolin-2-one** (P<sub>12</sub>):<sup>3</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>12</sub> as a pale yellow oil (0.064 g, 80%). Two isomers ratio 1.56:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.13 (brs, 1H, m<sub>j</sub>), 8.76 (brs, 1H, m<sub>n</sub>), 7.24 (d, *J* = 8.6 Hz, 2H, m<sub>j</sub>), 7.19 (t, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 7.13 (d, *J* = 7.4 Hz, 1H, m<sub>n</sub>), 7.02 – 6.95 (m, 2H, m<sub>n</sub>), 6.93 – 6.86 (m, 4H, m<sub>j</sub>), 6.78 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.68 (d, *J* = 8.6 Hz, 1H, m<sub>j</sub>), 6.56 (d, *J* = 7.4 Hz, 1H, m<sub>n</sub>), 3.84 (s, 3H, m<sub>j</sub>), 3.81 – 3.77 (m, 1H, m<sub>j</sub>), 3.76 (d, *J* = 3.2 Hz, 1H, m<sub>j</sub>), 3.72 (s, 3H, m<sub>n</sub>), 3.65 (d, *J* = 5.3 Hz, 1H, m<sub>n</sub>), 3.56 – 3.48 (m, 1H, m<sub>n</sub>) 1.63 (d, *J* = 7.2 Hz, 2H, m<sub>n</sub>), 1.19 (d, *J* = 6.8 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.9, 179.6, 158.4, 158.3, 142.2, 141.9, 134.8, 134.2, 129.0, 128.9, 128.2, 128.1, 128.0, 127.2, 125.2, 125.2, 122.0, 113.8, 113.4, 109.8, 109.7, 55.4, 55.2, 53.3, 52.8, 41.1, 38.9, 19.6, 13.9.



**3-(1-(3-chlorophenyl)ethyl)indolin-2-one (P**<sub>13</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>13</sub> as a pale yellow oil (0.055 g, 68%). Two isomers ratio 1.75:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer):  $\delta$  9.03 (s, 1H, m<sub>j</sub>), 8.70 (s, 1H, m<sub>n</sub>), 7.36 – 7.25 (m, 3H), 7.23 – 7.18 (m, 2H), 7.16 – 7.06 (m, 2H), 7.04 – 6.97 (m, 1H), 6.91 (t, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 3.84 – 3.72 (m, 2H, m<sub>j</sub>), 3.67 (d, *J* = 5.1 Hz, 1H, m<sub>n</sub>), 3.59 – 3.46 (m, 1H, m<sub>n</sub>), 1.62 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.21 (d, *J* = 6.7 Hz, 3H, m<sub>j</sub>).<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.4, 179.0, 145.0, 144.2, 142.1, 141.8, 134.4, 133.8, 129.7, 129.3, 128.4, 128.3, 128.3, 128.2, 127.7, 127.0, 126.7, 126.4, 126.2, 125.1, 125.0, 122.2, 109.9, 52.8, 52.3, 41.6, 39.4, 19.0, 13.7. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>15</sub>CINO] 272.0842; Found 272.0852.



**3-(1-(4-chlorophenyl)ethyl)indolin-2-one (P**<sub>14</sub>):<sup>3</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>14</sub> as a pale yellow oil (0.058 g, 71%). Two isomers ratio 1.47:1 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.18 (brs, 1H, m<sub>j</sub>), 8.85 (brs, 1H, m<sub>n</sub>), 7.32 (d, *J* = 8.5 Hz, 2H, m<sub>j</sub>), 7.25 (d, *J* = 8.5 Hz, 2H, m<sub>n</sub>), 7.19 (d, *J* = 7.9 Hz, 2H, m<sub>j</sub>), 7.09 (d, *J* = 8.4 Hz, 1H, m<sub>n</sub>), 7.01 (d, *J* = 7.7 Hz, 2H, m<sub>j</sub>), 6.80 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.59 (d, *J* = 7.4 Hz, 1H, m<sub>j</sub>), 3.82 – 3.73 (m, 2H, m<sub>j</sub>), 3.67 (d, *J* = 5.0 Hz, 1H, m<sub>n</sub>), 3.61 – 3.52 (m, 1H, m<sub>n</sub>), 1.62 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.22 (d, *J* = 6.9 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.6, 179.2, 142.1, 141.9, 141.3, 140.4, 132.6, 129.4, 129.3, 128.6, 128.3, 128.2, 128.1, 127.7, 126.9, 125.1, 125.0, 122.1, 110.0, 109.9, 52.9, 52.5, 41.2, 39.2, 19.2, 14.0.



**3-(1-(4-bromophenyl)ethyl)indolin-2-one (P**<sub>15</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>15</sub> as a yellow oil (0.068 g, 72%). Two isomers ratio 1.43:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.04 (s, 1H, m<sub>j</sub>), 8.70 (s, 1H, m<sub>n</sub>), 7.36 (d, *J* = 8.4 Hz, 1H,), 7.29 – 7.22 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.11 – 7.02 (m, 4H), 6.91 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.85 – 6.76 (m, 3H), 6.69 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.49 (d, *J* = 7.4 Hz, 1H, m<sub>j</sub>), 3.79 – 3.64 (m, 1H, m<sub>j</sub>), 3.62 (d, *J* = 6.1 Hz, 1H, m<sub>j</sub>), 3.56 (d, *J* = 5.1 Hz, 1H, m<sub>n</sub>), 3.49 – 3.40 (m, 1H, m<sub>n</sub>), 1.51 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.11 (d, *J* = 7.1 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.5, 179.2, 142.1, 141.9, 141.8, 140.9, 131.5, 131.1, 129.8, 129.7, 128.4, 128.2, 128.1, 127.7, 126.8, 125.1, 125.0, 122.1, 120.7, 120.6, 110.0, 109.9, 52.8, 52.4, 41.2, 39.3, 19.2, 13.9.



**3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P**<sub>16</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>16</sub> as a brown viscous oil (0.070 g, 81%). Two isomers ratio 1.5:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.28 (s, 1H, m<sub>j</sub>), 8.82 (s, 1H, m<sub>n</sub>), 7.92 – 7.83 (m, 3H), 7.78 – 7.72 (m, 1H), 7.71 – 7,64 (m, 1H), 7.58 – 7.50 (m, 3H), 7.45 – 7.39 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H, m<sub>n</sub>), 6.98 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.92 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 1H, m<sub>n</sub>), 6.98 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.92 (d, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 6.84 (t, *J* = 7.5 Hz, 1H, m<sub>j</sub>), 6.76 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.49 (d, *J* = 7.5 Hz, 1H, m<sub>j</sub>), 4.04 – 3.96 (m, 1H, m<sub>j</sub>), 3.93 (d, *J* = 3.6 Hz, 1H, m<sub>j</sub>), 3.79 (d, *J* = 3.6 Hz, 1H, m<sub>n</sub>), 3.76 – 3.69 (m, 1H, m<sub>n</sub>), 1.75 (d, *J* = 7.1 Hz, 3H, m<sub>n</sub>), 1.31 (d, *J* = 7.0 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.9, 179.4, 142.2, 141.9, 140.4, 139.8, 133.4, 133.3, 132.5, 132.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.0, 126.9, 126.7, 126.3, 126.2, 126.1, 125.9, 125.8, 125.5, 125.2, 125.1, 122.0, 109.9, 52.9, 52.5, 42.1, 39.6, 19.4, 13.5.



**3-(1-(4-chlorophenyl)propyl)indolin-2-one (P**<sub>17</sub>**):** The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>17</sub> as a yellowish solid (0.066 g, 78%). Two isomers ratio 1.5:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.10 (m<sub>n</sub>), 8.83(m<sub>j</sub>) (two s, 1H), 7.19 – 7.02 (m, 3H), 6.98 – 6.80 (m, 3H), 6.78 – 6.64 (m, 2H), 3.62 (m<sub>j</sub>), 3.56 (m<sub>n</sub>) (two d, J = 3.5 Hz, 1H), 3.29 – 3.16 (m, 1H), 2.13 – 1.67

(m, 2H), 0.84 (m<sub>j</sub>), 0.76 (m<sub>n</sub>) (two t, J = 7.3 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.6, 179.5, 142.0, 141.8, 139.1, 138.4, 132.5, 132.4, 130.0, 129.9, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 125.2, 124.7, 122.1, 122.0, 110.0, 109.9, 52.2, 51.3, 48.6, 48.1, 26.4, 22.7, 12.5, 12.4. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>17</sub>H<sub>17</sub>ClNO] 286.0999; Found 286.0982.



**3-(1-(thiophen-3-yl)ethyl)indolin-2-one (P**<sub>18</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>18</sub> as a yellowish oil (0.054 g, 74%). Two isomers ratio 2.32:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.24 (s, 1H, m<sub>j</sub>), 8.90 (s, 1H, m<sub>n</sub>), 7.27 – 7.24 (m, 1H, m<sub>j</sub>), 7.13 – 7.06 (m, 2H, m<sub>j</sub>), 7.02 (d, *J* = 4.6 Hz, 1H, m<sub>n</sub>), 6.97 (d, *J* = 4.8 Hz, 1H, m<sub>n</sub>), 6.91 (d, *J* = 4.6 Hz, 1H, m<sub>j</sub>), 6.69 (dd, *J* = 15.9, 6.3 Hz, 1H, m<sub>n</sub>), 6.37 (d, *J* = 7.4 Hz, 1H, m<sub>j</sub>), 3.79 – 3.70 (m, 2H, m<sub>j</sub>), 3.68 – 3.60 (m, 1H, m<sub>n</sub>), 3.55 (d, *J* = 4.6 Hz, 1H, m<sub>n</sub>), 1.52 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.07 (d, *J* = 6.8 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.8, 179.6, 144.4, 142.8, 142.2, 142.0, 128.2, 128.1, 128.1, 127.5, 127.3, 127.0, 125.9, 125.0, 124.9, 124.8, 122.1, 122.0, 121.3, 121.0, 109.9, 109.8, 52.5, 52.4, 37.3, 35.7, 19.6, 14.2. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>14</sub>NOS] 244.0796; Found 244.0784.



**3-(1-phenyloctyl)indolin-2-one** (**P**<sub>19</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>19</sub> as a pale yellowish oil (0.068 g, 71%). Two isomers ratio 1.47:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.34 (s, 1H, m<sub>n</sub>), 7.99 (s, 1H, m<sub>j</sub>), 7.24 – 7.12 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 2H, m<sub>j</sub>), 6.99 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.92 (d, *J* = 6.6 Hz, 1H, m<sub>n</sub>), 6.88 (d, *J* = 8.0 Hz, 2H, m<sub>j</sub>), 6.81 (d, *J* = 8.0 Hz, 2H, m<sub>j</sub>), 6.78 (d, *J* = 7.8 Hz, 1H, m<sub>n</sub>), 6.70 (d, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 3.68 (d, *J* = 4.8 Hz, 1H, m<sub>j</sub>), 3.65 (d, *J* = 3.4 Hz, 1H, m<sub>n</sub>), 3.49 – 3.43 (m, 1H, m<sub>n</sub>), 3.38 – 3.31 (m, 1H, m<sub>j</sub>), 2.12 – 1.99 (m, 2H, m<sub>j</sub>), 1.85 – 1.72 (m, 1H, m<sub>n</sub>), 1.32 – 1.16 (m, 17H), 0.86 (t, *J* = 6.8 Hz, 3H, m<sub>j</sub>), 0.82 (t, *J* = 7.1 Hz, 3H, m<sub>n</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.3, 179.2, 141.9, 141.7, 138.0, 137.2, 136.2, 129.0, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 125.4, 125.1, 122.0, 109.6, 109.5, 52.8, 51.6, 47.2, 46.3, 33.5, 32.0, 31.9, 29.7, 29.6, 29.3, 29.3, 27.8, 27.8, 22.8, 22.7, 21.2, 21.1, 14.2. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>22</sub>H<sub>28</sub>NO] 322.2171; Found 322.2178.



**3-(6-methylhept-5-en-2-yl)indolin-2-one (P**<sub>20</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>20</sub> as a colorless oil (0.055 g, 77%). Two isomers ratio 1.11:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.97 (s, 1H, m<sub>j</sub>), 8.87 (s, 1H, m<sub>n</sub>), 7.17 – 7.10 (m, 4H), 6.93 (t, *J* = 7.5 Hz, 2H), 6.83 (t, *J* = 7.4 Hz, 2H), 5.07 (t, *J* = 7.0 Hz, 1H, m<sub>j</sub>), 5.00 (t, *J* = 7.0 Hz, 1H, m<sub>n</sub>), 3.42 (d, *J* = 3.0 Hz, 1H, m<sub>j</sub>), 3.39 (d, *J* = 2.8 Hz, 1H, m<sub>n</sub>), 2.34 – 2.19 (m, 2H), 2.10 – 1.90 (m, 4H), 1.63 (s, 3H, m<sub>j</sub>), 1.59 (s, 3H, m<sub>n</sub>), 1.54 (s, 3H, m<sub>j</sub>), 1.50 (s, 3H, m<sub>n</sub>), 1.33 – 1.03 (m, 4H), 0.95 (d, *J* = 6.9 Hz, 3H, m<sub>n</sub>), 0.72 (d, *J* = 6.8 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.7, 180.1, 142.3, 142.1, 132.1, 131.7, 129.1, 128.0, 127.9, 127.8, 124.9, 124.4, 124.3, 124.1, 122.2, 122.1, 109.8, 109.7, 51.3, 51.1, 35.4, 35.2, 34.7, 32.9, 26.2, 26.0, 25.9, 25.8, 17.8, 17.7, 16.9, 15.2. HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>22</sub>NO] 244.1701; Found 244.1710.



**3-(5,9-dimethyl-1-phenyldec-8-en-1-yl)indolin-2-one (P**<sub>21</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>21</sub> as a yellowish oil (0.077 g, 68%). Two isomers ratio 1.47:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.48 (brs, 1H, m<sub>n</sub>), 8.16 (brs, 1H, m<sub>j</sub>), 7.25 – 7.13 (m, 6H), 7.10 – 7.04 (m, 3H), 7.03 – 6.96 (m, 1H), 6.95 – 6.90 (m, 3H), 6.78 (d, *J* = 7.7 Hz, 1H, m<sub>n</sub>), 6.70 (d, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 5.21 – 4.94 (m, 2H), 3.70 (d, *J* = 4.8 Hz, 1H, m<sub>j</sub>), 3.67 (d, *J* = 4.8 Hz, 1H, m<sub>n</sub>), 3.53 – 3.47 (m, 1H, m<sub>n</sub>), 3.42 – 3.35 (m, 1H, m<sub>j</sub>), 2.13 – 2.01 (m, 2H, m<sub>n</sub>), 1.98 – 1.84 (m, 4H, m<sub>j</sub>), 1.67 (s, 3H, m<sub>j</sub>), 1.66 (s, 3H, m<sub>n</sub>), 1.58 (s, 3H, m<sub>j</sub>), 1.56 (s, 3H, m<sub>n</sub>), 1.38 – 1.18 (m, 9H, m<sub>j</sub>), 1.14 – 1.02 (m, 2H, m<sub>n</sub>), 0.81 (t, *J* = 7.7 Hz, 3H, m<sub>j</sub>), 0.76 (t, *J* = 7.7 Hz, 3H, m<sub>n</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.4, 179.3, 141.9, 141.7, 141.1, 141.0, 140.3, 131.2, 131.1, 128.8,128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 126.8, 126.7, 125.4, 125.2, 125.1, 125.0, 122.0, 109.7, 109.6, 52.7, 52.6, 51.6, 51.5, 47.6, 46.7, 37.3, 37.2, 37.0, 36.9, 33.7, 32.4, 25.8, 25.6, 25.6, 25.2, 19.7, 19.6, 19.6, 19.5, 17.8, 17.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]<sup>+</sup> Calcd for [C<sub>26</sub>H<sub>33</sub>NNaO] 398.2460; Found 398.2462.



**6-chloro-3-cyclopentylindolin-2-one** ( $P_{22}$ ):<sup>2</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product  $P_{22}$  as a colourless solid (0.056 g, 79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.39 (s, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 3.49 (d, J = 5.3 Hz, 1H), 2.56 – 2.29 (m, 1H), 1.97 – 1.88 (m, 1H), 1.78 – 1.69 (m, 1H), 1.67 – 1.48 (m, 5H), 1.35 – 1.23 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.8, 143.2, 133.6, 127.6, 125.7, 122.1, 110.5, 49.0, 41.9, 30.0, 28.4, 25.2, 25.1.



