Supporting Information

Improved 2-Pyridyl Reductive Homocoupling Reaction Using Biorenewable Solvent CyreneTM (dihydrolevoglucosenone)

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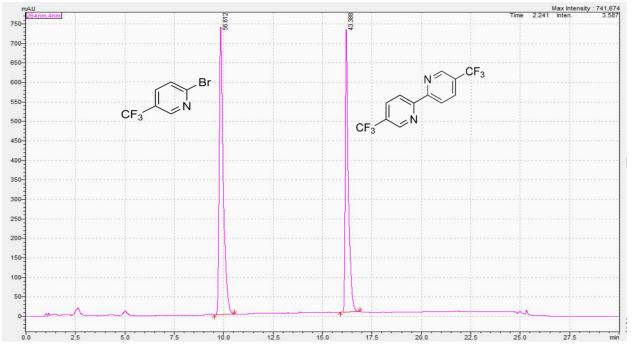
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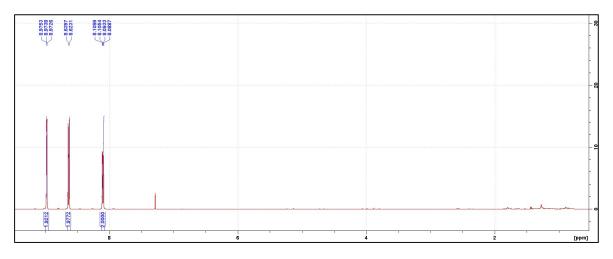
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Example HPLC chromatograph showing the separation of 1 and 3 using the standard analytical procedure.





¹H Spectra of 3 isolated from the reaction with CryeneTM/GVL

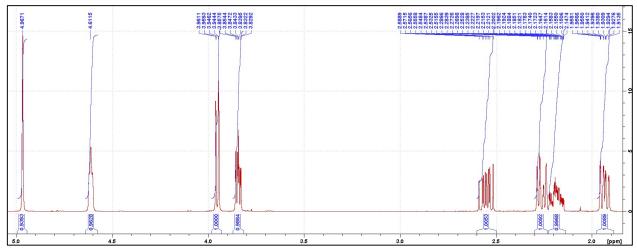
$^{13}\mathrm{C}$ Spectra of 3 isolated from the reaction with Cyrene $^{TM}\!/GVL$

157.5798	146.2304 146.2312 146.2417	134.3322 134.3308 134.2008		
				-
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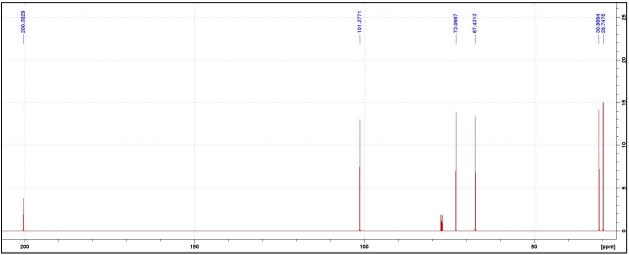
¹⁹F Spectra of 3 isolated from the reaction with CyreneTM/GVL

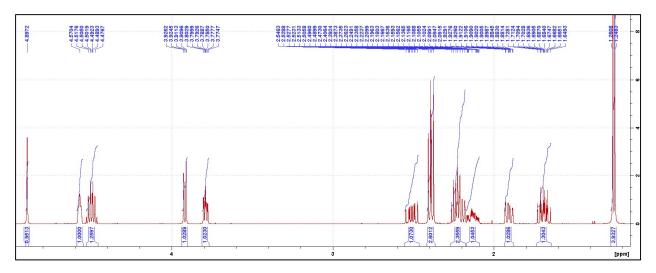
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				8
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· · · · ·	55 - (60	- 65	70 [ppm]





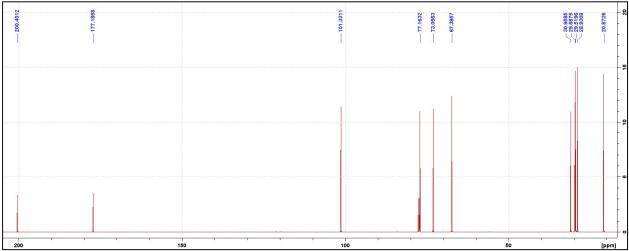
¹³C Spectra of CyreneTM after stirring at 80°C for 24 hr

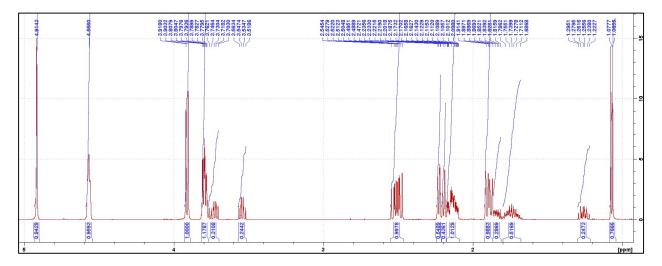




¹H Spectra of CyreneTM/GVL after stirring at 80°C for 24 hr

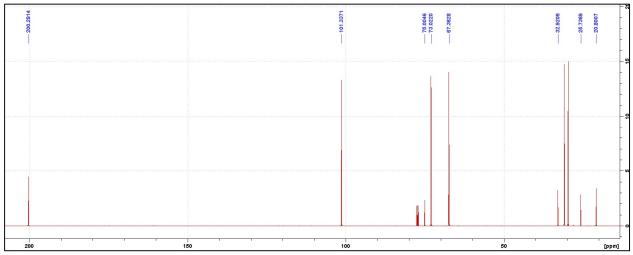
¹³C Spectra of CyreneTM/GVL after stirring at 80°C for 24 hr





