

# Reformulating Cyrene™

## Improving the properties and handling of Cyrene™

### Introduction

In order to meet environmental regulations, the search for greener alternatives to DMF and NMP has been an ongoing effort. Cyrene™ (Dihydrolevoglucosenone),<sup>1</sup> a fully biodegradable waste product, has emerged recently as an option.<sup>2</sup> Cyrene™'s high viscosity allows it to excel in some applications such as graphene dispersion, however high viscosity might not be ideal when compared to traditional solvents in regard to synthesis.

2-Methyltetrahydrofuran (2-MeTHF) has been on the market for at least 40 years and is a well-established alternative for ether solvents such as tetrahydrofuran (THF), which provides good water separation allowing for easier product recovery and solvent recovery than THF, further 2-MeTHF is made from renewable materials being derived from furfural.  $\gamma$ -Valerolactone (GVL) has become a novel green solvent in recent years, being used as an alternative for NMP and DMF for coupling reactions due to the low toxicity and the ability to make the solvent in a green method from renewable resources.

By blending Cyrene™ with these two renewably derived green solvents, we have been able to produce two new Cyrene™ mixtures that have lower viscosity which makes it easier for them to be used in automated processes while retaining the performance and product yields compared using Cyrene™ for common reactions such as HATU amide coupling, Suzuki-Miyaura cross-coupling, sonogashira cross-coupling and 2-pyridyl homocoupling.

By optimizing the greenness, low toxicity, and performance we put forward two new Cyrene™ mixtures: Cyrene™  $\gamma$ -Valerolactone (**920207**) and Cyrene™ 2-MeTHF (**920193**).

### Product Description

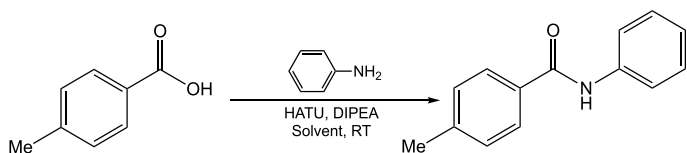
The two Cyrene™ Blends **920207** (Cyrene™  $\gamma$ -Valerolactone Blend) and **920193** (Cyrene™ 2-MeTHF Blend) are available from **SigmaAldrich.com**. Some of their properties are listed in the table below; more details can be found in the product detail pages at **SigmaAldrich.com**

Cat. No.	Description	Viscosity (cP)	Density (g/mL)
<b>920207</b>	Cyrene™ $\gamma$ -Valerolactone Blend	4.05	1.14
<b>920193</b>	Cyrene™ 2-MeTHF Blend	3.72	1.15
<b>807796</b>	Cyrene™, BioRenewable	10.5	1.25
<b>918660</b>	$\gamma$ -Valerolactone, BioRenewable, $\geq 99\%$ , ReagentPlus®	2.2	1.05
<b>673277</b>	2-Methyltetrahydrofuran, BioRenewable, anhydrous, $\geq 99\%$ , Inhibitor-free	0.5	0.86
<b>155810</b>	2-Methyltetrahydrofuran, BioRenewable, ReagentPlus®, $\geq 99.5\%$ , contains 150–400 ppm BHT as stabilizer	0.5	0.86
<b>414247</b>	2-Methyltetrahydrofuran, BioRenewable, anhydrous, $\geq 99.0\%$ , contains 250 ppm BHT as stabilizer	0.5	0.86
<b>319937</b>	N,N-Dimethylformamide (DMF)	0.9	0.94
<b>443778</b>	1-Methyl-2-pyrrolidinone (NMP)	1.7	1.03

### Product Applications

Both Cyrene™ Blends (**920207**, **920193**) have demonstrated their usefulness in several chemical transformations, as shown in the examples below. Likewise, comparable yields (vs neat Cyrene™, neat DMF, and neat NMP) were observed in the reactions tested (HATU amide coupling, Suzuki-Miyaura coupling, Sonogashira coupling, and 2-pyridyl homocoupling).