**3-cyclopentyl-5-fluoroindolin-2-one** (P<sub>23</sub>):<sup>2</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>23</sub> as a yellowish brown solid (0.047 g, 71%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.54 (brs, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.94 – 6.80 (m, 2H), 3.52 (d, *J* = 5.2 Hz, 1H), 2.53 – 2.36 (m, 1H), 1.98 – 1.86 (m, 1H), 1.79 – 1.71 (m, 1H), 1.69 – 1.47 (m, 5H), 1.37 – 1.24 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.8, 160.1, 157.7, 138.1, 130.9, 130.8, 114.3, 114.1, 112.8, 112.6, 110.3, 110.2, 49.8, 41.9, 29.9, 28.4, 25.2, 25.1. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -121.26.



**3-cyclohexyl-5-fluoroindolin-2-one** (P<sub>24</sub>):<sup>3</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>24</sub> as a brown solid (0.045 g, 65%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.03 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.94 – 6.79 (m, 2H), 3.36 (d, J = 2.2 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.80 – 1.52 (m, 5H), 1.45 – 1.09 (m, 5H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.2, 160.1, 157.8, 138.0, 130.4, 130.4, 114.2, 114.0, 112.9, 112.6, 110.2, 110.1, 52.7, 41.0, 30.4, 28.4, 26.7, 26.4, 26.1. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -121.14.



**6-chloro-3-(hexan-2-yl)indolin-2-one (P**<sub>25</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>25</sub> as a pale yellow oil (0.056 g, 74%). Two isomers ratio 1.55:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.50 (m<sub>j</sub>), 9.43 (m<sub>n</sub>) (two s, 1H), 7.17 – 7.12 (m, 1H), 7.03 – 6.93 (m, 2H), 3.48 (m<sub>j</sub>), 3.45(m<sub>n</sub>) (two d, J = 2.9 Hz, 1H), 2.42 – 2.20 (m, 1H), 1.58 – 1.25 (m, 6H), 1.02 (m<sub>n</sub>), 0.94 (m<sub>j</sub>) (one d, J = 6.9 Hz, one t, J = 6.9 Hz, 3H), 0.88 (m<sub>n</sub>), 0.78 (m<sub>j</sub>) (one t, J = 6.8 Hz, one d, J = 6.8 Hz, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  181.1, 180.4, 143.5, 143.3, 133.6, 133.5, 127.5, 126.4, 125.7, 125.2, 122.2, 122.1, 110.6, 110.5, 51.2, 50.7, 35.8, 35.5, 34.2, 32.5, 31.7, 29.9, 22.8, 22.7, 16.9, 15.4, 14.3, 14.2. HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>19</sub>ClNO] 252.1155; Found 252.1152.



**5-fluoro-3-(hexan-2-yl)indolin-2-one (P**<sub>26</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>26</sub> as a brown oil (0.045 g, 64%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.38 (m<sub>j</sub>), 9.28 (m<sub>n</sub>) (two s, 1H), 7.00 – 6.87 (m, 2H), 6.87 – 6.81 (m, 1H), 3.49 (m<sub>j</sub>), 3.45 (m<sub>n</sub>) (two d, J = 2.5 Hz, 1H), 2.39 – 2.20 (m, 1H), 1.59 – 1.21 (m, 6H), 1.01 (m<sub>j</sub>), 0.92 (m<sub>n</sub>), (one d, J = 7.0 Hz, one t, J = 6.9 Hz, 3H), 0.85 (m<sub>n</sub>), 0.77 (m<sub>j</sub>), (one t, J = 6.9 Hz, one d, J = 6.8 Hz, 3H). <sup>13</sup>C {1H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.9, 180.2, 160.2, 160.1, 157.8, 157.7, 138.3, 138.0, 130.8, 130.8, 129.7, 129.6, 114.3, 114.2, 114.1, 114.0, 113.0, 112.7, 112.4, 112.2, 110.3, 110.2, 110.1, 52.0, 51.5, 35.9, 35.5, 34.2, 32.5, 29.9, 29.8, 22.8, 16.9, 15.4, 14.2. <sup>19</sup>F {<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -121.20 (m<sub>j</sub>), -121.24 (m<sub>n</sub>). HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>19</sub>FNO] 236.1451; Found 236.1460.



**6-chloro-3-(1-phenylethyl)indolin-2-one (P**<sub>27</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>27</sub> as a pale yellow solid (0.050 g, 62%). Two isomers ratio 2.32:1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.86 (brs, 1H, m<sub>j</sub>), 8.51 (brs, 1H, m<sub>n</sub>), 7.41 – 7.35 (m, 2H, m<sub>j</sub>), 7.34 – 7.29 (m, 3H, m<sub>j</sub>), 7.22 – 7.16 (m, 1H, m<sub>n</sub>), 7.11 – 7.06 (m, 1H, m<sub>n</sub>), 6.94 (d, *J* = 8.1 Hz, 1H, m<sub>n</sub>), 6.91 (d, *J* = 1.7 Hz, 1H, m<sub>j</sub>), 6.86 (d, *J* = 8.0 Hz, 1H, m<sub>j</sub>), 6.80 (d, *J* = 1.3 Hz, 1H, m<sub>n</sub>), 6.41 (d, *J* = 8.0 Hz, 1H, m<sub>j</sub>), 3.53 – 3.78 (m, 1H, m<sub>j</sub>), 3.76 (d, *J* = 3.7 Hz, 1H, m<sub>j</sub>), 3.64 (d, *J* = 5.8 Hz, 1H, m<sub>n</sub>), 3.53 – 3.44 (m, 1H, m<sub>n</sub>), 1.65 (d, *J* = 7.2 Hz, 3H, m<sub>n</sub>), 1.21 (d, *J* = 7.0 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.5, 179.1, 143.2, 142.8, 142.5, 141.9, 133.8, 128.6, 128.3, 128.0, 127.9, 127.1, 127.0, 126.6, 126.2, 126.1, 125.4, 122.0, 121.9, 110.3, 52.7, 52.2, 41.9, 39.6, 19.4, 13.5. HRMS (ESI-TOF) *m*/*z*: [M + H]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>15</sub>CINO] 272.0842; Found 272.0852.



**5-fluoro-3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P<sub>28</sub>):** The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P<sub>28</sub>** as a pale yellow oil (0.055 g, 60%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  9.20 (s, 1H, m<sub>j</sub>), 8.76 (s, 1H, m<sub>n</sub>), 7.89 – 7.79 (m, 3H), 7.76 – 7.69 (m, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.44 – 7.36 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.93 – 6.75 (m, 3H), 6.68 –

6.61 (m,1H), 6.24 (d, J = 8.2 Hz, 1H), 3.99 – 3.90 (m, 1H, m<sub>j</sub>), 3.88 (d, J = 3.1 Hz, 1H, m<sub>j</sub>), 3.75 (d, J = 5.3 Hz, 1H, m<sub>n</sub>), 3.69 (m, 1H, m<sub>n</sub>), 1.71 (d, J = 7.0 Hz, 3H, m<sub>n</sub>), 1.29 (d, J = 7.0 Hz, 3H, m<sub>j</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.7, 179.2, 159.9, 159.8, 157.5, 157.4, 139.9, 139.2, 138.1, 137.8, 133.4, 133.3, 132.6, 132.5, 129.8, 129.7, 128.7, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 126.9, 126.5, 126.4, 126.2, 126.1, 126.0, 125.9, 125.7, 114.7, 114.6, 114.4, 114.3, 113.3, 113.2, 113.0, 112.9, 110.3, 110.2, 53.3, 53.0, 41.9, 39.7, 19.3, 13.6. <sup>19</sup>F {<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$  -120.70 (m<sub>j</sub>), -120.98 (m<sub>n</sub>). HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for [C<sub>20</sub>H<sub>16</sub>FNONa] 328.1114; Found 328.1128.



**5-bromo-3-(1-(4-chlorophenyl)propyl)indolin-2-one (P**<sub>29</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>29</sub> as a yellow solid (0.068 g, 62%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  8.85 (m<sub>n</sub>), 8.61 (m<sub>j</sub>) (two s, 1H), 7.43 – 7.28 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H, m<sub>n</sub>), 7.12 (d, *J* = 8.4 Hz, 1H, m<sub>j</sub>), 7.07 (d, *J* = 8.4 Hz, 1H, m<sub>n</sub>), 6.86 (d, *J* = 8.4 Hz, 1H, m<sub>j</sub>), 6.68 (m<sub>n</sub>), 6.64 (m<sub>j</sub>) (two d, *J* = 8.3 Hz, 1H), 3.72 (m<sub>j</sub>), 3.67 (m<sub>n</sub>) (two d, *J* = 3.3 Hz, 1H), 3.36 – 3.24 (m, 1H), 2.13 – 1.87 (m, 2H), 0.96 (m<sub>j</sub>), 0.88 (m<sub>n</sub>) (two t, *J* = 7.3 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.3, 178.7, 141.0, 140.7, 138.6, 137.9, 132.8, 132.7, 131.2, 131.0, 130.0, 129.9, 128.6, 128.3, 128.2, 127.8, 114.8, 114.7, 111.4, 111.2, 52.0, 51.4, 48.6, 48.3, 26.3, 23.0, 12.5, 12.4. HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>17</sub>H<sub>16</sub>BrClNO] 364.0104; Found 364.0086.



**3-cyclopentyl-1-phenylindolin-2-one** (**P**<sub>30</sub>):<sup>2</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>30</sub> as a pale yellow oil (0.068 g, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (t, J = 7.8 Hz, 2H), 7.43 – 7.34 (m, 4H), 7.20 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 3.69 (d, J = 5.1 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.00 – 1.87 (m, 1H), 1.85 – 1.77 (m, 1H), 1.70 – 1.53 (m, 5H), 1.46 – 1.36 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  177.1, 144.7, 134.7, 129.7, 128.4, 128.1, 127.8, 126.8, 124.9, 122.6, 109.2, 48.8, 42.6, 29.9, 28.2, 25.2, 25.1.



**3-cyclohexyl-1-methylindolin-2-one** (P<sub>31</sub>):<sup>1</sup> The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>31</sub> as a yellowish brown oil (0.040 g, 58%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.29 (t, J = 6.0 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.36 (d, J = 3.2 Hz, 1H), 3.21 (s, 1H), 2.23 – 2.12 (m, 1H), 1.81 – 1.64 (m, 2H), 1.50 – 1.38 (m, 1H), 1.33 – 1.24 (m, 1H), 1.17 – 1.09 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  177.6, 144.8, 128.2, 127.8, 124.5, 122.2, 107.9, 51.6, 41.1, 30.5, 28.4, 26.8, 26.4, 26.2, 26.1.



**3-cycloheptyl-1-methylindolin-2-one** (P<sub>32</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product P<sub>32</sub> as a pale yellow oil (0.038 g, 52%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 (d, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 3.8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 3.34 (d, *J* = 3.0 Hz, 1H), 3.12 (s, 3H), 2.31 – 2.20 (m, 1H), 1.71 – 1.63 (m, 2H), 1.59 – 1.47 (m, 5H), 1.41 – 1.32 (m, 5H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  177.6, 144.9, 128.3, 127.9, 124.4, 122.2, 107.9, 52.8, 42.4, 32.8, 30.5, 27.9, 27.6, 27.4, 27.1, 26.2. HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>22</sub>NO] 244.1701; Found 244.1693.



**3-cycloheptyl-1-phenylindolin-2-one (P**<sub>33</sub>): The crude product was purified by column chromatography (hexane/EtOAc 8:2 as eluent) to give pure product **P**<sub>33</sub> as a colourless solid (0.064 g, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (t, J = 7.7 Hz, 2H), 7.43 – 7.33 (m, 4H), 7.19 (t, J = 7.7 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.59 (d, J = 3.0 Hz, 1H), 2.48 – 2.34 (m, 1H), 1.87 – 1.76 (m, 2H), 1.66 – 1.58 (m, 5H), 1.51 – 1.40 (m, 5H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  177.0, 144.8, 134.8, 129.7, 128.2, 128.1, 127.7, 126.8, 124.6, 122.7, 109.2, 52.7, 43.0, 32.6, 30.6, 28.0, 27.5, 27.4, 27.1. HRMS (ESI-TOF) *m/z*: [M]<sup>+</sup> Calcd for [C<sub>21</sub>H<sub>23</sub>NO] 305.1780; Found 305.1769.



**3-cyclohexyl-3-hydroxyindolin-2-one (P**<sub>34</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>34</sub> as a white solid (0.057 g, 82%). <sup>1</sup>H NMR (400 MHz, DMSO –  $d_6$ )  $\delta$  10.18 (s, 1H), 7.23 – 7.12 (m, 2H), 6.93 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 5.73 (s, 1H), 1.90 – 1.82 (m, 1H), 1.79 – 1.67 (m, 2H), 1.60 – 1.46 (m, 3H), 1.18 – 1.04 (m, 3H), 1.01 – 0.89 (m, 1H), 0.69 – 0.55 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO –  $d_6$ )  $\delta$  179.6, 142.2, 131.2, 128.7, 124.6, 121.3, 109.3, 78.2, 45.1, 26.1, 26.0, 25.8, 25.6, 25.4. HRMS (ESI-TOF) m/z: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>16</sub>NO] 214.1232; Found 214.1242.



**3-cyclopentyl-3-hydroxyindolin-2-one (P**<sub>35</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>35</sub> as a white solid (0.049 g, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.45 (s, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 3.35 (s, 1H), 2.48 (m, 1H), 1.84 – 1.76 (m, 1H), 1.72 – 1.63 (m, 1H), 1.58 – 1.47 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  181.1, 140.8, 130.2, 129.6, 125.0, 123.0, 110.3, 78.7, 47.6, 26.6, 26.5, 25.6, 25.5. HRMS (ESI-TOF) *m/z*: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>13</sub>H<sub>14</sub>NO] 200.1075; Found 200.1078.



**3-cycloheptyl-3-hydroxyindolin-2-one (P**<sub>36</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>36</sub> as a white solid (0.056 g, 77%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.22 (s, 1H), 7.25 – 7.16 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.79 (s, 1H), 2.13 – 2.05 (m, 1H), 1.94 – 1.86 (m, 1H), 1.76 – 1.68 (m, 1H), 1.58 – 1.27 (m, 10H). <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  179.7, 142.3, 131.0, 128.8, 124.6, 121.4, 109.4, 78.1, 46.0, 28.0, 27.9, 27.4, 26.9, 26.6, 26.5. HRMS (ESI-TOF) *m/z*: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>15</sub>H<sub>18</sub>NO] 228.1388; Found 228.1398.



**3-(9H-fluoren-9-yl)-3-hydroxyindolin-2-one (P**<sub>37</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>37</sub> as a pale brown solid (0.077 g, 82%). <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.45 (s, 1H), 7.98 (d, J = 6.7 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 6.9 Hz,

2H), 7.21 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.68 (s, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1H), 5.79 (d, J = 6.9 Hz, 1H), 4.44 (s, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO- $d_6$ )  $\delta$  178.5, 143.1, 141.7, 141.6, 141.3, 140.6, 129.0, 128.7, 127.8, 127.5, 127.4, 126.6, 126.5, 124.4, 123.4, 120.8, 109.2, 77.5, 52.5. HRMS (ESI-TOF) *m*/*z*: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>21</sub>H<sub>14</sub>NO] 296.1075; Found 296.1060.