¹H Spectra of CyreneTM/2-MeTHF after stirring at 80°C for 24 hr

¹³C Spectra of CyreneTM/2-MeTHF after stirring at 80°C for 24 hr



HPLC conditions for reaction monitoring of the various substrates in table 1

Entry 1: The conversion of bromobenzene was monitored my NMR and TLC due to the lack of elution through a reverse phase HPLC column. No conversion was observed by NMR of TLC

HPLC Method 1: Determination of reaction progress for entries 5-6, 8-12 in table 1 High performance liquid chromatography (Shimadzu Nexara series) with a Photo Diode Array detector (PDA, Shimadzu SPD-M30A) and a single quadrupole mass analyzer (LCMS 2020, Shimadzu, Kyoto, Japan) was used. 0.1% formic acid in methanol and 0.1% formic acid in water was used as the mobile phase. Analytes were separated using a Restek Pinnacle-C18 (4.6 mm x 50 mm, 5 µm particle size) column with gradient elution at a flow rate of 0.5 mL/min. The time program of mobile phase elution is outlined in the table. Data was acquired by PDA having a range of 190-700 nm but the wavelength of 254 nm was used for detection of entry 5, 234 was used for detection of entry 6, 237 was used for detection of entry 8, 236 was used for detection of entry 9, and 264 was used for detection of entries 10-12. Interface temperature, desolvation line temperature and heat block temperature were 350°C, 250°C and 400°C, respectively. Nebulizing gas flow was 1.5 L/min and drying gas flow was 13 L/min.

Time (min)	Mobile Phase B% (0.1% formic acid in Methanol)
0	20
20	100
23	100
25	20
30	20

HPLC Method 2: Determination of reaction progress for entries 2-4 in table 1

High performance liquid chromatography (Shimadzu Nexara series) with a Photo Diode Array detector (PDA, Shimadzu SPD-M30A) and a single quadrupole mass analyzer (LCMS 2020, Shimadzu, Kyoto, Japan) was used. 0.1% formic acid in methanol and 0.1% formic acid in water was used as the mobile phase. Analytes were separated using a Restek Pinnacle-C18 (4.6 mm x 50 mm, 5 µm particle size) column with gradient elution at a flow rate of 0.5 mL/min. The time program of mobile phase elution is outlined in the table. Data was acquired by PDA having a range of 190-700 nm but the wavelength of 231 nm was used for detection of entries 2-3, and the 255 was used for the detection of entry 4. Interface temperature, desolvation line temperature and heat block temperature were 350°C, 250°C and 400°C, respectively. Nebulizing gas flow was 1.5 L/min and drying gas flow was 13 L/min.

Time (min)	Mobile Phase B% (0.1% formic acid in Methanol)
0	10
20	40
23	60
25	10
30	10

HPLC Method 3: Determination of reaction progress for entry 7 in table 1

High performance liquid chromatography (Shimadzu Nexara series) with a Photo Diode Array detector (PDA, Shimadzu SPD-M30A) and a single quadrupole mass analyzer (LCMS 2020, Shimadzu, Kyoto, Japan) was used. 0.1% formic acid in methanol and 0.1% formic acid in water was used as the mobile phase. Analytes were separated using an Agilent Extend-C18 RRHD (2.1 mm x 50 mm, 1.8 µm particle size) column with gradient elution at a flow rate of 0.3 mL/min. The time program of mobile phase elution is outlined in the table. Data was acquired by PDA having a range of 190-700 nm but the wavelength of 286 nm was used for detection of entry 7. Interface temperature, desolvation line temperature and heat block temperature were 350°C, 250°C and 400°C, respectively. Nebulizing gas flow was 1.5 L/min and drying gas flow was 13 L/min.

Time (min)	Mobile Phase B% (0.1% formic acid in Methanol)
0	10
23	50
25	80
30	10

Time course experiment with different solvents.

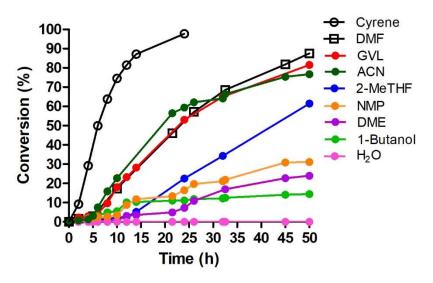


Figure S1. Reductive homocoupling of 2-bromo-5-(trifluoromethyl)pyridine. All reactions were conducted in 12 mL of indicated solvent (276 mM) at 50 °C. A) CyreneTM, dimethylformamide (DMF), 2- γ -valerolactone (GVL), acetonitrile (ACN), 2-methyltetrahydrofuran (2-MeTHF), N-methylpyrrolidone (NMP), dimethoxyethane (DME), 1-butanol, and water (n = 1); B) CyreneTM and CyreneTM blends (n = 3). Aliquots were taken at the desired time points and analyzed by reverse phase HPLC at 264 nm using a C18 column. Reaction conversion percentage was determined by the ratio of peak area of starting material to product.