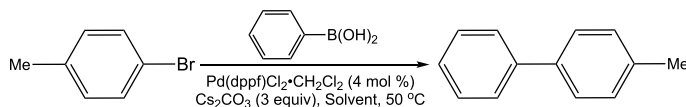
### Example of HATU Amide Coupling: Synthesis of 4-Methyl-N-phenylbenzamide



To a 20 mL Radley reaction tube was added *p*-toluic acid (170 mg, 1.25 mmol, 1 equiv), HATU (570 mg, 1.50 mmol, 1.2 equiv), *N,N*-diisopropylethylamine (655  $\mu$ L, 3.76 mmol, 3 equiv), and solvent (6 mL). The reaction mixture was stirred at room temperature for 30 minutes before addition of aniline (125  $\mu$ L, 1.37 mmol, 1.1 equiv). The reaction mixture was stirred further at room temperature for 2 hours. It was then diluted with EtOAc (10 mL) and washed with 1 M HCl (2 x 20 mL) and brine (20 mL). The organics were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give a residue which was subsequently purified by flash chromatography (silica gel, 0–20% EtOAc in petroleum ether) to afford the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.79 (s, 1H), 7.78–7.75 (m, 2H), 7.66–7.62 (m, 2H), 7.40–7.35 (m, 2H), 7.31–7.27 (m, 2H), 7.18–7.12 (m, 1H), 2.43 (s, 3H).

Entry	Solvent	Isolated Yield
1	Cyrene™	80.4%
2	Cyrene™ $\gamma$ -Valerolactone Blend	90.7%
3	Cyrene™ 2-MeTHF Blend	90.2%
4	<i>N,N</i> -Dimethylformamide (DMF)	94.8%
5	1-Methyl-2-pyrrolidinone (NMP)	92.6%

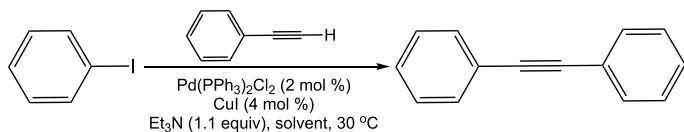
### Example of Suzuki–Miyaura Coupling: Synthesis of 4-Phenyltoluene



To a 20 mL Radley reaction tube was added Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (41.0 mg, 0.05 mmol, 4 mol %), 4-bromotoluene (214 mg, 1.25 mmol, 1 equiv), Cs<sub>2</sub>CO<sub>3</sub> (1.22 g, 3.75 mmol, 3 equiv), phenylboronic acid (228.7 mg, 1.88 mmol, 1.5 equiv) or phenylboronic acid MIDA ester (437.2 mg, 1.88 mmol, 1.5 equiv), solvent (5 mL), and water (9 mL). The tube was then capped and placed under N<sub>2</sub>. The reaction mixture was heated to 50 °C with stirring for 16 hours. The reaction mixture was cooled down to room temperature and diluted with EtOAc (10 mL) followed by washing with water (2 x 20 mL) and brine (2 x 20 mL). The organics were then dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give a yellow oil which was purified by filtering through a silica plug (eluted in 100% petroleum ether) to afford the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.63–7.59 (m, 2H), 7.54–7.51 (m, 2H), 7.48–7.43 (m, 2H), 7.38–7.33 (m, 1H), 7.30–7.27 (m, 2H), 2.43 (s, 3H).

Entry	Solvent	Isolated Yield
1	Cyrene™	85.0%
2	Cyrene™ $\gamma$ -Valerolactone Blend	99.1%
3	Cyrene™ 2-MeTHF Blend	95.4%
4	<i>N,N</i> -Dimethylformamide (DMF)	99.7%
5	1-Methyl-2-pyrrolidinone (NMP)	97.8%

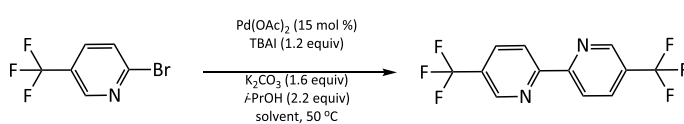
### Example of Sonogashira Coupling: Synthesis of Diphenylacetylene