**3-hydroxy-3-(1-phenylethyl)indolin-2-one (P38):** The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P38** as a pale brown solid (0.058 g, 76%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  10.19 (s, 1H, m<sub>n</sub>), 9.83 (s, 1H, m<sub>j</sub>), 7.34 (d, *J* = 7.3 Hz, 1H, m<sub>j</sub>), 7.18 (t, *J* = 6.5 Hz, 2H, m<sub>j</sub>), 7.12 (dd, *J* = 13.0, 6.7 Hz, 2H, m<sub>n</sub>), 7.04 (dd, *J* = 13.0, 6.7 Hz, 3H, m<sub>j</sub>), 6.96 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.81 (t, *J* = 7.5 Hz, 1H, m<sub>n</sub>), 6.72 (d, *J* = 6.8 Hz, 2H, m<sub>j</sub>), 6.67 (d, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 6.61 (d, *J* = 7.3 Hz, 1H, m<sub>j</sub>), 6.55 (d, *J* = 7.7 Hz, 1H, m<sub>j</sub>), 6.05 (s, 1H, m<sub>j</sub>), 5.98 (s, 1H, m<sub>n</sub>), 3.29 (q, *J* = 7.1 Hz, 2H, m<sub>n</sub>). <sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, DMSO- *d*<sub>6</sub>)  $\delta$  179.2, 179.0,142.1, 142.0, 140.6, 140.3, 130.2, 129.9, 129.4, 129.0, 128.8, 128.4, 127.4, 127.2, 126.5, 126.4, 125.2, 125.0, 121.0, 120.9, 109.2, 109.1, 78.5, 77.9, 46.4, 45.1, 14.6, 13.9. HRMS (ESI-TOF) *m*/*z*: [M - H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>14</sub>NO] 236.1075; Found 236.1083.



**6-chloro-3-cyclohexyl-3-hydroxyindolin-2-one (P**<sub>39</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>39</sub> as a pale brown solid (0.062 g, 78%). <sup>1</sup>H NMR (400 MHz, DMSO-  $d_6$ )  $\delta$  10.36 (s, 1H), 7.22 (d, J = 7.9 Hz, 1H), 6.99 (d, J = 9.2 Hz, 1H), 6.79 (s, 1H), 5.85 (s, 1H), 1.90 – 1.44 (m, 7H), 1.26 – 0.91 (m, 6H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO- $d_6$ )  $\delta$  179.5, 143.7, 133.0, 130.1, 126.1, 121.0, 109.4, 77.8, 44.9, 26.0, 25.9, 25.8, 25.6, 25.3. HRMS (ESI-TOF) m/z: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>15</sub>ClNO] 248.0842; Found 248.0856.



**5-bromo-3-cyclohexyl-3-hydroxyindolin-2-one (P**<sub>40</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>40</sub> as pale brown solid (0.075 g, 81%). <sup>1</sup>H NMR (400 MHz, DMSO-  $d_6$ )  $\delta$  10.47 (s, 1H), 7.44 – 7.28 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.75 – 1.38 (m, 6H), 1.24 – 1.13 (m, 4H). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO-  $d_6$ )  $\delta$  177.7, 142.4, 131.3, 130.2, 127.0, 112.9, 110.9, 51.0, 29.1, 28.3, 26.1, 25.9, 25.8. HRMS (ESI-TOF) *m*/*z*: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>14</sub>H<sub>15</sub>BrNO] 292.0337; Found 292.0347.



**5-fluoro-3-hydroxy-3-(1-phenylethyl)indolin-2-one (P**<sub>41</sub>): The crude product was purified by column chromatography (hexane/EtOAc 7:3 as eluent) to give pure product **P**<sub>41</sub> as a colourless solid (0.059 g, 78%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) (m<sub>j</sub>: major isomer, m<sub>n</sub>: minor isomer)  $\delta$  10.23 (s, 1H, m<sub>n</sub>), 9.90 (s, 1H, m<sub>j</sub>), 7.24 – 7.16 (m, 1H), 7.15 – 7.04 (m, 4H), 7.03 – 6.90 (m, 1H), 6.82 – 6.75 (m, 2H), 6.65 (dd, *J* = 8.4, 4.4 Hz, 1H, m<sub>n</sub>), 6.55 (dd, *J* = 8.4, 4.4 Hz, 1H, m<sub>j</sub>), 6.46 – 6.41 (m, 1H, m<sub>n</sub>), 6.22 (s, 1H, m<sub>j</sub>), 6.17 (s, 1H, m<sub>n</sub>), 3.31 (q, *J* = 7.1 Hz, 1H, m<sub>n</sub>), 3.22 (q, *J* = 7.1 Hz, 1H, m<sub>j</sub>), 1.47 (d, *J* = 7.2 Hz, 3H, m<sub>j</sub>), 1.18 (d, *J* = 7.2 Hz, 1H, m<sub>n</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  179.2, 158.9, 158.7, 156.5, 156.3, 140.3, 140.0, 138.3, 138.2, 132.3, 132.2, 131.9, 131.8, 129.3, 128.5, 127.6, 127.4, 126.8, 126.7, 115.4, 115.2, 115.1, 115.0, 113.1, 112.9, 112.8, 112.5, 110.0, 109.97, 78.9, 78.2, 46.4, 45.3, 14.4, 13.8. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  -122.12 (m<sub>j</sub>), -122.18 (m<sub>n</sub>). HRMS (ESI-TOF) *m*/*z*: [M – H<sub>2</sub>O]<sup>+</sup> Calcd for [C<sub>16</sub>H<sub>13</sub>FNO] 254.0981; Found 254.0975.

<sup>1</sup>H and <sup>13</sup>C NMR spectrum:



Figure S01. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclohexylindolin-2-one (P<sub>1</sub>).



Figure S02. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclohexylindolin-2-one (P<sub>1</sub>).



Figure S03. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclopentylindolin-2-one (P<sub>2</sub>).



Figure S04. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclopentylindolin-2-one (P<sub>2</sub>).



Figure S05. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cycloheptylindolin-2-one (P<sub>3</sub>).



Figure S06. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cycloheptylindolin-2-one (P<sub>3</sub>).



Figure S07. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclododecylindolin-2-one (P4).



Figure S08. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclododecylindolin-2-one (P<sub>4</sub>).



Figure S09. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-isopropylindolin-2-one (P<sub>5</sub>).



Figure S10.  ${}^{13}C{}^{1}H$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-isopropylindolin-2-one (P<sub>5</sub>).



Figure S11. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(pentan-3-yl)indolin-2-one (P<sub>6</sub>).



Figure S12. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-(pentan-3-yl)indolin-2-one (P<sub>6</sub>).



Figure S13. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(hexan-2-yl)indolin-2-one (P7).



**Figure S14.** <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-(hexan-2-yl)indolin-2-one (**P**<sub>7</sub>).



Figure S15. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(4-phenylbutan-2-yl)indolin-2-one (P<sub>8</sub>).



Figure S16.  ${}^{13}C{}^{1}H$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(4-phenylbutan-2-yl)indolin-2-one (P<sub>8</sub>).


Figure S17. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-butoxypropan-2-yl)indolin-2-one (P<sub>9</sub>).







Figure S19. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-phenylethyl)indolin-2-one (P<sub>10</sub>).





Figure S21. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(p-tolyl)ethyl)indolin-2-one (P<sub>11</sub>).



Figure S22. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(p-tolyl)ethyl)indolin-2-one (P<sub>11</sub>).





Figure S23. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(4-methoxyphenyl)ethyl)indolin-2-one (P<sub>12</sub>).



Figure S24. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(4-methoxyphenyl)ethyl)indolin-2-one (P<sub>12</sub>).





Figure S25. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(3-chlorophenyl)ethyl)indolin-2-one (P<sub>13</sub>).



Figure S26. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(3-chlorophenyl)ethyl)indolin-2-one (P<sub>13</sub>).





Figure S27. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(4-chlorophenyl)ethyl)indolin-2-one (P<sub>14</sub>).



Figure S28. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(4-chlorophenyl)ethyl)indolin-2-one (P<sub>14</sub>).

## $\begin{array}{c} -9.04\\ -8.70\\ -8$



Figure S29. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(4-bromophenyl)ethyl)indolin-2-one (P<sub>15</sub>).



Figure S30. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(4-bromophenyl)ethyl)indolin-2-one (P<sub>15</sub>).

9.928 9.8288 9.8288 9.8288 9.828 9.828 9.828 9.828 9.828 9.828 9.828



Figure S31. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P<sub>16</sub>).



Figure 852.  $C{H}$  NMIR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(P<sub>16</sub>).

9.10 



Figure S33. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(4-chlorophenyl)propyl)indolin-2-one (P<sub>17</sub>).



Figure S34. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(4-chlorophenyl)propyl)indolin-2-one (P<sub>17</sub>).





Figure S35. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-(thiophen-3-yl)ethyl)indolin-2-one (P<sub>18</sub>).



Figure S36. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-(thiophen-3-yl)ethyl)indolin-2-one (P<sub>18</sub>).









**Figure S38.** <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-(1-phenyloctyl)indolin-2-one (**P**<sub>19</sub>).



Figure S40. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(6-methylhept-5-en-2-yl)indolin-2-one (P<sub>20</sub>).



**Figure S41.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(5,9-dimethyl-1-phenyldec-8-en-1-yl)indolin-2-one (**P**<sub>21</sub>).



Figure S42.  ${}^{13}C{}^{1}H$  NMR (101 MHz, CDCl<sub>3</sub>) of 3-(5,9-dimethyl-1-phenyldec-8-en-1-yl)indolin-2-one (P<sub>21</sub>).



Figure S43. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 6-chloro-3-cyclopentylindolin-2-one (P<sub>22</sub>).



Figure S44. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 6-chloro-3-cyclopentylindolin-2-one (P<sub>22</sub>).



Figure S45. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-5-fluoroindolin-2-one (P<sub>23</sub>).



Figure S46. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-5-fluoroindolin-2-one (P<sub>23</sub>).



Figure S47. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-5-fluoroindolin-2-one (P<sub>23</sub>).









Figure S50. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>) of 3-cyclohexyl-5-fluoroindolin-2-one (P<sub>24</sub>).



Figure S51. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 6-chloro-3-(hexan-2-yl)indolin-2-one (P<sub>25</sub>).



Figure S52. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 6-chloro-3-(hexan-2-yl)indolin-2-one (P<sub>25</sub>).



Figure S53. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(hexan-2-yl)indolin-2-one (P<sub>26</sub>).



Figure S54. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(hexan-2-yl)indolin-2-one (P<sub>26</sub>).



Figure S55. <sup>19</sup>F{<sup>1</sup>H} NMR (377 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(hexan-2-yl)indolin-2-one (P<sub>26</sub>).



Figure S56. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 6-chloro-3-(1-phenylethyl)indolin-2-one (P<sub>27</sub>).



Figure S57. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, CDCl<sub>3</sub>) of 6-chloro-3-(1-phenylethyl)indolin-2-one (P<sub>27</sub>).

7,788 7,777 7,788 7,7777 7,7777 7,777 7,777 7,777 7,777 



Figure S58. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P<sub>28</sub>).



Figure S59. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P<sub>28</sub>).





Figure S60.  ${}^{19}F{}^{1}H$  NMR (377 MHz, CDCl<sub>3</sub>) of 5-fluoro-3-(1-(naphthalen-2-yl)ethyl)indolin-2-one (P<sub>28</sub>).



**Figure S61.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 5-bromo-3-(1-(4-chlorophenyl)propyl)indolin-2-one (**P**<sub>29</sub>).



Figure S62.  ${}^{13}C{}^{1}H$  NMR (101 MHz, CDCl<sub>3</sub>) of 5-bromo-3-(1-(4-chlorophenyl)propyl)indolin-2-one (P<sub>29</sub>).



Figure S63. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-1-phenylindolin-2-one (P<sub>30</sub>).



Figure S64. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-1-phenylindolin-2-one (P<sub>30</sub>).



Figure S65. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclohexyl-1-methylindolin-2-one (P<sub>31</sub>).



Figure S66. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclohexyl-1-methylindolin-2-one (P<sub>31</sub>).



Figure S67. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cycloheptyl-1-methylindolin-2-one (P<sub>32</sub>) ('\*' is H-grease).



Figure S68. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cycloheptyl-1-methylindolin-2-one (P<sub>32</sub>).



**Figure S69.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cycloheptyl-1-phenylindolin-2-one (**P**<sub>33</sub>) ('\*' is H-grease).



Figure S70. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cycloheptyl-1-phenylindolin-2-one (P<sub>33</sub>).



Figure S71. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) of 3-cyclohexyl-3-hydroxyindolin-2-one (P<sub>34</sub>).



Figure S72. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO- $d_6$ ) of 3-cyclohexyl-3-hydroxyindolin-2-one (P<sub>34</sub>).



**Figure S73.** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-3-hydroxyindolin-2-one (**P**<sub>35</sub>) (\*\*' is H-grease).



Figure S74. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) of 3-cyclopentyl-3-hydroxyindolin-2-one (P<sub>35</sub>).



Figure S75. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) of 3-cycloheptyl-3-hydroxyindolin-2-one (P<sub>36</sub>).



Figure S76. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, DMSO-*d*<sub>6</sub>) of 3-cycloheptyl-3-hydroxyindolin-2-one (**P**<sub>36</sub>).



Figure S77. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ) of 3-(9H-fluoren-9-yl)-3-hydroxyindolin-2-one (P<sub>37</sub>).



Figure S78. <sup>13</sup>C $\{^{1}H\}$  NMR (101 MHz, DMSO-*d*<sub>6</sub>) of 3-(9H-fluoren-9-yl)-3-hydroxyindolin-2-one (**P**<sub>37</sub>).



Figure S79. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ) of 3-hydroxy-3-(1-phenylethyl)indolin-2-one (P<sub>38</sub>).



Figure S80. <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, DMSO- $d_6$ ) of 3-hydroxy-3-(1-phenylethyl)indolin-2-one (P<sub>38</sub>).



Figure S81. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ) of 6-chloro-3-cyclohexyl-3-hydroxyindolin-2-one (P<sub>39</sub>).



S69



Figure S83. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ) of 5-bromo-3-cyclohexyl-3-hydroxyindolin-2-one (P<sub>40</sub>).



Figure S84.  ${}^{13}C{}^{1}H$  NMR (101 MHz, DMSO- $d_6$ ) of 5-bromo-3-cyclohexyl-3-hydroxyindolin-2-one (P40).



Figure S85. <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ) of 5-fluoro-3-hydroxy-3-(1-phenylethyl)indolin-2-one (P<sub>41</sub>).



Figure S86.  ${}^{13}C{}^{1}H$  NMR (101 MHz, DMSO- $d_6$ ) of 5-fluoro-3-hydroxy-3-(1-phenylethyl)indolin-2-one (P<sub>41</sub>).



Figure S87.  ${}^{19}F{}^{1}H$  NMR (377 MHz, DMSO- $d_6$ ) of 5-fluoro-3-hydroxy-3-(1-phenylethyl)indolin-2-one (P<sub>41</sub>).
#### Mechanistic studies for $C(\alpha)$ -alkylation of oxindole:

#### (a) Catalyst Poisoning test:



In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), cyclohexanol (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10- phenanthroline (0.054 g, 10 mol%), NaO*t*Bu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. To this reaction mixture,  $PMe_3/CS_2$  (5 mol%) was added. Then the reaction mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature upon completion and concentrated in vacuum. The purification of product was done by column chromatography using hexane/EtOAc as eluent. The isolation of the expected product **P**<sub>1</sub> in good yield suggested the homogeneous behaviour of the catalyst.

Ta	ble	<b>S5</b> :	Produc	t %vield	upon	varying	of	cataly	st r	ooisoners:
				•				•		

Entry	Catalyst Poisoners (3 mol%)	Yields
1	PMe <sub>3</sub>	(0.051 g, 80%)
2	$CS_2$	(0.053 g, 83%)

#### (b) Radical scavenging test:



In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), cyclohexanol (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10- phenanthroline (0.054 g, 10 mol%), NaO*t*Bu (0.044 g, 0.45 mmol), radical scavenger (1 equiv.) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature upon completion and concentrated in vacuum. The purification of product was done by column chromatography using hexane/EtOAc as eluent. The isolation of the expected product in **P**<sub>1</sub> high yields (listed below) suggested a mechanistic path which does not follow radical pathway.

Entry	Radical Scavenger (1 equiv)	Yields
1	TEMPO	(0.052 g, 82%)
2	BHT	(0.048 g, 75%)

#### Table S6: Product %yield upon varying of radical quencher:

#### (c) Dehydrogenation of benzyl alcohol: Dihydrogen detection



To an oven-dried 10 mL resealable vial,  $FeCl_2$  (0.1 mmol, 1 equiv.), 1,10phenanthroline (0.4 mmol, 2 equiv.), cyclohexanol (2.0 mmol, 20 equiv.), NaO*t*Bu (4.0 mmol, 4 equivalent), anisole (3 mL) were added inside the glove box. The vial was sealed and the reaction mixture was heated at 150 °C for 16 h. Then, the gaseous phase inside the vial was analysed on GC (TCD detector) which showed the formation of dihydrogen.