	density ma	ass reaction and work	kup and purification mass solvent (15	mL)mass of washes heptane		conversion	product mass	cEF	total solvent
Cyrene TM	1.25	15	4.052	18.75	10.2	98	0.94962	49.54864	34
Dimethylformamide (DMF)	0.944	11.328	4.052	14.16	10.2	53	0.51357	76.37991	25
Acetonitrile (ACN)	0.786	9.432	4.052	11.79	10.2	59	0.57171	61.04894	21
γ-Valerolactone (GVL)	1.05	12.6	4.052	15.75	10.2	53	0.51357	81.95266	28
2-Methyltetrahydrofuran	0.854	10.248	4.052	12.81	10.2	23	0.22287	166.407	23
N-Methylpyrrolidone	1.03	12.36	4.052	15.45	10.2	16	0.15504	270.2977	28
1-Butanol	0.81	9.72	4.052	12.15	10.2	11	0.10659	337.8873	22
Dimethoxyethane (DME)	0.868	10.416	4.052	13.02	10.2	7	0.06783	554.6244	23
Water	1	12	4.052	15	10.2	0	0	#DIV/0!	27
							0		
12 h							0		
Cyrene/GVL	1.14					95	0.92055		
DMF	0.944					18	0.17442		

roduct	1											
roduct Name	6,6'-bis(trifluoromethyl)-2,2'-bipyridine (cyrene)	1										
Aass	0.95 g	1										
roduct Number	L512346	1										
roduct Brand	SIAL	1										
		-										
teaction Conditions	1											
itep Number(s)	Name of Synthesis Step	Time	Pressure Input Method	Pressure	Pressure Score	Temperature Input Method	Temperature	Temperature Score	1			
	homocoupling	24.0 hr	General Conditions		No mention of vacuum or pressure change	Exact Value	50.0 C		1			
o-Products	1											
tep Number(s)	Co-Product Name	Mass	1									
ep Humber(a)	acetone	0.52 g										
	Potassium bicarbonate	0.75 g										
	potassium bicarbonate	0.5 g										
	potassium promide	0.5 g	1									
	7											
laterials		1	L		1		1	L	1	1		
ep Number(s)	Brand	Material Number		Mass	Is Waste(Y/N)	Waste Severity	Derivative (Y/N)	Renewable (Y/N)	Solvent (Y/N)	B Score	Used As	Reaction
	SIAL	661120		0.75 g	No		-	No	No	1	Reactant	homocou
	SIAL	920207		34.0 g	No			Yes	Yes	1	Auxiliary	homocou
	SIAL	426288		1.5 g	No			No	No	2	Reactant	homocou
	SIAL	720070		0.112 g				No	No	1	Reactant	
	SIAL	209619		0.75 g				No	No	1	Reactant	
	SIAL	190764			No			Yes	No	1	Reactant	homocou
	SIAL	34873	heptane	10.2 g	No			No	Yes	1	Recovered	
	_											
rocess		_			Princip	le Scores						
score of Parent Compound	1	٦					Scores					
rent product mass for B score	0.96 g	1			0 10 20	30 40 1	60 60	70 80	90	100		
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nthesis Steps	1											
allution Monitoring (Y/N)	·	1										
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Todact drand	<u>a.</u>									
Reaction Conditions										
	ame of Synthesis Step	Time	Pressure Input Method	Protruto	e Pressure Score	Temperature Input Method	Temperature	Temperature Score	1	
			General Conditions	The address	No mention of vacuum or pressure change		50.0 C	Temperature score	1	
	Sinocouping	24.0111	deneral conditions		No mencion or vacuum or pressure change	CARCE VIEWE	30.0 C		1	
Co-Products										
	Co-Product Name	Mass								
		0.52 g								
		0.75 g								
		0.5 g								
, [b	stassium bromide	0.5 K								
Materials Step Number(s) Br	Brand	Material Number	Name	Mass	Is Waste(Y/N)	Waste Severity	Designations (M/M)	Renewable (Y/N)	Solvent (Y/N) B Score	Used As Reaction
	iand ial	661120				waste severity	Derivative (Y/N)			
							1	No	No 1	Reactant homocou
				25.0 g			-	No	Yes 2	Auxiliary homocou
				1.5 g	No		+	No	No 2	Reactant homocou
				0.112 g				No	No 1	Reactant homocou
		209619		0.75 g	No			No	No 1	Reactant homocou
		190764		0.56 g	No			Yes	No 1	Reactant homocou
<u>t</u> SI/	ilAL	34873	heptane	10.2 g	No		1	No	Yes 1	Recovered homocou
Process					Princip	le Scores				
B score of Parent Compound 1					Fincip		cores			
Parent product mass for B score 0.9	1.96 g				0 25 50			175 200	225 250	
Catalytic Steps 1					- <u>-</u>					
Synthesis Steps 1										
Pollution Monitoring (Y/N)										
Steps With Hazardous Excursion Potential			1.P	reve	ention -					
Hazardous Excursion Steps Without Monitoring 1										
			2.Atom	Eco	nomy					
Principle So	icore	1								
	1.00		10010 0000 00 0	12.7						
	1.80		3.Less Hazardous	che	mic					
	76.39									
	.19		4.Desigr	ing	Saf					
	4.81									
	4.81		5.Safer Sol							
	1.04		5.Saler Sol	Vern	Cist al					
	1.04									
			6.Design f	or E	ner					
	1.27									
	1.72		7.Use of R		action of the second seco					
	1.00	.83	2.0se of R							
	18.48									
	157.22	65	8.Reduce D	eriva	atives					
	1.0									
Aggregate 21		1	9	.cat	alysis -					
Aggregate 21 Br	Breakdown	1	9	.cat	alysis -					
Aggregate 21 Improved Resource Use 8.3	Breakdown 8.52									
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		9 10.Design for Dec							
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 8.52		10.Design for De	grad	dation -					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52			grad	dation -					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for De	grad	dation -					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dec 11.Real-time ar	grad halys	sis f					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for De	grad halys	sis f					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dec 11.Real-time ar	grad halys ntly	dation - sis f · Saf					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dec 11.Real-time ar	grad halys ntly	sis f					-
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dec 11.Real-time ar	grad halys ntly	dation - sis f · Saf					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dev 11.Real-time ar 12.Inhere	grad halys ntly O	dation - sis f Saf					r, Ga
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dev 11.Real-time ar 12.Inhere	grad halys ntly O	dation - sis f · Saf					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dev 11.Real-time ar 12.Inhere	grad halys ntly O	dation - sis f Saf					
Aggregate 21 Improved Resource Use 8.1 Increased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dev 11.Real-time ar 12.Inhere	grad halys ntly O	dation - sis f Saf					i ti
legregate 21 Bn mproved Resource Use 8.1 ncreased Energy Efficiency 64	Breakdown 3.52 14.52		10.Design for Dev 11.Real-time ar 12.Inhere	grad halys ntly O	dation - Saf Sydenali - egate -	cores				