Figure S88. GC chromatogram of hydrogen gas evolved in the dehydrogenation of cyclohexanol.

# (d) C=C bond formation by Knoevenagel condensation: Involvement of aldehyde intermediate



**Procedure A**: In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), acetophenone (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10-phenanthroline (0.054 g, 10 mol%), NaO*t*Bu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature upon completion and concentrated in vacuum. The residue was purified by column chromatography using hexane/EtOAc as an eluent to afford pure product 3-(1-phenylethylidene)indolin-2-one (**M**<sub>1</sub>) as a yellow oil (0.059 g, 84%). The desired product **M**<sub>1</sub> was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies.

**Procedure B:** In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), acetophenone (0.06 g, 0.6 mmol), NaO*t*Bu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature upon completion and concentrated in vacuum. The residue was purified by column chromatography using hexane/EtOAc as an eluent to afford pure product 3-(1-phenylethylidene)indolin-2-one (**M**<sub>1</sub>) as a yellow oil (0.053 g, 75%). The desired product **M**<sub>1</sub> was characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies.<sup>4</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.99 (s, 1H), 7.55 – 7.46 (m, 3H), 7.33 (d, *J* = 6.5 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.64 (t, *J* = 7.7 Hz, 1H), 6.17 (d, *J* = 7.8 Hz, 1H), 2.84 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 155.6, 143.1, 139.9, 129.3, 128.5, 128.2, 126.6, 124.0, 123.5, 123.2, 121.4, 109.5, 23.0.



Figure S89. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of 3-(1-phenylethylidene)indolin-2-one (M<sub>1</sub>).



# (e) Hydrogenation of α,β-unsaturated compound: Involvement of α,β-unsaturated intermediate



In a dried pressure tube fitted with a magnetic stir bar, a mixture of  $M_1$  (0.07 g, 0.30 mmol), cyclohexanol (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10-phenanthroline (0.054 g, 10 mol%), NaO*t*Bu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was stirred at 150 °C for 16 h. The reaction mixture was cooled down to room temperature upon completion and concentrated in vacuum. The residue was purified by column chromatography using hexane/EtOAc as an eluent to afford pure product **P**<sub>10</sub> as a colourless oil (0.54 g, 76%).

#### Mechanistic studies for $C(\alpha)$ -alkylation and C-H hydroxylation of oxindole:

(a) One-pot alkylation-hydroxylation of 2-oxindole under inert and aerobic condition:



**Path-A**: In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), cyclohexanol (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10- phenanthroline (0.054 g, 10 mol%), NaOtBu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. After cooling down to room temperature and the reaction mixture was stirred under nitrogen for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 8.5:1.5) as eluent to give the desired product. The successful isolation of product **P**<sub>1</sub> in a high yield implies that under the nitrogen atmosphere, there is an absence of any hydroxylated product.

**Path-B**: In a dried pressure tube fitted with a magnetic stir bar, a mixture of 2-oxindole (0.040 g, 0.30 mmol), cyclohexanol (0.06 g, 0.6 mmol), FeCl<sub>2</sub> (0.020 g, 5 mol%), 1,10- phenanthroline (0.054 g, 10 mol%), NaOtBu (0.044 g, 0.45 mmol) and anisole (1 mL) was added under a nitrogen atmosphere. Then the reaction mixture was heated at 150 °C in a preheated oil bath for 16 h. After cooling down to room temperature and the reaction mixture was stirred under nitrogen for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 7:3) as eluent to give the desired product. The successful isolation of the anticipated product  $P_{30}$  in a favorable yield indicates that in the presence of air, hydroxylated products are likely to form.

(b) Hydroxylation of 3-alkyl-2-oxindole under inert and aerobic condition:



**Path-A**: In a dried pressure tube fitted with a magnetic stir bar, a mixture of 3cyclohexylindolin-2-one ( $P_1$ ) (0.043 g, 0.20 mmol), NaO*t*Bu (0.020 g, 0.2 mmol) and anisole (1 mL) was added. Then the reaction mixture was stirred under nitrogen at room temperature for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 8.5:1.5) as eluent to give the desired product. The successful isolation of product  $P_1$  in a high yield implies that under the nitrogen atmosphere, there is an absence of any hydroxylated product.

**Path-B**: In a dried pressure tube fitted with a magnetic stir bar, a mixture of 3cyclohexylindolin-2-one ( $P_1$ ) (0.043 g, 0.20 mmol), NaOtBu (0.020 g, 0.2 mmol) and anisole (1 mL) was added. Then the reaction mixture was stirred under oxygen (using oxygen ballon) at room temperature for 16 h. Finally, concentrated by removing the solvent under vacuum, and the residue was purified by column chromatography with hexane/ethyl acetate (hexane/ethyl acetate = 7:3) as eluent to give the desired product. The successful isolation of the desired product  $P_{30}$  in a favorable yield indicates that in the presence of oxygen, this is a base catalyzed hydroxylation process.

#### (c) Radical scavenging test:



In a dried pressure tube fitted with a magnetic stir bar, a mixture of 3-cyclohexylindolin-2-one ( $\mathbf{P}_1$ ) (0.043 g, 0.20 mmol), NaOtBu (0.020 g, 0.2 mmol), radical scavenger (1 equiv.) and anisole (1 mL) was added under aerobic condition. Then the reaction mixture was stirred at room temperature for 16 h. Upon completion of the reaction, the reaction mixture was concentrated in vacuum. The purification of product was done by column chromatography using hexane/EtOAc as eluent. The isolation of the expected product in  $\mathbf{P}_{30}$  high yields (listed below) suggested a mechanistic path which does not follow radical pathway.

T٤	able	e S7:	: Pro	duct	%yi	eld	upon	varying	of	radical	quenche	er:
					•							

Entry	Radical Scavenger (1 equiv)	Yields
1	TEMPO	(0.052 g, 82%)
2	BHT	(0.048 g, 80%)

### X-ray structure determination

Crystallographic data and structure determinations details are compiled in Table S7. The crystals were obtained by slow evaporation of P5, P18 and P34 in DCM at r.t. The crystals were coated with silicon oil on a glass slide and a suitable single crystal was mounted on a glass fibre. Crystal data were collected with a Rigaku Oxford diffractometer and with an INCOATEC micro source (Cu-K $\alpha$  radiation,  $\lambda = 1.54184$  Å, multilayer optics) at 100 K and 293 K respectively. The structure was determined using direct methods employed in ShelXT,<sup>5</sup> OleX,<sup>6</sup> and refinement was carried out using least-square minimization implemented in ShelXL.<sup>7</sup> All nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom positions were fixed geometrically in idealized positions and were refined using a riding model. CCDC 2354252 (for P5), CCDC 2354253 (for P18) and CCDC 2354254 (for P34) contains the supplementary crystallographic data for this paper.

	<b>P</b> 5	<b>P</b> 18	<b>P</b> 34
Empirical formula	$C_{11}H_{13}NO$	C <sub>13</sub> H <sub>14</sub> ClNO	$C_{32}H_{30}N_2O_4$
CCDC	2354252	2354253	2354254
Formula weight (g mol <sup>-1</sup> )	175.22	235.70	506.58
Temperature	297.15	100.01(10)	100.04(10)
Wavelength	1.54184	1.54184	1.54184
Crystal system	monoclinic	monoclinic	monoclinic
Space group	<i>I2/a</i>	$P2_l/n$	Ia
<i>a</i> (Å)	21.3851(7)	10.9223(2)	7.2634(2)
<i>b</i> (Å)	5.29270(10)	5.97560(10)	24.2647(7)
<i>c</i> (Å)	18.3278(6)	18.2274(4)	14.6681(4)
$\alpha$ (deg)	90	90	90
$\beta$ (deg)	111.340(4)	103.405(2)	95.182(2)
$\gamma$ (deg)	90	90	90
volume (Å <sup>3</sup> )	1932.20(11)	1157.24(4)	2574.60(12)
Ζ	8	4	4
$\rho_{\rm calc}  ({ m g/cm^3})$	1.205	1.353	1.307
$\mu (\mathrm{mm}^{-1})$	0.610	2.729	0.693
<i>F</i> (000)	752.0	496.0	1072.0
Crystal Size	$0.2 \times 0.2 \times 0.1 \text{ mm}^3$	$0.2 \times 0.2 \times 0.1 \text{ mm}^3$	$0.2 \times 0.2 \times 0.1 \text{ mm}^3$
$2\theta$ Range (deg)	8.878 - 150.942	8.654 - 150.748	7.064 - 156.516
Index Ranges	$-26 \le h \le 26, -6 \le k \le$	$-13 \le h \le 13, -7 \le k$	$-9 \le h \le 4, -$
	6, $-23 \le 1 \le 22$	$\leq 6, -22 \leq l \leq 22$	$25 \le k \le 30, -18 \le 1$
			$\leq 18$
Reflections collected	10008	9232	10691
Independent reflections	1973(0.0364)	2344 (0.0465)	3351 (0.0592)
(R <sub>int</sub> )			
Completeness to theta = $25.07^{\circ}$	99.7	99.9	99.96
Refinement method	Full-matrix least-	Full-matrix least-	Full-matrix least-
	squares on F <sup>2</sup>	squares on F <sup>2</sup>	squares on F <sup>2</sup>

Table S8. Crystallographic Data and Refinement Parameters for P5 and P63.

Data/Restraints/paramete	1973/0/120	2344/0/145	3351/2/347
rs			
Goodness-of-fit on F2	1.055	1.068	1.074
Final <i>R</i> indices $[I \ge 2\sigma(I)]$	$R_1 = 0.0403, wR_2 =$	$R_1 = 0.0364, wR_2 =$	$R_1 = 0.0436, wR_2 =$
	0.1097	0.0998	0.1102
<i>R</i> indices (all data)	$R_1 = 0.0473, wR_2 =$	$R_1 = 0.0386, wR_2 =$	$R_1 = 0.0485$ , wR <sub>2</sub> =
	0.1157	0.1017	0.1155
Largest diff. peak/hole (e	0.12/-0.21	0.46/-0.37	0.22/-0.21
Å <sup>-3</sup> )			

Figure S91. Molecular Structure of complex P5 showing 50% Ellipsoids



Figure S92. Molecular Structure of complex P<sub>18</sub> showing 50% Ellipsoids



Figure S93. Molecular Structure of complex P<sub>34</sub> showing 50% Ellipsoids



Supplementary Informa	tion: App	endix 2		Summary of	f Zero Pass	Metrics Toolkit											
Yield, conversion, select	ivity, AE, I	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06			anisole	10.00	1.00	9.95			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	2.00	100.15	0.02	1,10-Phen	0.18												
NaOtBu	1.41	96.10	0.01								0.00						0.00
Total	4.74	329.40			0.24		0.00				9.95		0.00				22.55
								Flag									
molecular	weight	of product	× 10	0		Yield	90.0	90.0									
$AE = \frac{1}{total molecua}$	lr weigh	t of reacto	nts × 10	U		Conversion	100.0	100.0									
						Selectivity	90.0	90.0					mass	mw	mol		
$RME = \frac{mass of iso}{mass of iso}$	lated pr	oduct × 10	0			AE	65.4					Product	1.937	215.296	0.0089969		
total mass	of react	tants ^ 10	•			RME	40.8						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solven	ts (Red fl	ag for any of	the follow	ing)			l in the second s	list Highly Hazardou	is Solvents	Below							
Et <sub>2</sub> O, E	Benzene, C	Cl <sub>4</sub> , chlorofor	m, DCE, nit	romethane, C	S <sub>2</sub> , HMPA			Non	e								
Health and Safety (Zero	Pass)																
Health & safety (Red flag	g for any o	of the followi	ng)			l	ist substa	nces plus the red fla	agged H-coc	les below							
Highly explosive H200, H201, H202, H203						None											
Explosive thermal runaway H240					None												
Fatally toxic H300, H310, H330						None											
Mutagenic H350					None												
Repro-	Repro-toxic H360						None										
Serious environmental implications				H420				None									

# Table S9. Method A (anisole, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 16 h): Zero Pass CHEM21 green metrics toolkit

upplementary Information: Appendix 2				Summary of	f Zero Pass	Metrics Toolkit											
Yield, conversion, select	ivity, AE, I	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06						0.00			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	4.01	100.15	0.04	1,10-Phen	0.18												
NaOtBu	1.41	96.10	0.01								0.00						0.00
Total	6.75	329.40			0.24		0.00				0.00		0.00				22.55
								Flag									
ME molecular	weight	of product	v 10	0		Yield	90.0	90.0									
$AE = \frac{1}{total \ moleculr \ weight \ of \ reactants} \times 100$						Conversion	100.0	100.0									
						Selectivity	90.0	90.0					mass	mw	mol		
$RME = \frac{mass of iso}{mass of iso}$	lated pr	$\frac{oduct}{x} \times 10$	0			AE	65.4					Product	1.937	215.296	0.0089969		
total mass	of react	tants				RME	28.7						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solven	its (Red fl	ag for any of	the follow	ing)				List Highly Hazardou	is Solvents	Below							
Et <sub>2</sub> O, E	Benzene, C	Cl <sub>4</sub> , chlorofor	rm, DCE, nit	romethane, C	S <sub>2</sub> , HMPA			Nor	ie								
Health and Safety (Zero	Pass)																
Health & safety (Red flag	g for any o	of the follow	ing)				.ist substa	nces plus the red fl	agged H-coc	les below							
Highly explosive H200, H201, H202, H203								None									
Explosive thermal runaway H240								None									
Fatally toxic H300, H310, H330								None									
Mutagenic H350							None										
Repro-toxic H360						None											
Serious environmental implications H420								None									

# Table S10. Method B (neat, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 8 h): Zero Pass CHEM21 green metrics toolkit

Supplementary Information: Appendix 2			Summary of	f Zero Pass	Metrics Toolkit												
Yield, conversion, select	ivity, AE,	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06			Toluene	10.00	1.00	9.95			Ethyl acetate	20.00	0.90	18.04
Cyclohexanol	2.00	100.15	0.02	1,10-Phen	0.18												
NaOtBu	1.41	96.10	0.01								0.00						0.00
Total	4.74	329.40			0.24		0.00				9.95		0.00				18.04
								Flag									
molecular	0		Yield	91.0	91.0												
AE = total molecua	lr weigh	nt of reacto	ints ^ 10	0		Conversion	100.0	100.0									
						Selectivity	91.0	91.0					mass	mw	mol		
$RME = \frac{mass of iso}{mass of iso}$	lated pr	$\frac{oduct}{x} \times 10$	0			AE	65.4					Product	1.959	215.296	0.0090991		
total mass	of react	tants	-			RME	41.3						mass				
												Unreacted limiting					
Solvents (Zero Pass)												reactant	0.000				
Highly hazardous solver	nts (Red f	lag for any of	the follow	ving)				List Highly Hazardou	is Solvents	Below							
Et <sub>2</sub> O, I	Benzene, C	CCl <sub>4</sub> , chlorofor	m, DCE, nit	romethane, C	S <sub>2</sub> , HMPA			Nor	e								
Health and Safety (Zero	Pass)																
Health & safety (Red fla	g for any o	of the follow	ing)				.ist substa	nces plus the red fl	agged H-coc	les below							
Highly explosive H200, H201, H202, H203								None									
Explosive thermal runaway H240							None										
Fatally toxic H300, H310, H330								None									
Mutagenic H350							None										
Repro-toxic H360								None									
Serious environme	cations		H420				None										

# Table S11. Method C (toluene, [Co] 10 mol%, KOH 2 eq, 150 °C, 16 h): Zero Pass CHEM21 green metrics toolkit

upplementary Information: Appendix 2			Summary of	Zero Pass	Metrics Toolkit												
Yield, conversion, select	ivity, AE, I	RME															
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06			anisole	10.00	1.00	9.95			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	2.00	100.15	0.02	1,10-Phen	0.18												
NaOtBu	1.41	96.10	0.01								0.00						0.00
Oxygen	0.16	32.00	0.01								0.00						0.00
Total	4.90	361.40			0.24		0.00				9.95		0.00				22.55
								Flag									
$AE = \frac{molecular weight of produ}{total molecular weight of read}$		of product	$\frac{t}{10}$ × 10	0		Yield	90.0	90.0									
$AL = \frac{1}{total \ molecualr \ weight \ of \ read}$		t of reacto	ants 🗍 🔭			Conversion	100.0	100.0									
mass of isolated modulet					Selectivity	90.0	90.0					mass	mw	mol			
$RME = \frac{mass of iso}{tatal mass}$	latea pr	$\frac{oauct}{10} \times 10$	00			AE	64.0					Product	2.081	231.295	0.0089972		
totai mass	oj reaci	ants				RME	42.4						mass				
Solvents (Zero Pass)												Unreacted limiting	0.000				
Highly bazardous solven	te (Rod fl	ag for any of	the follow	ing)				ist Highly Hazarda	c Solvente P	lolow		Teactailt	0.000				
Ft. O. F	Renzene (	Cl chlorofo	rm DCF nit	romethane (	S. HMPA			List Highly Hazaluot		Selow							
Lt <sub>2</sub> 0, L	Jenzene, e		ini, DCL, int	i officiliarie, e	5 <sub>2</sub> , 111011 A			NOI	C								
Health and Safety (Zero	Pass)																
Health & safety (Red flag	for any o	of the follow	ing)				ist substa	nces plus the red fl	agged H-cod	es below							
Highly explosive H200, H201, H202, H203							None	00									
Explosive thermal runaway H240							None										
Fatally toxic H300, H310, H330							None										
Mutagenic H350							None										
Repro-toxic				H360				None									
Serious environmental implications				H420				None									

# Table S12. Method D (anisole, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 32 h): Zero Pass CHEM21 green metrics toolkit

Supplementary Information: Appendix 2				Summary o	f First Pass	Metrics Toolki	t											
Yield. AE. RME. MI/PMI a	nd OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06				anisole	10.00	1.00	9.95			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	2.00	100.15	0.02	1,10-Phen	0.18													
NaOtBu	1.41	96.10	0.01									0.00						0.00
Total	4.74	329.40			0.24		0.00	)				9.95		0.00				22.55
							NR 1.1			Flag								
							Yield		90.0	90.0								
							Conversion		100.0	100.0					Mass	N/1\A/	Mol	
PME - mass of isola	ted product	100					AF		50.0 65.4	90.0			Prod	uct	1 937	215 296	0.01	
total mass of	reactants ^						RME		40.8	OF	62.5	1			mass	210.200	0.01	_
													Unreacted	limiting				
AE = molecular	weight of pr	oduct ×	100				PMI total		19.4				react	ant	0.00			
total molecua	lr weight of 1	reactants					PMI Reacti	on	7.7					1				
							PMI reacta	nts.										
mass intensity $=$ $\frac{t_0}{-}$	otal mass in	a process or	process st	tep			reagents, c	atlyst	2.6									
	ma	iss of produ	ct				PMI reactio											
$OE = \frac{RME}{4E} \times 100$							solvents		5.1									
							PMI Work	n	11.6									
							PMI Work	10 10	11.0									
							chemical	ιp	0.0									
							PMI worku	n										
							solvents	P	11.6									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, EtOH	l, nBuOH, Ad	Oipr, AcOnBu	u, PhOMe, N	/leOH, tBuOH,												
		BnOH, ethy	lene glycol,	acetone, ME	(, MIBK, <b>AcC</b>	DEt, sulfolane		PhOM	le									
Problematic solvents: (ad if substitution does advantages)	cceptable only not offer	DMSO, cy AcOMe, THF, <b>cyclohexa</b>	vclohexanon , heptane, M ne, chlorobe	e, DMPU, Acc le-cyclohexar nzene, formi	DH, Ac2O, A ne, toluene, c acid, pyrid	cetonitrile, xylene, MTBE, ine, Me-THF		none	2									
Hazardous solvents: The have significant health a concerns.	ese solvents ind/or safety	dioxane, pe	entane, TEA DMA, NMP	, diisopropyl e , methoxyeth	ether, DME, anol, hexan	, DCM, DMF, e		none	2									
Highly hazardous solvents which are agre solvents which are agre used, even in scre	ighly hazardous solvents: The vents which are agreed not to be used, even in screening				ne, CS <sub>2</sub> , HMPA		none	2										
Catalyst/enzyme (First Pa	ass)	takos place	Groop Elas	Tick		Eacilar	acovoru of a	atalyst /	0071/000	Groop Flag	Tick							
Catalyst or enzyme used, or reaction takes place Green Flag X Faci				Facile r	ecovery of c	atalyst/	enzyme	Green Flag										
Use of stoichiometric quantities of reagents Flag					cataly	/st/enzyme	not reco	vered	Amber Flag	х								
Use of reagents in excess			Red Flag															

# Table S13. Method A (anisole, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 16 h): First Pass CHEM21 green metrics toolkit

Critical elements													_								
Supply remaining	Flag colour	Note element	1 H	]	Remainin until deple known re	years tion of serves						He									
5-50 years	Red Flag		3	Be	(based on curr extracti	ent rate of on)			5 6 B C	7 8 N	n <sup>°</sup> F	10 Ne									
50-500 years	Amber Flag		6.941 11 Na	9.012182 12 Mg	5-50 ye 50-100 y 100-500	ars ears /ears			10.811 12.0107 13 14 AI Si	14.00674 15.9 15 16 P	994 18.99	140 20.1797 18 Ar									
+500 years	Green Flag	Fe	22.9897 19 <b>K</b>	7 24.3050 20 21 Ca Sc	22 23 Ti V	24 25 26 Cr Mn Fe	27 28 Co Ni	29 30 Cu Zn	26.98153 28.0855 31 27 Ga Ge	39.97376 323 33 34 As	66 35.45 25 6e B	7 19.948	+								
			39.0983 37	40.078 44.95591 38 39	47.867 50.9415 40 41	51.9961 54.93804 55.845 42 43 44	58.93320 58.6934 45 46	63.546 65.39 47 44		74.92160 78.9 51 52	6 79.90 53	83.80									
			<b>Rb</b> 85.4678	Sr Y 87.62 88.9085	Zr Nb 91.224 92.90638	Mo Tc Ru 95.54 (98) 101.07	Rh Pd 102.9055 106.42	Ag Cd	In Sn 114818 118.760	Sb 127	e   60 126.9	Xe 131.29									
			55 Cs 112,905	56 57 <b>Ba La*</b> 4 137.327 138.9055	72 73 Hf Ta 178.49 180.9479	74 75 76 W Re Os 181.84 186.207 191.23	i Ir Pt 192.217 195.078	79 80 Au Hg 196.9665 200.59	51 82 TI Pb 204.3833 220.2	83 84 Bi F	o A	86 Rn (222)									
			87 Fr	88 89 Ra Ac‡	104 105 Rf Db	106 107 108 Sg Bh Hs	109 110 Mt Ds	111 112 Ra Uut	113 114 D Uut Uug	115 116 Uup	v UL	s Uuo									
			(223)	226.025 (227)	(257) (260)	(263) (262) (265)	(266) (271)	(272) (285)	(284) (285)	(288) (29	)										
					58 59	60 61	Q (3)		66 67	68 69	70	71									
				Lanthanide	ES* CE 140.9077 144	24 (145) 150.36	151.964 157.25 1	GG ID 58.9253 158.9253	162.50 164.9303	167.36 168.	1042 173.0	174.967									
				Actinide	s‡ Th 1	Pa U Np	Pu Am	Cm Bk	Cf Es	Fm N	d No	Lr									
					232.0381 231	0289 238.0289 (237)	(244) (243) (	247) (247)	(251) (252)	(257) (258	(259)	(262)									
Energy (First Pass)			Tick								Tick										
Reaction run between	0 to 70°C	Green Flag				Reaction run a	at reflux		Red Flag												
Reaction run between -20 140°C	) to 0 or 70 to	Amber Flag	x		Reaction r	un 5°C or more	e below the s	olvent													
Reaction run below -20 or	r above 140°C	Red Flag				boiling p	oint		areen Flag		x										
Batch/flow	Gree	n Flag	Tick		Work Up	quenchi	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchi filtratio	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag Z	Tick X		Work Up	quenchi filtratic centrifuga	ing on ation		Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up	quenchi filtratic centrifuga crystallisa perature distilla	ing on ation ation ation/evapora	tion/	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C	ing on ation ation ation/evapora C at atmosphe	tion/ ric	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C cchange, quenc	ing on ation ation ation/evapora C at atmosphe ching into aqu	tion/ ric Jeous	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag Pr Flag S	Tick X		Work Up	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen solven solven pmatography/i	ing on ation ation/evapora Cat atmosphe ching into aqu it ion exchange	ition/ ric Jeous	Green Flag Amber Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag ;	Tick X		Work Up Low temp sublim solvent ex	quenchi filtratic centrifuga crystallisa eerature distilla ation (< 140 °C exchange, quen solven pomatography/i high tempe	ing on ation tition ation/evapora 2 at atmosphe ching into aqu it ion exchange erature	tion/ ric Jeous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag ;	Tick X		Work Up	quenchi filtratic centrifuga crystallisa berature distilika ation (< 140 °C kchange, quen solven bomatography/i high tempe nultiple recrys	ing an ation ation/evapora 2 at atmosphe ching into aqu t ion exchange erature tallisation	tion/ ric reous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation tion cat atmosphe ching into aqu ti ion exchange erature tallisation	tion/ ric leous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation ation cat atmosphe ching into aqu it ion exchange erature tallisation List subst	tion/ ric Jeous F	Green Flag Amber Flag Red Flag d H-codes	Chrom	List atogra	phy ces anc	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag : Flag :	Tick X Amb	er Flag	Work Up	quenchi filtratic centrifugg crystallisa erature distili ation (< 140 °C kchange, quen solven solven matography/i high tempe nultiple recrys	ing on attion attion attion attion attion attion attion/evaporation/evaporation/evaporation attion/evaporation atting into aquit tallisation atting a	tion/ ric Jeous	Green Flag Amber Flag Red Flag d H-codes	Chrom	List atogra	phy ces and	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety Highly explosive	Greer Ambe	n Flag : er Flag : Flag : Flag : H202, H203	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven ponatography/i high tempe multiple recrys	ng on attion tition C at atmosphe ching into aqu t t ion exchange rature tallisation List subst	tion/ ric Jeous A	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es	List su 2-oxind Cyclohex	bstances a ole: H302, anol: H30	and H-c , H312, )2, H311	codes H332,; 2, H315;			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway	Greer Ambe Red H200, H201, H230, H2	n Flag : er Flag : Flag : H202, H203 : 240, H250 :	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga cerystalias perature distilla ation (< 140 <sup>°</sup> C cchange, quenn solven pomatography/i high tempe multiple recrys een Flag do r amber codes present green flag	ng on tition tition attorn/evapora. at atmospheric at atmospheric at atmospheric at atmospheric at atmospheric attore attallisation bit bits subst	ition/ ric leous /	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es Bu:	List su 2-oxind Cyclohex H332,H3 H251	ole: H302, anol: H30 19, H335 1, H314, H.	and H-c , H312, ,2, H31: NaOtB 335, H3				
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic	Greer Ambe Red H200, H201, H230, H2 H300, H3	n Flag : er Flag : Flag : H202, H203 : 240, H250 : 310, H330 :	Tick X Amt H205, H H301, H	er Flag 220, H224 241 311, H331,	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/i high tempe multiple recrys ten Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous c ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	atogra bstan exano	phy ces and 1: H412 3351	d H-code 2; NaOte	es 0	List su 2-oxind Cyclohex H332, H3 H255 Ethylace	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22!	and H-cc , H312, , 2, H31: NaOtB 335, H312	H332,; 2, H315; u: H225, 336, 9, H336.			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity	Creer Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H340, H350,	n Flag 2 er Flag 2 Flag 4 H202, H203 240, H250 310, H330 H360, H370, H320	Tick X Amb H205, H H301, H H301, H H341, H	er Flag 220, H224 241 311, H331, 351, H331, 351, H361, 1 H373	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/ri high tempe multiple recrys en Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	List atogra bbstan exano	phy ces and	d H-codi	es l	List su 2-oxind Cyclohex H332, H3 H255 Ethylace Anisole: I	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H215	and H-c , H312, ,2, H311 NaOtBi 335, H319 365; FeCl 219-1	codes H332,; 2, H315; u: H225, 336, ), H336. I <sub>2</sub> : H290,			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental immireations	Greer Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	n Flag : r Flag : Flag : , H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 :	Tick X Amb H205, H H301, H H341, H H341, H H341, H H341, H H341, H	er Flag 2220, H224 241 311, H331, 351, H361, 1, H373 , H412	Work Up	quenchi filtratic centrifuge crystallisa erature distilla ation (< 140 °C cchange, quen solven omatography/i high tempe multiple recrys een Flag d or amber codes present green flag	ng on	ition/ ric reous ances and	Green Flag Amber Flag Red Flag I H-codes ne: H410	Chromotoria Chromotoria	List atogra bbstan	phy ces and 1: H412 1351	d H-cod	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: I H30: Pho	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H226, H33 2, H315, H enanthroli	and H-o , H312, 12, H312, NaOtBia 335, H3 5, H319 36; FeCl 318; 1, 1; h3: H31	H332,; ; 2, H315; ; 336, 1, H336, 2; H290, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	<b>Gree</b> Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410,	n Flag Flag H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420	Tick X Amb H205, H H301, H H341, H H34	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412	Work Up	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys do r amber codes present green flag	ng on stion stion C at atmosphe ching into aqui t con exchange rrature tallisation List subst	ances and	Green Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bbstan	phy ces and i: H4122	l l H-code	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: H300 Pho	bstances a ole: H302, anol: H30 19, H335 1, H314, H H314, H H226, H33 2, H315, H enanthroli	and H-c 12, H312, 1335, H313 1335, H313 1335, H319 1336; FeCl 1318; 1, 1, ine: H30	H332,; , H315; , H315; , H336, , H336, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	Greet           Ambe           Red           H200, H201,           H230, H2           H300, H3           H340, H350, H3           H400, H410,           H3           S of environn	n Flag r Flag Flag , H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420 mental concern	Тіск X Атиб H205, H H301, H H301, H H301, H H301, H	er Flag 220, H224 241 251, H361, 1, H373 1, H412	Work Up	quenchi filtratic cervifuga cervifuga cervifuga erature distilla ation (< 140 °C kcchange, quen solven omatography/i high tempe multiple recrys een Flag do ramber codes present green flag	ng on attion attion attion/evapora. at atmospheric at atmospheric at atmospheric attino attion/evapora. Attino attion exchange arature attilisation attice attilisation attive attilisation atttilisation attilisation attilisation attilisation atttil	ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su Cycloh	List atogra bstan exano	phy ces and i: H4122	d H-cod 2; NaOtB	es l	List su 2-oxind Cyclohex H332,H3 H251 Ethylace Anisole: I H300, Phe	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H315, H enanthroli	and H-c 1, H312, 12, H31: NaOtB 1335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 345, H31, H31 345, H31, H31 345, H31, H31 345, H31, H31, H31, H31, H31, H31, H31, H31	:odes H332,; ;, H315; 336, , H336, , H336, , H336, J, H36			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica Chemical identified as Chemical identified as	Green           Ambe           Ambe           H200, H201,           H200, H201,           H300, H3           H300, H3           H300, H3           H400, H410,           H300, H3           Substances of ec which are u	n Flag : r Flag : Flag : H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 : mental concernor : Very High Concernor : Hand Concernor : Very High Concernor : Very High Concernor : Hand Concernor : Very High Concernor : Hand Concernor : Very High Concernor : Hand Concernor : Hand Concernor : Very High Concernor : Hand Concernor :	Tick X X H205, H H301, H H341, H H341, H H341, H H401 Cern by	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412 Red Flag	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys ten Flag do a amber codes present green flag	ng on a stion state stat	ances and nanthroli	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bstan i sexano	phy :: H4122 :3351	d H-codi	ез I	List su 2-oxind Cyclohex H332, H3 H257 Ethylace Anisole: H300 Phe	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H222; H226, H33 2, H315, H enanthroli	and H-dd , H312, 22, H312 7, H312 7, H312 7, H319 7, H	H332,; 2, H315; 1, H325, 1, H325, 1, H336, 1, H336, 1, H336, 1, H290, 1, H290, 1, H290, 1, H290, 1, H290, 1, H290, 1, H336, 1, H366, 1, H3			