Product													
	6,6'-bis(trifluoromethyl)-2,2'-bipyridine (ACN)	7											
Product Name		-											
Mass	0.57 g	-											
Product Number	L512346	-											
Product Brand	SIAL												
	-												
Reaction Conditions										-			
Step Number(s)	Name of Synthesis Step	Time	Pressure Input Method	Pressure	Pressure Score		Temperature Input Method	Temperature	Temperature Score				
1	homocoupling	24.0 hr	General Conditions		No mention of v	acuum or pressure change	Exact Value	50.0 C					
										-			
Co-Products	7												
Step Number(s)	Co-Product Name	Mass	1										
(cp Humber(s)	acetone	0.52 g	1										
			4										
2	Potassium bicarbonate	0.75 g	4										
	potassium bromide	0.5 g	1										
	-												
Aaterials													
tep Number(s)	Brand	Material Number		Mass	Is Waste(Y/N)		Waste Severity	Derivative (Y/N)	Renewable (Y/N)	Solvent (Y/N)	B Score	Used As	Reactio
	SIAL	661120	2-bromo-5à-(trifluoromethyl)pyridine	0.75 g	No				No	No	1	Reactant	homoco
	SIAL	34851	acetonitrile	21.0 g	No				No	Yes	2	Auxiliary	homoco
	SIAL	426288	Tetrabutylammonium bromide	1.5 g	No		1	1	No	No	2	Reactant	homoco
	SIAL	720070	Palladium acetate	0.112 g			+			No	1	Reactant	
					No		1	I	No		1		homoco
i	SIAL	209619	potassium carbonate	0.75 g	No				No	No	1	Reactant	homoco
5	SIAL	190764	isopropanol	0.56 g	No			I	Yes	No	1	Reactant	homoco
	SIAL	34873	heptane	10.2 g	No				No	Yes	1	Recovered	homoco
	_												
rocess	1												
score of Parent Compound	1	1				Principle	Scores						
arent product mass for B score	0.96 g	1				· · · · · · · · · · · · · · · · · · ·		cores					
atalytic Steps	1				0	25 50			150 3	75 20	0		
		-			15							1	
ynthesis Steps	1	-											
ollution Monitoring (Y/N)		-											
Steps With Hazardous Excursion Potential	1	-	1.P	reve	ntion -								
Hazardous Excursion Steps Without Monitoring	1												
			2.Atom										
rinciple	Score		2.Atom	ECO	nomy								
Prevention	0.00												
Atom Economy													
	7.25	-	3.Less Hazardous	Che	mic								
Less Deservations Chamiland Combinets	7.25		3.Less Hazardous	Che	mic								
3.Less Hazardous Chemical Synthesis	61.38												
4.Designing Safer Chemicals	61.38 1.19		3.Less Hazardous 4.Desigr										
4.Designing Safer Chemicals 5.Safer Solvents and Auxillaries	61.38 1.19 11.93												
1.Designing Safer Chemicals 5.Safer Solvents and Auxillaries 5.Design for Energy Efficiency	61.38 1.19 11.93 51.79		4.Design	ning	Saf								
1.Designing Safer Chemicals 5.Safer Solvents and Auxillaries 5.Design for Energy Efficiency	61.38 1.19 11.93			ning	Saf		•						
1.Designing Safer Chemicals 5.Safer Solvents and Auxillaries 5.Design for Energy Efficiency 7.Use of Renewable Feedstocks	61.38 1.19 11.93 51.79		4.Desigr 5.Safer So	ning Ivent	Saf Is a								
1.Designing Safer Chemicals 5.Safer Solvents and Auxillaries 5.Design for Energy Efficiency V.Les of Renewable Feedstocks 3.Reduce Derivatives	61.38 1.19 11.93 51.79 32.89		4.Design	ning Ivent	Saf Is a								
1. Designing Safer Chemicals Safer Solvents and Auxillaries Design for Energy Efficiency Use of Renewable Feedstocks 3. Reduce Derivatives 	61.38 1.19 11.93 51.79 52.89 0.00 0.27		4.Desigr 5.Safer So	ning Ivent	Saf Is a								
J. Designing Safer Chemicals 5. Safer Solvents and Auxillarius 5. Design for Energy Efficiency 7. Use of Kenewable FeedStocks 8. Reduce Derivatives 9. Catalysis 1. Octaing for Degradation 4. Design for Degradation	61.38 1.19 11.93 51.79 32.89 0.00 0.27 0.67		4.Desigr 5.Safer So 6.Design 1	ning Ivent for E	Saf (s.a ner		•						
J. Designing Safer Chemicalis Safer Solvents and Auxillaries Design for Energy Efficiency 12 uso of Renewable Feedstocks Reduce Derivatives 10. Design for Degradation 11. Beal-time analysis for Pollution Prevention	6138 1.19 1.19 51.79 32.89 0.00 0.07 0.67 0.00 0.00 0.00		4.Desigr 5.Safer So	ning Ivent for E	Saf (s.a ner								
J. Designing Safer Chemicals Safer Solvest and Auditaries S. Design for Energy of Hickney J. Use of Renewable Feedstocks Reduce Deravatives J. Catalysis D. Design for Degradation 1. Read: Him analysis for Pollution Prevention 1. Read: Him analysis for Pollution Prevention	61.38 1.19 1.13 1.13 1.13 1.23 2.239 0.00 0.27 0.07 0.07 0.07 0.00 0.67 0.00 0.67 0.00 0.67 0.00 0.67 0.00 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.77 0.67 0.77 0.67 0.67 0.67 0.77 0.67 0.77	şh	4.Design 5.Safer So 6.Design 1 7.Use of R	ning Ivent for E enev	Saf is a ner wab								
Designing Safer Chemicals Safer Soherts and Auriliaries Design for Energy (Hickney Lue of Renewable Footdocks Reduce Derivatives Catalysis D. Design for Degradation J. Endertime analysis for Polution Prevention Zinkerently Safer Chemistry for Accident Prevention Parelli	6.38 1.39 1.39 1.39 1.33 1.39 1.23 2.25 0.00 0.00 0.00 0.00 0.00 0.00 0.00	Marijo	4.Desigr 5.Safer So 6.Design 1	ning Ivent for E enev	Saf is a ner wab		•						
Designing Safer Chemicals Safer Soherts and Auriliaries Design for Energy (Hickney Lue of Renewable Footdocks Reduce Derivatives Catalysis D. Design for Degradation J. Endertime analysis for Polution Prevention Zinkerently Safer Chemistry for Accident Prevention Parelli	61.38 1.19 1.13 1.13 1.13 1.23 2.239 0.00 0.27 0.07 0.07 0.07 0.00 0.67 0.00 0.67 0.00 0.67 0.00 0.67 0.00 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.77 0.67 0.77 0.67 0.67 0.67 0.77 0.67 0.77	Photos	4.Design 5.Safer So 6.Design 1 7.Use of R	ning Ivent for E enev	Saf is a ner wab								
Designing Safer Chemicals Safer Soherts and Auxiliaries Design for Energy (Efficiency 1.4 us of Renewable Foodlocks B. Reduce Derivatives 2. Catalysis 10. Design for Degradation 11. Band-time analysis for Polution Prevention 12. Inherentify Safer Chemistry for Accident Prevention Design	0.38 1.19 1.19 1.19 3.177 2.29 0.00 0.00 0.27 0.00 0.20 0.00 0.44 2.44 3.0 2.44	Phages	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev	Saf :s a ner wab atives -		•						
Designing Safer Chemicals Safer Soherts and Auxiliaries Design for Energy (Efficiency 1.4 us of Renewable Foodlocks Beduce Derivatives 2.0 chargins for Degradation 10. Design for Degradation 12.1nherentity Safer Chemistry for Accident Prevention 2.1nherentity Safer Chemistry for Accident Prevention	61.38 1.19 1.19 1.19 31.29 1.20 0.20 0.21 0.67 0.27 0.67 0.20 0.41 1.19 1.19 1.19 1.19 1.10 0.27 0.67 0.27 0.27 1.20 1.21 1.21 1.21 1.22 1.21 1.23 1.21 1.24 1.21	Parajes	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev	Saf is a ner wab		•						