Supplementary Informat	tion: Appendix	2		Summary o	of First Pass	Metrics Toolki	it											
Yield, AE, RME, MI/PMI a	and OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06							0.00			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	4.01	100.15	0.04	1,10-Phen	0.18													
NaOtBu	1.41	96.10	0.01						1			0.00						0.00
Total	6.75	329.40			0.24		0.0	0				0.00		0.00				22.55
										Flag								
							Yield		90.0	90.0								
							Conversion	n	100.0	100.0					Maaa	B.434/	Mal	
mass of isola	ted product	100							90.0	90.0			Brod	uct	1 027	215 206	0.01	
total mass of	f reactants 🔨	100					RME		28.7	OF	43 0		Piou	uci	1.557	213.290	0.01	_
									20.7		43.3		Unreacted	limiting	mass			
AF - molecular	weight of pr	oduct	( 100				PMI total		15 3				react	ant	0.00			
total molecua	ılr weight of 1	reactants '	100				PMI React	ion	3.6				react		0.00			
							DMI reacto	anto	510									
mass intensity - t	otal mass in	a process o	or process s	tep			roagonts of	drits,	26									
mass mensicy =	ma	iss of prod	uct				reagents, t	catiyst	5.0									
$OE = \frac{RME}{4E} \times 100$							PMI reacti solvents	ion	0.0									
AL																		
							PMI Work	up	11.6									
							PMI Work	up										
							chemical		0.0									
							PMI worku	up										
							solvents		11.6									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, Etc BnOH, etl	)H, nBuOH, A Iylene glycol,	cOipr, AcOnB acetone, MEI	u, PhOMe, N <, MIBK, <b>Act</b>	ИеОН, tBuOH, <b>DEt,</b> sulfolane		neat	t									
Problematic solvents: (a if substitution does advantages	cceptable only not offer )	DMSO, AcOMe, TH cyclohex	cyclohexanor IF, heptane, M <b>ane</b> , chlorob	ne, DMPU, Act Me-cyclohexar enzene, formi	OH, Ac2O, A ne, toluene, c acid, pyrid	cetonitrile, xylene, MTBE, line, Me-THF		none	e									
Hazardous solvents: The have significant health a concerns.	nese solvents and/or safety	dioxane,	pentane, TEA DMA, NMI	, diisopropyl ( 2, methoxyeth	ether, DME anol, hexan	, DCM, DMF, le		none	e									
Highly hazardous sol solvents which are agre used, even in scre	vents: The eed not to be eening	Et <sub>2</sub> O, Benz	ene, CCl₄, chlo	proform, DCE,	nitrometha	ne, CS <sub>2</sub> , HMPA		none	e									
<b>a</b> , <b>b</b> , <b>f</b> =	<u> </u>																	
Catalyst/enzyme (First Pa	ass)	takes place	Green Elec	Tick		Eacilar	ecovery of	cataluct/	enzyme	Green Elag	Tick							
Use of stoichiometri	c quantities of	reagents	Amber			catal	yst/enzyme	not reco	overed	Amber Flag	х							
Use of rea	gents in excess		Red Flag									<u> </u>						

# Table S14. Method B (neat, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 8 h): First Pass CHEM21 green metrics toolkit

Critical elements													_								
Supply remaining	Flag colour	Note element	1 H	]	Remainin until deple known re	years tion of serves						He									
5-50 years	Red Flag		3	Be	(based on curr extracti	ent rate of on)			5 6 B C	7 8 N	n <sup>°</sup> F	10 Ne									
50-500 years	Amber Flag		6.941 11 Na	9.012182 12 Mg	5-50 ye 50-100 y 100-500	ars ears /ears			10.811 12.0107 13 14 AI Si	14.00674 15.9 15 16 P	994 18.99	140 20.1797 18 Ar									
+500 years	Green Flag	Fe	22.9897 19 <b>K</b>	7 24.3050 20 21 Ca Sc	22 23 Ti V	24 25 26 Cr Mn Fe	27 28 Co Ni	29 30 Cu Zn	26.98153 28.0855 31 27 Ga Ge	39.97376 323 33 34 As	66 35.45 25 6e B	7 19.948	+								
			39.0983 37	40.078 44.95591 38 39	47.867 50.9415 40 41	51.9961 54.93804 55.845 42 43 44	58.93320 58.6934 45 46	63.546 65.39 47 44		74.92160 78.9 51 52	6 79.90 53	83.80									
			<b>Rb</b> 85.4678	Sr Y 87.62 88.9385	Zr Nb 91.224 92.90638	Mo Tc Ru 95.54 (98) 101.07	Rh Pd 102.9055 106.42	Ag Cd	In Sn 114818 118.760	Sb 127	e   60 126.9	Xe 131.29									
			55 Cs 112,905	56 57 <b>Ba La*</b> 4 137.327 138.9055	72 73 Hf Ta 178.49 180.9479	74 75 76 W Re Os 181.84 186.207 191.23	i Ir Pt 192.217 195.078	79 80 Au Hg 196.9665 200.59	51 82 TI Pb 204.3833 220.2	83 84 Bi F	o A	86 Rn (222)									
			87 Fr	88 89 Ra Ac‡	104 105 Rf Db	106 107 108 Sg Bh Hs	109 110 Mt Ds	111 112 Ra Uut	113 114 D Uut Uug	115 116 Uup	v UL	s Uuo									
			(223)	226.025 (227)	(257) (260)	(263) (262) (265)	(266) (271)	(272) (285)	(284) (285)	(288) (29	)										
					58 59	60 61	Q (3)		66 67	68 69	70	71									
				Lanthanide	ES* CE 140.9077 144	24 (145) 150.36	151.964 157.25 1	GG ID 58.9253 158.9253	162.50 164.9303	167.36 168.	1042 173.00	174.967									
				Actinide	s‡ Th 1	Pa U Np	Pu Am	Cm Bk	Cf Es	Fm N	d No	Lr									
					232.0381 231	0289 238.0289 (237)	(244) (243) (	247) (247)	(251) (252)	(257) (258	(259)	(262)									
Energy (First Pass)			Tick								Tick										
Reaction run between	0 to 70°C	Green Flag				Reaction run a	at reflux		Red Flag												
Reaction run between -20 140°C	) to 0 or 70 to	Amber Flag	x		Reaction r	un 5°C or more	e below the s	olvent													
Reaction run below -20 or	r above 140°C	Red Flag				boiling p	oint		areen Flag		x										
Batch/flow	Gree	n Flag	Tick		Work Up	quenchi	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchi filtratio	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag Z	Tick X		Work Up	quenchi filtratic centrifuga	ing on ation		Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up	quenchi filtratic centrifuga crystallisa perature distilla	ing on ation ation ation/evapora	tion/	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C	ing on ation ation ation/evapora C at atmosphe	tion/ ric	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C cchange, quenc	ing on ation ation ation/evapora C at atmosphe ching into aqu	tion/ ric Jeous	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag Pr Flag S	Tick X		Work Up	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen solven solven pmatography/i	ing on ation ation/evapora Cat atmosphe ching into aqu it ion exchange	ition/ ric Jeous	Green Flag Amber Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag ;	Tick X		Work Up Low temp sublim solvent ex	quenchi filtratic centrifuga crystallisa eerature distilla ation (< 140 °C exchange, quen solven pomatography/i high tempe	ing on ation tition ation/evapora 2 at atmosphe ching into aqu it ion exchange erature	tion/ ric Jeous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag ;	Tick X		Work Up	quenchi filtratic centrifuga crystallisa berature distilika ation (< 140 °C kchange, quen solven bomatography/i high tempe nultiple recrys	ing an ation ation/evapora 2 at atmosphe ching into aqu t ion exchange erature tallisation	tion/ ric reous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation tion cat atmosphe ching into aqu ti ion exchange erature tallisation	tion/ ric leous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation ation cat atmosphe ching into aqu it ion exchange erature tallisation List subst	tion/ ric Jeous F	Green Flag Amber Flag Red Flag d H-codes	Chrom	List atogra	phy ces anc	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag : Flag :	Tick X Amb	er Flag	Work Up	quenchi filtratic centrifugg crystallisa erature distilla ation (< 140 °C kchange, queni solven omatography/i high tempe nultiple recrys	ing on attion attion attion attion attion attion attion/evaporation/evaporation/evaporation attion/evaporation atting into aquit tallisation atting a	tion/ ric Jeous	Green Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety Highly explosive	Greer Ambe	n Flag : er Flag : Flag : Flag : H202, H203	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven ponatography/i high tempe multiple recrys	ng on attion tition C at atmosphe ching into aqu t t ion exchange rature tallisation List subst	tion/ ric Jeous A	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es	List su 2-oxind Cyclohex	bstances a ole: H302, anol: H30	and H-c , H312, )2, H311	codes H332,; 2, H315;			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway	Greer Ambe Red H200, H201, H230, H2	n Flag : er Flag : Flag : H202, H203 : 240, H250 :	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga cerystalias perature distilla ation (< 140 <sup>°</sup> C cchange, quenn solven pomatography/i high tempe multiple recrys een Flag do r amber codes present green flag	ng on tition tition attorn/evapora. at atmospheric at atmospheric at atmospheric at atmospheric at atmospheric attore attorne tallisation list subst	ition/ ric leous ances and	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es Bu:	List su 2-oxind Cyclohex H332,H3 H251	ole: H302, anol: H30 19, H335 1, H314, H.	and H-c , H312, ,2, H31: NaOtB 335, H3	H332,; 2, H315; u: H225, 336,			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic	Greer Ambe Red H200, H201, H230, H2 H300, H3	n Flag : er Flag : Flag : H202, H203 : 240, H250 : 310, H330 :	Tick X Amt H205, H H301, H	er Flag 220, H224 241 311, H331,	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/i high tempe multiple recrys ten Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous c ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	atogra bstan exano	phy ces and l: H412 3351	d H-code 2; NaOte	es 0	List su 2-oxind Cyclohex H332, H3 H255 Ethylace	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22!	and H-cc , H312, , 2, H31: NaOtB 335, H312	H332,; 2, H315; u: H225, 336, 9, H336.			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity	Creer Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H340, H350,	n Flag 2 er Flag 2 Flag 4 H202, H203 240, H250 310, H330 H360, H370, H320	Tick X Amb H205, H H301, H H301, H H341, H	er Flag 220, H224 241 311, H331, 351, H331, 351, H361, 1 H373	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/ri high tempe multiple recrys en Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	List atogra bbstan exano	phy ces and	d H-codi	es l	List su 2-oxind Cyclohex H332, H3 H255 Ethylace Anisole: I	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H215	and H-c , H312, ,2, H311 NaOtBi 335, H319 365; FeCl 219-1	codes H332,; 2, H315; u: H225, 336, ), H336. I <sub>2</sub> : H290,			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental immireations	Greer Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	n Flag : r Flag : Flag : , H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 :	Tick X Amb H205, H H301, H H341, H H341, H H341, H H341, H H341, H	er Flag 2220, H224 241 311, H331, 351, H361, 1, H373 , H412	Work Up	quenchi filtratic centrifuge crystallisa erature distilla ation (< 140 °C cchange, quen solven omatography/i high tempe multiple recrys een Flag d or amber codes present green flag	ng on	ition/ ric reous ances and	Green Flag Amber Flag Red Flag I H-codes ne: H410	Chromotoria Chromotoria	List atogra bbstan	phy ces and 1: H412 1351	d H-cod	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: I H30: Pho	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H226, H33 2, H315, H enanthroli	and H-o , H312, 12, H312, NaOtBia 335, H3 5, H319 36; FeCl 318; 1, 1; h3: H31	H332,; ; 2, H315; ; 336, 1, H336, 2; H290, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	<b>Gree</b> Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410,	n Flag Flag H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420	Tick X Amb H205, H H301, H H341, H H34	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412	Work Up	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys do r amber codes present green flag	ng on attion stion stion stion stion stion stion stion stion stronger stion stion stronger st	ances and	Green Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bbstan	phy ces and i: H4122	l H-code	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: H300 Pho	bstances a ole: H302, anol: H30 19, H335 1, H314, H H314, H H226, H33 2, H315, H enanthroli	and H-c 12, H312, 1335, H313 1335, H313 1335, H319 1336; FeCl 1318; 1, 1, ine: H30	H332,; , H315; , H315; , H336, , H336, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	Greet           Ambe           Red           H200, H201,           H230, H2           H300, H3           H340, H350, H3           H400, H410,           H3           S of environn	n Flag r Flag Flag , H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420 mental concern	Тіск X Атв H205, H H301, H H301, H H301, H H301, H	er Flag 220, H224 241 251, H361, 1, H373 1, H412	Work Up	quenchi filtratic cervifuga cervifuga cervifuga erature distilla ation (< 140 °C kcchange, quen solven omatography/i high tempe multiple recrys een Flag do ramber codes present green flag	ng on attion attion attion/evapora. at atmospheric at atmospheric at atmospheric attino attion/evapora. Attino attion exchange arature atallisation attice attises attises attises attice attises attis	ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su Cycloh	List atogra bstan exano	phy ces and i: H4122	d H-cod 2; NaOtB	es l	List su 2-oxind Cyclohex H332,H3 H251 Ethylace Anisole: I H300, Phe	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H315, H enanthroli	and H-c 1, H312, 12, H31: NaOtB 1335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 345, H31, H31 345, H31, H31 345, H31, H31 345, H31, H31, H31, H31, H31, H31, H31, H31	:odes H332,; ; H315; 2, H315; 336, , H336, , H336, , H336, J, H336			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica Chemical identified as Chemical identified as	Green           Ambe           Ambe           H200, H201,           H200, H201,           H300, H3           H300, H3           H300, H3           H400, H410,           H300, H3           Substances of ec which are u	n Flag : r Flag : Flag : H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 : mental concernor : Very High Concernor : No. 2000 : 1000 : 1	Tick X X H205, H H301, H H341, H H341, H H341, H H401 Cern by	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412 Red Flag	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys ten Flag do a amber codes present green flag	ng on a stion state stat	ances and nanthroli	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bstan i sexano	phy :: H4122 :3351	d H-codi	ез I	List su 2-oxind Cyclohex H332, H3 H257 Ethylace Anisole: H300 Phe	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H222; H226, H33 2, H315, H enanthroli	and H-dd , H312, 22, H312 7, H312 7, H312 7, H319 7, H	H332,; 2, H315; 1, H325, 1, H325, 1, H325, 1, H336, 1, H336, 1, H336, 1, H290, 1, H290, 1, H290, 1, H290, 1, H336, 1, H366, 1, H3			

Supplementary Informat	ion: Appendix	2		Summary of	of First Pass	Metrics Toolki	t											
Yield, AE, RME, MI/PMI a	nd OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	[Co]	0.48				Toluene	10.00	0.87	8.67			Ethyl acetate	20.00	0.90	18.04
Cyclohexanol	2.00	100.15	0.02															
КОН	1.12	46.10	0.02									0.00						0.00
Total	4.46	279.40			0.48		0.00	0				8.67		0.00				18.04
										Flag								
							Yield		91.0	91.0	)							
							Conversion	1	100.0	100.0	)				Mass	5.4347	D4ol	
DME_ mass of isola	ted product	100					Selectivity		91.0	91.0	)		Prod	uct	1 050	215 206	0.01	
total mass of	reactants	100							44.0	OF	57.1		FIOU		mass	213.230	0.01	-
									++.0	02	57.1		Unreacted	limiting	muss			
AF = molecular	weight of pr	oduct ×	100				PMI total		16.2				react	ant	0.00			
total molecua	lr weight of 1	reactants ົ	100				PMI Reacti	on	6.9				reade		0.00			
							DMI roacta	nto										
$mass intensity = \frac{t}{t}$	otal mass in	a process or	r process s	tep			reagents c	atlyst	2.5									
nices inconsity -	ma	iss of produ	ıct				reagents, e	aciyse	2.5									
$OE = \frac{RME}{M} \times 100$							solvents	on	4.4									
AE																		
							PMI Worku	qu	9.2									
							PMI Worku	μ										
							chemical		0.0									
							PMI worku	ıp										
							solvents		9.2									
Solvents (First Pass)							List	solvent	s below									
Preferred solve	ents	water, EtOH BnOH, ethy	H, nBuOH, Ad Iene glycol,	cOipr, AcOnB acetone, ME	u, PhOMe, N K, MIBK, <b>Act</b>	ЛеОН, tBuOH, <b>DEt,</b> sulfolane		none	2									
Problematic solvents: (a if substitution does advantages	cceptable only not offer )	DMSO, cy AcOMe, THF <mark>cyclohexa</mark>	yclohexanon , heptane, N ne, chlorobe	ie, DMPU, Ac 1e-cyclohexai enzene, formi	OH, Ac2O, A ne, toluene, c acid, pyrid	cetonitrile, xylene, MTBE, ine, Me-THF		Tolue	ne									
Hazardous solvents: Th have significant health a concerns.	ese solvents and/or safety	dioxane, p	entane, TEA DMA, NMP	, diisopropyl , methoxyeth	ether, DME hanol, hexan	, DCM, DMF, e		none	2									
Highly hazardous sol solvents which are agre used, even in scre	vents: The ed not to be eening	Et <sub>2</sub> O, Benzen	ne, CCl₄, chlc	oroform, DCE,	nitrometha	ne, CS <sub>2</sub> , HMPA		none	2									
a												-						
Catalyst/enzyme (First Pa	ass)	takos place	Groop Floo	Tick		Eacilar	acovoru of a	atalyst/	0071/000	Groop Flag	Tick							
Use of stoichiometric	c quantities of	reagents	Amber	^		catal	vst/enzyme	not reco	vered	Amber Flag	x							
			Flag			Catal	,,,			Amoer Hag								
Use of reag	gents in excess		Red Flag															

# Table S15. Method C (toluene, [Co] 10 mol%, KOH 2 eq, 150 °C, 16 h): First Pass CHEM21 green metrics toolkit

Critical elements								1			_					
Supply remaining	Flag colour	Note element	1 H		Remainin until deple known re	g years etion of eserves				He						
5-50 years	Red Flag		3	4	(based on curr extracti	ent rate of		5 6 B C	7 8 9	10 E No						
50-500 years	Amber Flag	Со	6.941 11 Na	9.012182 12 Mg	5-50 ye 50-100 y	vears		10.811 12.0107 13 14 Al Si	14.00674 15.9994 1 15 16 1 P S	r RC 18.99840 20.1797 17 18 CI Ar	-					
+500 years	Green Flag		22.9897 19 K	20 23 Ca Sc	22 23 Ti V	24 25 26 Cr Mn F	27 28 29 Fe Co Ni Cu	26.98153 28.0855 30 31 32 Zn Ga Ge	39.97376 32.066 3 33 34 3 As Se	15.4527 19.948 15 26 Br Kr						
			39.0983 37	40.078 44.95591 38 39	47.867 50.9415 40 41	51.9961         54.93804         55.8           42         43         44	45 58.93320 58.6934 63.546 45 46 47		X4.92160         78.96         7           51         52         5	9.904 83.80 B 54	-					
			Rb 85.4678	Sr Y 87.62 88.9085	Zr Nb 91.224 92.90638	Mo Tc R	tu Rh Pd Ag	Cd In Sn	Sb Te	I Xe						
			55 Cs 132.905	56 57 <b>Ba La*</b> 4 137.327 138.9055	72 73 Hf Ta 180.9479	74 75 75 W Re C 183.84 196.207 190	77         78         79           Ds         Ir         Pt         Au           23         199.217         195.078         196.9665	80         81         82           Hg         Ti         Pb           200.59         204.3831         270.2	83 84 8 Bi Po 208.0804 (209) (	s 86 At Rn 210) (222)						
			87 Fr	88 89 Ra Ac‡	104 105 Rf Db	106 107 108 Sg Bh H	109 110 111 Is Mt Ds Rg	112 113 114 Uub Uut Uug	115 116 1 Uup Lv	117 118 Uus Uuo						
			(223)	226.025 (227)	(257) (260)	(263) (262) (265	i) (266) (271) (272)	(285) (284) (285)	(288) (292)							
					54 59	60 61		5 66 67	68 69 7	0 71						
				Lanthanide	es * Ce 140.9077 144	Pr Nd Pm 4.24 (145) 150.36	5m Eu Gd 151.964 157.25 158.9253 1	ID         Dy         HO           158.9253         262.50         264.9303	Er Im 167.26 168.9342 1	YD Lu 73.04 174.967						
				Actinide	s‡ Th	Pa U Np	Pu Am Cm	Bk Cf Es	Fm Md	No Lr						
					232.0381 23	1.0289 238.0289 (237)	(244) (243) (247)	247) (251) (252)	(257) (258) (2	(262)						
Energy (First Pass)			Tick						Tick							
Reaction run between	0 to 70°C	Green Flag				Reaction run	at reflux	Red Flag	x							
Reaction run between -20 140°C	) to 0 or 70 to	Amber Flag	x		Reaction	run 5°C or mo	re below the solvent									
Reaction run below -20 or	r above 140°C	Red Flag				boiling	point	Green Flag								
				<b>-</b>												
Batch/flow	Creation	- Flag	Tick		Work Up				List							
Batch/flow Flow Batch	Gree	n Flag	Tick		Work Up	quench	ning		List							
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up	quench filtrati centrifug	ning ion gation	Green Flag	List							
Batch/flow Flow Batch	Greet Ambe	n Flag er Flag	Tick X		Work Up	quench filtrati centrifug crystallis	ning ion gation sation	Green Flag	List							
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up	quench filtrat centrifug crystallis perature distil	ning ion sation sation lation/evaporation/ C at atmospheric	Green Flag	List							
Batch/flow Flow Batch	Green Ambe	n Flag presented to the second s	Tick X		Work Up	quench filtrat centrifug crystallis perature distil lation (< 140 <sup>c</sup> xchange, que	ning ion gation gation lation/evaporation/ <sup>2</sup> C at atmospheric nching into aqueous	Green Flag	List							
Batch/flow Flow Batch	Greet Ambe	n Flag : er Flag :	Tick X		Work Up	quench filtrat centrifug crystallis perature distil iation (< 140 <sup>c</sup> xchange, quen solve omatography	ning ion gation lation/evaporation/ 'C at atmospheric nching into aqueous nt ion exchange	Green Flag Amber Flag	List							
Batch/flow Flow Batch	Gree Ambe	n Flag : er Flag ;	Tick X		Work Up	quench filtrati centrifug crystallis berature distil iation (< 140 <sup>C</sup> xchange, quen solve omatography, high temp	ning ion gation lation/evaporation/ C at atmospheric nching into aqueous nt /ion exchange ererature	Green Flag Amber Flag Red Flag	List	raphy						
Batch/flow Flow Batch	Greet Ambe	n Flag : er Flag ;	Tick X		Work Up Low temp sublim solvent e	quench filtrat centrifug crystallis perature distil ation (< 140 <sup>c</sup> xchange, quer solve omatography, high temp multiple recry	ning ion sation lation/evaporation/ C at atmospheric nching into aqueous nt /ion exchange ererature stallisation	Green Flag Amber Flag Red Flag	List	raphy						
Batch/flow Flow Batch	Greet Ambe	n Flag :	Tick X		Work Up	quench filtrat centrifug crystallis berature distil ation (< 140 <sup>c</sup> xchange, quer solve omatography, high temp multiple recry	hing ion sation lation/evaporation/ iC at atmospheric ching into aqueous nt /ion exchange everature stallisation	Green Flag Amber Flag Red Flag	List	rephy						
Batch/flow Flow Batch Health & safety	Greet Ambe	n Flag :	Tick X		Work Up Low temp sublim solvent e	quench filtrati centrifug crystallis berature distil ation (< 140 <sup>C</sup> xchange, quen solve omatography, high temp multiple recry	hing ion gation lation/evaporation/ 'C at atmospheric nching into aqueous int /ion exchange ierature stallisation	Green Flag Amber Flag Red Flag	List Chromatog	raphy ances and	1 H-codes	List sul	bstances and H	-codes		
Batch/flow Flow Batch Health & safety	Gree Ambe	n Flag : r Flag :	Tick X Amb	Per Flag	Work Up	quench filtrat centrifug crystalli berature distil lation (< 140 <sup>°</sup> solve omatography, high temp multiple recry een Flag	ning ion gation lation/evaporation/ 'C at atmospheric atmospheric ching into aqueous int /ion exchange werature stallisation List substances	Green Flag Amber Flag Red Flag	List substa	raphy	1 H-codes	List sul	bstances and H	-codes		
Batch/flow Flow Batch Health & safety Highly explosive	Greet Ambe Red H200, H201,	n Flag	Tick X Amt H205, H	Per Flag 2220, H224	Work Up Low temp sublim solvent e chr flagged H	quencl filtrat centrifug crystallis berature distil ation (< 140 <sup>°</sup> xchange, quen solve omatography, high temp multiple recry high temp multiple recry een Flag do r amber codes preser	ning ion gation lation/evaporation// C at atmospheric nching into aqueous nt //ion exchange errature stallisation List substances	Green Flag Amber Flag Red Flag and H-codes	List substa	raphy ances and	1 H-codes	List sul	bstances and H	H-codes		
Batch/flow Flow Batch Health & safety Highly explosive Explosive thermal runaway	Gree Ambe Ambe Red H200, H201, H230, H2	n Flag 2r Flag Flag H202, H203 240, H250	Tick X Amb H205, H	Per Flag 1220, H224	Work Up Low temp sublim solvent e chr flagged H then	quench filtrat centrifug crystallis perature disti tation (< 140° xchange, queu solve omatography, high temp multiple recry bigh temp multiple recry een Flag ed or amber t codes preser green flag	ning ion sation lation/evaporation/ 'C at atmospheric nching into aqueous nt /ion exchange inerature stallisation List substances	Green Flag Amber Flag Red Flag and H-codes	List Substa	traphy	l H-codes	List sul	bstances and H ple: H302, H31 anol: H302, H3	I-codes 2, H332,; 12, H315;		
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic	Greet Ambe Red H200, H201, H230, H2 H300, H3	n Flag er Flag Flag H202, H203 240, H250 310, H330	Tick X Amt H205, H H205, H H301, H	eer Flag 2220, H224 2241 311, H331,	Work Up	quencl filtrat centrifug crystallis berature disti ation (< 140° xchange, quen solve omatography, high temp multiple recry een Flag ad or amber I codes preser green flag	ning ion gation lation/evaporation// C at atmospheric nching into aqueous nt //ion exchange ererature stallisation List substances	Green Flag Amber Flag Red Flag and H-codes	Chromatog List substa	traphy ances and	1 H-codes	List sul 2-oxinde Cyclohex H332, H311	bstances and H ble: H302, H31 anol: H302, H3 9, H335 KOH: F	L-codes 2, H332,; 12, H315; 1290, H302, 0		
Batch/flow Flow Batch Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity	<u>Greet</u> Атьбе Атьбе Н200, H201, H230, H2 H300, H3 H340, H350, H3	n Flag 2 Flag 2 Flag 4 Flag 4 H202, H203 240, H250 310, H330 H360, H370, H360, H370,	Tick X Amt H205, H H301, H H341, H H341, H H341, H H341, H	Per Flag 220, H224 241 251, H331, 1, H373	Work Up	quenci filtrat centrifug crystallis beerature distil attion (< 140 <sup>C</sup> xchange, queu solve omatography, high temp multiple recry een Flag een Flag d or amber 1 codes preser green flag	hing join gation sation lation/evaporation/ 'C at atmospheric nching into aqueous nt /ion exchange uerature estature List substances	Green Flag Amber Flag Red Flag and H-codes	Cyclof	rraphy nnces and	1 H-codes H412	List sul 2-oxindo Cyclohex H332, H314, Ett H314, Ett H316.	bstances and H anol: H302, H31 anol: H302, H3 9, H335 KOH: H 9, H325 KOH: H226	2, H332,; 12, H315; 129, H315; 1290, H302, 25, H319, H336		
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	<b>Red</b> H200, H201, H230, H2 H340, H350, H340, H410, H400, H410	Flag Flag H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H412, H250	Tick X Amt H205, H H301, H H301, H H311, H H312 H401	eer Flag 2220, H224 2241 311, H331, 351, H361, 1, H373 1, H412	Work Up	quencl filtrat centrifug crystallis perature disti ation (< 140° xchange, quen solve omatography, high temp multiple recry een Flag ad or amber codes preser green flag	ning ion gation lation/evaporation// C at atmospheric nching into aqueous nt //on exchange errature stallisation List substances	Green Flag Amber Flag Red Flag and H-codes	Chromatog List substa	raphy ances and hexanol: I	<mark>1 H-codes</mark> H412	List sul 2-oxinde Cyclohex H332, H314, Etl H336.	bstances and H ole: H302, H31 anol: H302, H3 9, H335 KOH: F hylacetate: H22 Anisole: H226	L-codes 2, H332,; 12, H315; 1290, H302, 25, H319, , H336		
Batch/flow Flow Batch Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications	Red H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	n Flag r Flag Flag H202, H203 40, H250 310, H330 H360, H370, 372 , H411, H420	Tick X Amt H205, H H301, H H341, H H341, H H341, H H341, H H341, H H341, H	eer Flag [220, H224 [241 [311, H331, [1, H373] [1, H412]	Work Up	quenci filtrat centrifug crystallis berature distil ation (< 140 <sup>°</sup> xchange, quen solve omatography, high temp multiple recry ben Flag d or amber codes preser green flag	hing ion sation lation/evaporation/ C at atmospheric nching into aqueous nt List substances stallisation	Green Flag Amber Flag Red Flag and H-codes	List substa	raphy ances and hexanol: I	<mark>I H-codes</mark> H412	List sul 2-oxinde Cyclohex H332, H319 H314, Et H336.	bstances and H ole: H302, H31 anol: H302, H3 9, H335 KOH: F hylacetate: H22 Anisole: H226	H-codes 2, H332,; 12, H315; 1290, H302, 25, H319, , H336		
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	<b>Red</b> H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	n Flag 1 r Flag 2 Flag 2 H202, H203 2 240, H250 3 10, H330 1 H360, H370, 372 , H411, H420 3 mental concern	Tick X Amb H205, H H301, H H341, H H34	Per Flag (220, H224 (241 (241 (241 (241 (241) (2	Work Up	quench filtrat centrifug crystallis earature distil ataion (< 140 <sup>°</sup> xchange, quen solve omatography, high temp multiple recry ed or amber codes presen green flag bstances of v	hing ion gation lation/evaporation/ /C at atmospheric nching into aqueous nt //ion exchange ererature stallisation List substances nt Nor ery high concern	Green Flag Amber Flag Red Flag and H-codes	List substa	raphy ances and hexanol: I	H412	List sul 2-oxinde Cyclohex H332, H319 H314, Eti H336.	bstances and H ple: H302, H31 anol: H302, H3 9, H335 KOH: H hylacetate: H22 Anisole: H226	L-codes 2, H332,; 12, H315; 1290, H302, 25, H319, , H336		