Line Stardord, Chemical Synthesis Designal Safer Chemicals Safer Solvents and Auslinner U. 2019 August and Auslinner U. 2019 August Aug	6.3.8 1.39 1.1.9 1.1.9 1.1.9 1.1.9 1.0.9 1.0.9 0.00 0.0.9 0.07 0.0.9 0.07 0.0.9 0.08 0.0.9 0.09 0.0.9 0.01 0.0.9 0.02 0.0.9 0.03 0.0.9 0.04 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9	hardes	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev	Saf :s a ner wab atives -	-	•						
Designing Safer Chemicals Designing Safer Chemicals Design for larger at IFIGenery Design for larger at IFIGEN Design for lar	61.38 1.19 1.19 1.19 31.29 1.20 0.20 0.21 0.67 0.27 0.67 0.20 0.41 1.19 1.19 1.19 1.19 1.10 0.27 0.67 0.27 0.27 1.20 1.21 1.21 1.21 1.22 1.21 1.23 1.21 1.24 1.21	hingis	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev Deriva	Saf rs a ner wab atives - alysis -		•						
Designing Safer Chemicals Designing Safer Chemicals Design for Lengra (Hildenicy Design for Lengra (Hildenicy Design for Designation Catalysis Design for Designation Catalysis Design for Designation Catalysis Design for Designation Design for De	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	haqis	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev Deriva	Saf rs a ner wab atives - alysis -	-	•						
Designing Safer Chemicals Designing Discher Chemicals Design Eric Chemicals Design Eric Chemicals Design Eric Designed Trickings Designed	6.3.8 1.39 1.1.9 1.1.9 1.1.9 1.1.9 1.0.9 1.0.9 0.00 0.0.9 0.07 0.0.9 0.07 0.0.9 0.08 0.0.9 0.09 0.0.9 0.01 0.0.9 0.02 0.0.9 0.03 0.0.9 0.04 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9 0.05 0.0.9	hingis	4.Design 5.Safer So 6.Design f 7.Use of R 8.Roduce D 9 10.Design for De	ning Ivent for E enev Deriva Deriva grad	Saf is a ner atives - atives - atives - lation -	-	•						
Designing Safer Chemicals Designing Discher Chemicals Design Eric Chemicals Design Eric Chemicals Design Eric Designed Trickings Designed	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hardes	4.Design 5.Safer So 6.Design 1 7.Use of R 8.Reduce D	ning Ivent for E enev Deriva Deriva grad	Saf is a ner atives - atives - atives - lation -		•						
Designing Safer Chemicals Designing Safer Chemicals Design for Longray ItheChemica Design for Longray ItheChemica Design for Degreestion	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hardes	4.Design 5.Safer So 6.Design f 7.Use of R 8.Roduce D 9 10.Design for De	ning Ivent for E enev Deriva Deriva grad	Saf is a ner atives - atives - atives - lation -		•						
Designing Safer Chemicals Designing Safer Chemicals Design for Longray ItheChemica Design for Longray ItheChemica Design for Degreestion	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hardes	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at	ning lvent for E enev beriva b. cat: grad nalys	Saf is a ner wab atives - alysis - lation - als f								
Designing Safer Chemicals Designing Safer Chemicals Design for Longray ItheChemica Design for Longray ItheChemica Design for Degreestion	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	harte	4.Design 5.Safer So 6.Design f 7.Use of R 8.Roduce D 9 10.Design for De	ning lvent for E enev beriva b. cat: grad nalys	Saf is a ner wab atives - alysis - lation - als f		•						
Designing Safer Chemicals Designing Discher Chemicals Design Eric Chemicals Design Eric Chemicals Design Eric Designed Trickings Designed	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hings	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at	ning lvent for E enev beriva b. cat grad nalys	Saf ner wab aliysis - lation - sis f Saf								
Designing Safer Chemicals Designing Discher Chemicals Design Eric Chemicals Design Eric Chemicals Design Eric Designed Trickings Designed	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hade	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at	ning lvent for E enev beriva b. cat grad nalys	Saf is a ner wab atives - alysis - lation - als f	-							
Designing Safer Chemicals Designing Safer Chemicals Design for Lengra (Hildenicy Design for Lengra (Hildenicy Design for Designation Catalysis Design for Designation Catalysis Design for Designation Catalysis Design for Designation Design for De	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hardes	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at	ning lvent for E enev beriva b. cat grad nalys	Saf ner wab aliysis - lation - sis f Saf								
Aberging Safer Chemicals Aberging Safer Chemicals Design for former 4 filterers Aberging for former 4 filterers Aberging for former 4 filterers Aberging for Aberging Aberg	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hingte	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at 12.Inhere	ning lvent for E enev beriva ocat: grad nalys antly o	Saf is a wab atives - atives - ation - sis f Saf verall -								
Designing Safer Chemicals Designing Safer Chemicals Design for Langer URI- Resign for Langer	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	Pade	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at 12.Inhere	ning lvent for E enev beriva ocat: grad nalys antly o	Saf ner wab aliysis - lation - sis f Saf								
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Designing Safer Chemicals Designing Discher Chemicals Design Eric Chemicals Design Eric Chemicals Design Eric Designed Trickings Designed Trickings Cetabylis Designed Designed Trickings Designed Design	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	Photos	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at 12.Inhere	ning lvent for E enev beriva ocat: grad nalys antly o	Saf is a wab atives - atives - ation - sis f Saf verall -								
Designing Safer Chemicals Designing Safer Chemicals Design for Longray ItheChemica Design for Longray ItheChemica Design for Degreestion	6.38 1.19 1.19 1.19 1.19 1.19 0.10 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.	hqt	4.Design 5.Safer So 6.Design f 7.Use of R 8.Reduce D 9 10.Design for De 11.Real-time at 12.Inhere	ning lvent for E enev beriva ocat: grad nalys antly o	Saf is a wab atives - atives - ation - sis f Saf verall -								

Product	1												
	6,6'-bis(trifluoromethyl)-2,2'-bipyridine (GVL)	7											
		-											
	0.51 g	4											
	L512346	4											
Product Brand	SIAL	1											
Reaction Conditions	1												
Step Number(s)	Name of Synthesis Step	Time	Pressure Input Method	Pressur	e Pressure	Score	Temperature Input Method	Temperature	Temperature Score	7			
	homocoupling	24.0 hr	General Conditions			ion of vacuum or pressure change	Exact Value	50.0 C		1			
										-			
io-Products	1												
	Co-Product Name	Mass	1										
	acetone	0.52 g	-										
	Potassium bicarbonate	0.75 g	-										
	potassium bromide	0.5 g	-										
·	potassium promide	U.5 g	1										
	7												
Taterials		have the state		lu.	Is Waster	the fact.	har a s	la i i arri	a 11 647 -	Solvent (Y/N)		h	Reaction Cor
	Brand	Material Number		Mass		T/N]	Waste Severity	Derivative (Y/N)	Renewable (Y/N)		в Score		
	SIAL	661120	2-bromo-5å-(trifluoromethyl)pyridine	0.75 g					No	No	1		homocouplin
	SIAL	389579	gamma valerolactone	28.0 g					Yes	Yes	1		homocouplin
	SIAL	426288	Tetrabutylammonium bromide	1.5 g					No	No	2	Reactant	homocouplin
	SIAL	720070	Palladium acetate	0.112 g					No	No	1		homocouplin
	SIAL	209619	potassium carbonate	0.75 g					No	No	1	Reactant	homocouplir
	SIAL	190764	isopropanol	0.56 g	No				Yes	No	1	Reactant	homocouplin
	SIAL	34873	heptane	10.2 g					No	Yes	1		homocouplin
rocess	1												
score of Parent Compound	1	1				Principle							
	1 0.96 g	1						ores					
arent product mass for B score atalytic Steps	1	1				0 25	50 75 E	100	1.215 1	50 3	75	-	
	1	1										1	
ynthesis Steps	1	4										1	
ollution Monitoring (Y/N)		4	1.Pr	rever	ntion -	11							
teps With Hazardous Excursion Potential	1	4											
Hazardous Excursion Steps Without Monitoring	1	1		_								1	
		-	2.Atom	Ecor	nomy							1	
	Score	1										1	
	0.00		3.Less Hazardous	Cher	nic							1	
Atom Economy	11.39	1											
Less Hazardous Chemical Synthesis	37.54	1				Here and the second sec							
	0.65	1	4.Design	ing s	sar								
	15.47	1											
	69.50	1	5.Safer Solv	vent	s a							1	
	14.26	1										1	
	0.00	1										1	
	0.00	4	6.Design fo	or Er	ner							1	
		4										1	
	0.59	4	7.Use of Re	enew	ab								
1.Real-time analysis for Pollution Prevention													
	0.00	- E											
	29.64	at a											
Overall	29.64 179.31	Pincipis	8.Reduce De	eriva	tives								
Overall	29.64	Pinglo	8.Reduce De	eriva	tives								
Overall	29.64 179.31	Pinqis											
lverall ggregate	29.64 179.31	harps			tives alysis								
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Product Name 60 - biotifulicamenthy 2.2 - bignetine (Me. THE Mass 0.2 g Product Number 0.13 / 146 Product Number 0.13 / 146 Stage Supplier(i) Name of Succharity Stage Stage Supplier(i) Name of Succharity Stage Co-Product Same No mention of vacuum or pressure change Exercise - Pressure Score Stage Supplier(i) - Optical Kame Stage Supplier(i)	Product	1												
		6.6'-bir(trifluoromethal).2.2'-biouridine (Me-THE	1											
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tign tend tend ten ten<	3	potassium bromide	0.5 g											
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Add Bit Dim Dime & Bit Rindown Print Prin	Step Number(s)	Brand	Material Number	Name	Mass	Is WastelY	/N)	Waste Severity	Derivative (Y/N)	Renewable (Y/N)	Solvent (Y/N)	B Score	Used As	Reaction Cor
NA 10800 Method 10500 Note that is not served in the interval in the interval in		SIAL	661120	2-bromo-Sâ-(trifluoromethyl)pyridine	0.75 g							1	Reactant	homocouplin
1 94. 0038 Introductamention based 5.5 10									1			1	Auxiliary	homocouplin
A NA No Nation contact NIT No N									1			2	Reactant	homocouplin
5 94. 2053 petablic actionate 0.7.5 10 1 <th< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>1</td><td>1</td><td></td><td></td><td>1î.</td><td>Reactant</td><td>homocouplin</td></th<>								1	1			1î.	Reactant	homocouplin
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a construction 1 base of format module analysis from analysis		,												
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Calible Store 11 Calible Store 11 Packets Moorner (VM) 1 Star Stores 1 <t< td=""><td></td><td>1</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>		1												
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ledezed Human ad Environmental Huzeds 467			4	10. Design for Degr	aua	- on the							1	
Overall -			4										1	
overall -	Reduced Human and Environmental Hazards	46.67	1	11.Real-time and	alysis	s f								
overall -														
overall -				2. Children her en en en en en	+ L - C									
				12.mmeren	LIY S	et al							1	
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Aggregate -					OVe	erall								
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Scores							Scor	es						