Supplementary Informat	ion: Appendix	2		Summary o	f First Pass	Metrics Toolki	t											
Yield, AE, RME, MI/PMI a	nd OE																	
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass	(g)	Reaction solvent	Volume (cm <sup>3</sup> )	Density (g ml <sup>-1</sup> )	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml <sup>-1</sup> )	Mass (g)
2-oxindole	1.33	133.15	0.01	FeCl2	0.06				anisole	10.00	1.00	9.95			Ethyl acetate	25.00	0.90	22.55
Cyclohexanol	2.00	100.15	0.02	1,10-Phen	0.18													
NaOtBu	1.41	96.10	0.01									0.00						0.00
Oxygen	0.16	32.00	0.01		0.24		0.00					0.00		0.00				0.00
Iotai	4.90	361.40	_		0.24		0.00			Flag		9.95		0.00				22.55
							Yield		90.0	90 0								
							Conversion		100.0	100.0								
<b>C</b> · · · ·							Selectivity		90.0	90.0					Mass	MW	Mol	1
$RME = \frac{mass of isolat}{tatal mass of isolat}$	ea proauct × 1	100					AE		64.0				Prod	uct	2.081	231.295	0.01	]
total mass of	reactants						RME		42.4	OE	66.3				mass			
molecular	weight of m	oduct											Unreacted	limiting				
$AE = \frac{motocolumnation}{total molecular}$	r weight of r	eactants ×	100				PMI total		18.1				react	ant	0.00			
cotat motocaa	in weight of i	cuccunts					PMI Reactio	on	7.3									
te	tal mass in	a process or	process st	tep			PMI reactar	nts,										
mass intensity = -	ma	ss of produ	ict	-			reagents, ca	atlyst	2.5									
							PMI reactio	n										
$OE = \frac{RME}{AE} \times 100$							solvents		4.8									
AL																		
							PMI Worku	р	10.8									
							PMI Worku	р										
							chemical		0.0									
							PMI workup solvents	0	10.8									
Columnts (First Dess)																		
Solvents (First Pass)		weter EtOI		Oine AcOnD			List s	solvent	s below									
Preferred solve	ints	BnOH, ethy	lene glycol,	acetone, ME	(, MIBK, <b>Act</b>	DEt, sulfolane		PhON	le									
Problematic solvents: (a if substitution does advantages	cceptable only not offer	DMSO, cy AcOMe, THF <b>cyclohexa</b>	yclohexanon , heptane, M <b>ne</b> , chlorobe	e, DMPU, Act Ae-cyclohexar enzene, formi	DH, Ac2O, A ne, toluene, c acid, pyrid	cetonitrile, xylene, MTBE, line, Me-THF		none	2									
Hazardous solvents: The have significant health a concerns.	ese solvents nd/or safety	dioxane, p	entane, TEA DMA, NMP	, diisopropyl ( , methoxyeth	ether, DME anol, hexan	, DCM, DMF, e		none	2									
Highly hazardous sol solvents which are agre used, even in scre	vents: The ed not to be ening	Et <sub>2</sub> O, Benzer	ne, CCl₄, chlo	oroform, DCE,	nitrometha	ne, CS <sub>2</sub> , HMPA		none	2									
Cataluat /annuma /First D	 			Tiele							Tiele							
Catalyst/enzyme (First Pa	d or reaction	takes place	Green Elag	ТСК		Facile r	ecovery of ca	atalyst/	enzyme	Green Flag	TICK							
Cutaryst of enzyme use	a, or reaction	takes place	Amber	~		raciler		ataryst/		Green Hag								
Use of stoichiometric	quantities of	reagents	Flag			cataly	/st/enzyme n	ot reco	vered	Amber Flag	x							
Use of reag	ents in excess		Red Flag															

# Table S16. Method D (anisole, [Fe] 5 mol%, 1,10-Phen 10 mol%, NaOtBu 1.5 eq, 150 °C, 32 h): First Pass CHEM21 green metrics toolkit

Critical elements													_								
Supply remaining	Flag colour	Note element	1 H	]	Remainin until deple known re	years tion of serves						He									
5-50 years	Red Flag		3	Be	(based on curr extracti	ent rate of on)			5 6 B C	7 8 N	, °,	10 Ne									
50-500 years	Amber Flag		6.941 11 Na	9.012182 12 Mg	5-50 ye 50-100 y 100-500	ars ears /ears			10.811 12.0107 13 14 AI Si	14.00674 15.9 15 16 P	994 18.99	140 20.1797 18 Ar									
+500 years	Green Flag	Fe	22.9897 19 <b>K</b>	7 24.3050 20 21 Ca Sc	22 23 Ti V	24 25 26 Cr Mn Fe	27 28 Co Ni	29 30 Cu Zn	26.98153 28.0855 31 27 Ga Ge	39.97376 323 33 34 As	66 35.45 25 6e B	7 19.948									
			39.0983 37	40.078 44.95591 38 39	47.867 50.9415 40 41	51.9961 54.93804 55.845 42 43 44	58.93320 58.6934 45 46	63.546 65.39 47 44		74.92160 78.9 51 52	6 79.90 53	83.80									
			<b>Rb</b> 85.4678	Sr Y 87.62 88.9085	Zr Nb 91.224 92.90638	Mo Tc Ru 95.54 (98) 101.07	Rh Pd 102.9055 106.42	Ag Cd	In Sn 114818 118.760	Sb 127	e   60 126.9	Xe 131.29									
			55 Cs 112,905	56 57 <b>Ba La*</b> 4 137.327 138.9055	72 73 Hf Ta 178.49 180.9479	74 75 76 W Re Os 181.84 186.207 191.23	i Ir Pt 192.217 195.078	79 80 Au Hg 196.9665 200.59	51 82 TI Pb 204.3833 220.2	83 84 Bi F	o A	86 Rn (222)									
			87 Fr	88 89 Ra Ac‡	104 105 Rf Db	106 107 108 Sg Bh Hs	109 110 Mt Ds	111 112 Ra Uut	113 114 D Uut Uug	115 116 Uup	v UL	s Uuo									
			(223)	226.025 (227)	(257) (260)	(263) (262) (265)	(266) (271)	(272) (285)	(284) (285)	(288) (29	)										
					58 59	60 61	Q (3)		66 67	68 69	70	71									
				Lanthanide	ES* Ce 140.9077 144	24 (145) 150.36	151.964 157.25 1	GG ID 58.9253 158.9253	162.50 164.9303	167.36 168.	1042 173.00	174.967									
				Actinide	s‡ Th 1	Pa U Np	Pu Am	Cm Bk	Cf Es	Fm N	d No	Lr									
					232.0381 231	0289 238.0289 (237)	(244) (243) (	247) (247)	(251) (252)	(257) (258	(259)	(262)									
Energy (First Pass)			Tick								Tick										
Reaction run between	0 to 70°C	Green Flag				Reaction run a	at reflux		Red Flag												
Reaction run between -20 140°C	) to 0 or 70 to	Amber Flag	x		Reaction r	un 5°C or more	e below the s	olvent													
Reaction run below -20 or	r above 140°C	Red Flag				boiling p	oint		areen Flag		x										
Batch/flow	Gree	n Flag	Tick		Work Up	quenchi	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag	Tick X		Work Up	quenchi filtratio	ing				List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag Z	Tick X		Work Up	quenchi filtratic centrifuga	ing on ation		Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag 2	Tick X		Work Up	quenchi filtratic centrifuga crystallisa perature distilla	ing on ation ation ation/evapora	tion/	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag er Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C	ing on ation ation ation/evapora C at atmosphe	tion/ ric	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag :	Tick X		Work Up	quenchi filtratic centrifuga crystallisa verature distilla ation (< 140 °C cchange, quenc	ing on ation ation ation/evapora C at atmosphe ching into aqu	tion/ ric Jeous	Green Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag Pr Flag S	Tick X		Work Up Low temp sublim solvent e	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen solven solven pmatography/i	ing on ation ation/evapora Cat atmosphe ching into aqu it ion exchange	ition/ ric Jeous	Green Flag Amber Flag		List										
Batch/flow Flow Batch	Greer Ambe	n Flag r Flag ;	Tick X		Work Up Low temp sublim solvent ex	quenchi filtratic centrifuga crystallisa eerature distilla ation (< 140 °C exchange, quen solven pomatography/i high tempe	ing on ation tition ation/evapora 2 at atmosphe ching into aqu it ion exchange erature	tion/ ric Jeous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag ;	Tick X		Work Up	quenchi filtratic centrifuga crystallisa berature distilika ation (< 140 °C kchange, quen solven bomatography/i high tempe nultiple recrys	ing an ation ation/evapora 2 at atmosphe ching into aqu t t ion exchange erature tallisation	tion/ ric reous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation tion cat atmosphe ching into aqu ti ion exchange erature tallisation	tion/ ric leous	Green Flag Amber Flag Red Flag	Chrom	List	phy									
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag :	Tick X		Work Up	quenchi filtratic centrifuge crystallisa erature distill ation (< 140 °C cchange, quen solven omatography/i high tempe nultiple recrys	ing on ation ation cat atmosphe ching into aqu it ion exchange erature tallisation List subst	tion/ ric Jeous F	Green Flag Amber Flag Red Flag d H-codes	Chrom	List atogra	phy ces anc	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety	Greer Ambe	n Flag : er Flag : Flag :	Tick X Amb	er Flag	Work Up	quenchi filtratic centrifugg crystallisa erature distili ation (< 140 °C kchange, quen solven solven matography/i high tempe nultiple recrys	ing on attion attion attion attion attion attion attion/evaporation/evaporation/evaporation attion/evaporation atting into aquit tallisation atting a	tion/ ric Jeous	Green Flag Amber Flag Red Flag d H-codes	Chrom	List atogra	phy ces and	d H-codd	es	List su	bstances a	and H-c	codes			
Batch/flow Flow Batch Health & safety Highly explosive	Greer Ambe	n Flag : er Flag : Flag : Flag : H202, H203	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven ponatography/i high tempe multiple recrys	ng on attion tition C at atmosphe ching into aqu t t ion exchange rature tallisation List subst	tion/ ric Jeous A	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es	List su 2-oxind Cyclohex	bstances a ole: H302, anol: H30	and H-c , H312, )2, H311	codes H332,; 2, H315;			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway	Greer Ambe Red H200, H201, H230, H2	n Flag : er Flag : Flag : H202, H203 : 240, H250 :	Tick X Amb H205, H	er Flag 220, H224	Work Up	quenchi filtratic centrifuga cerystalias perature distilla ation (< 140 <sup>°</sup> C cchange, quenn solven pomatography/i high tempe multiple recrys een Flag do r amber codes present green flag	ng on tition tition attorn/evapora. at atmospheric at atmospheric at atmospheric at atmospheric at atmospheric attore attallisation bit bits subst	ition/ ric leous ances and	Sreen Flag Amber Flag Red Flag d H-codes	Chrom List su	List atogra	phy ces and	d H-code	es Bu:	List su 2-oxind Cyclohex H332,H3 H251	ole: H302, anol: H30 19, H335 1, H314, H.	and H-c , H312, ,2, H312 NaOtB 335, H3	H332,; 2, H315; u: H225, 336,			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic	Greer Ambe Red H200, H201, H230, H2 H300, H3	n Flag : er Flag : Flag : H202, H203 : 240, H250 : 310, H330 :	Tick X Amt H205, H H301, H	er Flag 220, H224 241 311, H331,	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/i high tempe multiple recrys ten Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous c ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	atogra bstan exano	phy ces and l: H412 3351	d H-code 2; NaOte	es 0	List su 2-oxind Cyclohex H332, H3 H255 Ethylace	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22!	and H-cc, 14, H312, 12, H31: NaOtB 1335, H312	H332,; 2, H315; u: H225, 336, 9, H336.			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity	Creer Ambe Ambe Red H200, H201, H230, H2 H300, H3 H340, H350, H340, H350,	n Flag 2 er Flag 2 Flag 4 H202, H203 240, H250 310, H330 H360, H370, H320	Tick X Amb H205, H H301, H H301, H H341, H	er Flag 220, H224 241 311, H331, 351, H331, 351, H361, 1 H373	Work Up	quenchi filtratic centrifuga crystalise perature distilla ation (< 140 °C cchange, quen- solven panatography/ri high tempe multiple recrys en Flag d or amber codes present green flag	ng on ition ation/evapora. at atmosphe ching into aqui ti ion exchange rature tallisation List subst	tion/ ric reous ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su	List atogra bbstan exano	phy ces and	d H-codi	es l	List su 2-oxind Cyclohex H332, H3 H255 Ethylace Anisole: I	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H215	and H-c , H312, ,2, H311 NaOtBi 335, H319 365; FeCl 219-1	codes H332,; 2, H315; u: H225, 336, ), H336. I <sub>2</sub> : H290,			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental immicrations	Greer Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410	n Flag : r Flag : Flag : , H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 :	Tick X Amb H205, H H301, H H341, H H341, H H341, H H341, H H341, H	er Flag 2220, H224 241 311, H331, 351, H361, 1, H373 , H412	Work Up	quenchi filtratic centrifuge crystallisa erature distilla ation (< 140 °C cchange, quen solven omatography/i high tempe multiple recrys een Flag d or amber codes present green flag	ng on	ition/ ric reous ances and	Green Flag Amber Flag Red Flag I H-codes ne: H410	Chromotoria Chromotoria	List atogra bbstan	phy ces and 1: H412 1351	d H-cod	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: I H30: Pho	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H226, H33 2, H315, H enanthroli	and H-o , H312, 12, H312, NaOtBia 335, H3 5, H319 36; FeCl 318; 1, 1; h3: H31	H332,; ; 2, H315; ; 336, 1, H336, 2; H290, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications	<b>Gree</b> Ambe Ambe H200, H201, H230, H2 H300, H3 H340, H350, H3 H400, H410,	n Flag Flag H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420	Tick X Amb H205, H H301, H H341, H H34	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412	Work Up	quenchi filtratic centrifuga crystallisa erature distilla ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys do r amber codes present green flag	ng on stion stion C at atmosphe ching into aqui t toon exchange trature tallisation List subst	ances and	Green Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bbstan	phy ces and i: H4122	l H-code	es l	List su 2-oxind Cyclohex H332, H3 H251 Ethylace Anisole: H300 Pho	bstances a ole: H302, anol: H30 19, H335 1, H314, H H314, H H226, H33 2, H315, H enanthroli	and H-c 12, H312, 1335, H313 1335, H313 1335, H319 1336; FeCl 1318; 1, 1, ine: H30	H332,; , H315; , H315; , H336, , H336, <b>10-</b> 01			
Batch/flow Flow Batch Health & safety Health & safety Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica	Greet           Ambe           Red           H200, H201,           H230, H2           H300, H3           H340, H350, H3           H400, H410,           H3           S of environn	n Flag r Flag Flag , H202, H203 240, H250 310, H330 H360, H370, 372 , H411, H420 mental concern	Тіск X Атв H205, H H301, H H301, H H301, H H301, H	er Flag 220, H224 241 251, H361, 1, H373 1, H412	Work Up	quenchi filtratic cervifuga cervifuga cervifuga erature distilla ation (< 140 °C kcchange, quen solven omatography/i high tempe multiple recrys een Flag do ramber codes present green flag	ng on attion attion attion/evapora. at atmospheric at atmospheric at atmospheric attino attion/evapora. Attino attion exchange arature attilisation attice attilisation attive attilisation atttilisation attilisation attilisation attilisation atttil	ances and	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chrom List su Cycloh	List atogra bstan exano	phy ces and i: H4122	d H-cod 2; NaOtB	es l	List su 2-oxind Cyclohex H332,H3 H251 Ethylace Anisole: I H300, Phe	bstances a ole: H302, anoi: H30 19, H335 1, H314, H tate: H22! H226, H33 2, H315, H enanthroli	and H-c 1, H312, 12, H31: NaOtB 1335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 335, H31 345, H31, H31 345, H31, H31 345, H31, H31 345, H31 345, H31 345, H31 345, H31 345, H31 345, H314	:odes H332,; ; H315; 2, H315; 336, , H336, , H336, , H336, J, H366, J, H366			
Batch/flow Flow Batch Health & safety Health & safety Highly explosive Explosive thermal runaway Toxic Long Term toxicity Environmental implications Use of chemica Chemical identified as Chemical identified as	Green           Ambe           Ambe           H200, H201,           H200, H201,           H300, H3           H300, H3           H300, H3           H400, H410,           H300, H3           Substances of ec which are u	n Flag : r Flag : Flag : H202, H203 : 240, H250 : 310, H330 : H360, H370, 372 : , H411, H420 : mental concernor : Very High Concernor : Hand Concernor : Very High Concernor : Very High Concernor : Hand Concernor : Very High Concernor : Hand Concernor : Very High Concernor : Hand Concernor : Hand Concernor : Very High Concernor : Hand Concernor :	Tick X X H205, H H301, H H341, H H341, H H341, H H401 Cern by	er Flag 220, H224 241 311, H331, 351, H361, 1, H373 1, H412 Red Flag	Work Up	quenchi filtratic centrifuga crystallisa erature distilk ation (< 140 °C cchange, quen- solven omatography/i high tempe multiple recrys ten Flag do a amber codes present green flag	ng on a stion state stat	ances and nanthroli	Sreen Flag Amber Flag Red Flag d H-codes ne: H410	Chronn List su Cycloh	List atogra bstan i sexano	phy :: H4122 :3351	d H-codi	ез I	List su 2-oxind Cyclohex H332, H3 H257 Ethylace Anisole: H300 Phe	bstances a ole: H302, anol: H30 19, H335 1, H314, H tate: H222; H226, H33 2, H315, H enanthroli	and H-dd , H312, 22, H312 7, H312 7, H312 7, H319 7, H	H332,; 2, H315; 1, H325, 1, H325, 1, H325, 1, H336, 1, H336, 1, H336, 1, H290, 1, H290, 1, H290, 1, H290, 1, H336, 1, H366, 1, H3			

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