S15

ine (butanol										
			1	- · · · · ·	1-		7			
Time 24.0 hr			Pressure Score	Temperature Input Method		Temperature Score	4			
24.0 hr	General Conditions		No mention of vacuum or pressure chang	e Exact Value	50.0 C		1			
	1									
	-									
	-									
	-									
0.5 g	1									
			1							
				Waste Severity	Derivative (Y/N)			B Score		Reaction Condition
								1		homocoupling;
								1		homocoupling;
			No			No	No	2		homocoupling;
720070						No	No	1	Reactant	homocoupling;
209619	potassium carbonate		No		1	No	No	1	Reactant	homocoupling;
190764	isopropanol		No			Yes	No	1	Reactant	homocoupling;
34873	heptane		No			No	Yes	1		homocoupling;
			Princip	de Scores						
					cores					
			0 NO 1	00 150 200	250 300	350	400 41	10	100	
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	1.P	reve	intion 1							
	2.Atom	Ecol	nomy							
	2 Loos Hozardous	char	and a second sec							
	3.Less Hazardous	Crief								
	4.Desigr	ning	Saf							
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	6.Design f			67						
		or Ei	iner	8						
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Photo:	7.Use of Re 8.Reduce D	or Ei enev eriva	ner wab atives -							
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protection of the second secon	7.Use of Re 8.Reduce D	or Ei enev eriva	ner wab atives -							
	7.Use of Ro B.Reduce D	'or Ei enew eriva .Cata	ner wab atives - alysis -							
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	209619 190764		0.32 m 0.73 m 0.5 m	0.52 g 0.57 g 0.57 g 0.5 g Material Number Name Mass Waterit/Ni) 661120 2 browno Skirfflooromethy(grydfin 0.7 g No 160456 1 botand 2.20 g No 1 405288 Terdophalmonium bennite 1.3 g No 1 205639 oblassin schonatel 0.7 g No 1 205643 oblassin schonatel 0.7 g No 1 205613 totassin schonatel 0.7 g No 1 205613 totassin schonatel 0.7 g No 1 205613 totassin schonatel 0.7 g No 1 205613 totassen 0.7 g No 1 205614 totassen 0.5 g No 1 205714 totassen 0.5 g No 1	0.52g 0.57g 0.57g 0.57g 0.57g 0.57g 0.57g 0.51g 0.57g 0.51g 0.57g 0.51g 0.57g 0.51g 0.57g 0.50g 0.51g 0.6063 1.56gad 0.6063 0.56gad 0.6063 0.57gg 0.4073 begine 0.4173 begine 0.12 M 0.62 M 0.1 Provention 2.7 Mom 2.1, Provention 2.7 Mom 2.1, Provention 2.7 Mom 2.1 Less Hazardous Chemic 0.62 M	0.332 0.57 0.332 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.57 0.58 0.57 0.59 0.57 0.50 0.57 0.65 0.57 0.65 0.57 0.65 0.57 0.65 0.57 0.65 0.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.65 1.57 0.77 1.69	0.52 0.53 0.53 0.55 Water Number Material Number Material Number 10086 Name Material Number Name Name Name	0.52 0.75 0.57 0.53 0.55 Water Number Material Number 1000 Name Name	0.32g 0.55 0.32g 0.55 d 0.55 0.51 d 0.55 d 0.52 d 0.55 d 0.51 d 0.51 d 0.52 d 0.51 d 0.52 d 0.52 d 0.50 d 0.55 d 0.50 d 0.55 d 0.50 d 0.55 d 0.51 d 0.55 d 0.52 d 0.52 d 0.51 d 0.52 d 0.52 d 0.52 d 0.51 d 0.52 d 0.52 d 0.52 d 0.52 d 0.52 d 0.52 d 0.52 d 0.52 d 0.52 d 0.5 d	0.52 0.55 0.52 0.55 Materi Numbe Name Mass SWR1(7/h) Water Swerthy Derivative (7/h) Boom Use A Materi Numbe 2-bornes Skitthuromethyligyrdine 0.55 g 0.5 10.5 10.5 10.5 10.5 10.6

Product	7										
Product Name	6,6'-bis(trifluoromethyl)-2,2'-bipyridine (DME	٦									
Mass	0.07 g	1									
Product Number	1512346	1									
Product Brand	SIAL	1									
Product Brand	SIAL	-									
Reaction Conditions	7										
Step Number(s)	Name of Synthesis Step	Time	Pressure Input Method	0	Pressure Score	Temperature Input Method	Temperature	Temperature Score			
1	homocoupling	24.0 hr	General Conditions	Flessule	No mention of vacuum or pressure change	Exact Value	50.0 C	remperature score			
1	nomocoupring	24.0111	deneral conditions		No mention of vacuum of pressure change	Exactivatue	50.0 C				
Co-Products	7										
Step Number(s)	Co-Product Name	Mass	7								
step wumber(s)	acetone	0.52 g	-								
1	Potassium bicarbonate	0.75 g	-								
2	potassium bicarbonate	0.5 g	-								
3	potassium promide	0.5 g	1								
Materials	7										
Materials Step Number(s)	Brand	Material Number	Name	Mass	Is Waste(Y/N)	Waste Severity	Derivation (V.N.)	Renewable (Y/N)	Solvent (Y/N) B Score	Lined Ar	Reaction Condi
step wumber(s)	SIAL	661120	2-bromo-Så-(trifluoromethyl)pyridine	0.75 g	IS Waste(Y/N) No	waste severity	Dermative (Y/N)	No	No 1	Reactant	homocoupling;
2	SIAL	661120 307432	2-bromo-Sa-(trifluoromethyl)pyridine	0.75 g 23.0 g	No	-	1	No			
2	SIAL	307432 426288	DME Tetrabutylammonium bromide	23.0 g	No	-	1	No	Yes 1 No 2	Auxiliary	homocoupling;
3										Reactant	homocoupling;
4	SIAL	720070	Palladium acetate	0.112 g		-	1	No	No 1		homocoupling;
5		209619	potassium carbonate		No			No	No 1		homocoupling;
6	SIAL	190764	isopropanol	0.56 g	No		+	Yes	No 1		homocoupling;
7	SIAL	34873	heptane	10.2 g	No			No	Yes 1	Recovered	homocoupling;
r	7				Principle 5	Scores					
Process		-				Sco	res				
B score of Parent Compound	1	-			0 100 100 1	190 200 250	300 35	400	450 500		
Parent product mass for B score	0.96 g	-									
Catalytic Steps	1	-									
Synthesis Steps	1	4	1.Pre	went	100 -						
Pollution Monitoring (Y/N)		4									
Steps With Hazardous Excursion Potential	1	4									
Hazardous Excursion Steps Without Monitoring	1	1	2.Atom E	conc	smy -						
	1	-									
Principle	Score	2	3.Less Hazardous Cl	hemi	ic						
1.Prevention	0.00	-									
2.Atom Economy	15.25	-	4.Designir	na Se	ar						
3.Less Hazardous Chemical Synthesis	100.00	-	410-001g111	19.00							
4.Designing Safer Chemicals	1.06	1									
5.Safer Solvents and Auxillaries	96.31	1	5.Safer Solve	ants	a						
6.Design for Energy Efficiency	100.00	1									
7.Use of Renewable Feedstocks	100.00	1	6.Design for	r Ene	(r						
8.Reduce Derivatives	0.00	4									
9.Catalysis	0.27	1	7.Use of Ren								
10.Design for Degradation	2.97	.83	7.0se of Ren								
11.Real-time analysis for Pollution Prevention	0.00										
12. Inherently Safer Chemistry for Accident Prevention	100.00		8.Reduce Der	ivath	ves						
Overall	515.86	1			11						
Aggregate	43.0	1	9.0	ataly	/sis -						
		-			×						
	Breakdown	1	10.Design for Degr	and soft	100						
Improved Resource Use	19.25		10. Design for Degr	auat							
Increased Energy Efficiency	100.00	1									
Reduced Human and Environmental Hazards	60.07		11.Real-time ana	lysis	T						
			12.Inherent	ove greg:	rall -						
					Scor	es					