To a 20 mL Radley reaction tube was added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (17.5 mg, 0.02 mmol, 2 mol %), CuI (9.5 mg, 0.05 mmol, 4 mol %), iodobenzene (139.5 μL, 1.25 mmol, 1 equiv), phenylacetylene (178 μL, 1.62 mmol, 1.3 equiv), Et<sub>3</sub>N (190 μL, 1.36 mmol, 1.1 equiv), and solvent (2.5 mL). The tube was then capped and placed under N<sub>2</sub>. The reaction mixture was heated to 30 °C with stirring for about 2 hours before the vessel was vented and the cap removed. The solution was then diluted with EtOAc (5 mL) and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organics were then dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a yellow oil which was purified by filtering through a silica plug (eluted in 100% petroleum ether) to afford the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.58–7.50 (m, 4H), 7.38–7.31 (m, 6H).

Entry	Solvent	Isolated Yield
1	Cyrene™	95.0%
2	Cyrene™ γ-Valerolactone Blend	98.3%
3	Cyrene™ 2-MeTHF Blend	91.9%
4	N,N-Dimethylformamide (DMF)	99.0%
5	1-Methyl-2-pyrrolidinone (NMP)	99.8%

### Example of 2-Pyridyl Homocoupling: Synthesis of 5,5'-Bis(trifluoromethyl)-2,2'-bipyridine



To a 20 mL Radley reaction tube was added 2-bromo-5'-(trifluoromethyl)pyridine (0.75 g, 3.32 mmol, 1 equiv), Pd(OAc)<sub>2</sub> (112.5 mg, 0.05 mmol, 15 mol %), TBAI (1.50 g, 4.06 mmol, 1.2 equiv), K<sub>2</sub>CO<sub>3</sub> (0.75 g, 5.43 mmol, 1.6 equiv), and solvent (12 mL). The tube was then capped and placed under N<sub>2</sub>. The reaction mixture was heated to 50 °C with stirring for about 30 minutes before addition of 2-propanol (0.56 mL, 7.32 mmol, 2.2 equiv). The reaction mixture was maintained at 50 °C for 18 hours. The reaction mixture was cooled down to room temperature, and then filtered through Celite®. The Celite pad was further washed with dichloromethane (20 mL X 2). The filtrate was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a dark brown oil that was taken up in petroleum ether (3 x 30 mL). The petroleum ether layers were combined and concentrated under reduced pressure to afford the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.99 (m, 2H), 8.65 (m, 2H), 8.12 (m, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>, 471 MHz) δ -62.69.

Entry	Solvent	Scale	Isolated Yield
1	Cyrene™ 2-MeTHF Blend	500 mg	49.9%
2	Cyrene™ 2-MeTHF Blend	5 g	51.5%
3	Cyrene™ 2-MeTHF Blend	50 g	52.3%

1. Cyrene™ is a trademark of Circa Group Pvt Ltd.

2. (a) J. Sherwood, M. De bruyn, A. Constantinou, L. Moity, C. Rob McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunta, J. H. Clark, Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents. *Chem. Commun.* **2014**, 50, 9650. (b) K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson, A. J. B. Watson, Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation. *Beilstein J. Org. Chem.* **2016**, *12*, 2005. (c) K. L. Wilson, J. Murray, C. Jamieson, A. J. B. Watson, Cyrene as a bio-based solvent for HATU mediated amide coupling. *Org. Biomol. Chem.* **2018**, *16*, 2851. (d) J. E. Camp, Bio-available solvent cyrene: synthesis, derivatization, and applications. *ChemSusChem* **2018**, *11*, 3048. (e) C. Grune, J. Thamm, O. Werz, D. Fischer, Cyrene™ as an alternative sustainable solvent for the preparation of poly(lactic-co-glycolic acid) nanoparticles. *J. Pharm. Sci.* **2020**, *110*, 959. (f) K. Pan, Y. Fan, T. Leng, J. Li, Z. Xin, J. Zhang, L. Hao, J. Gallop, K. S. Novoselov, Z. Hu, Sustainable production of highly conductive multilayer graphene ink for wireless connectivity and IoT applications. *Nat. Commun.* **2018**, *9*, 5197. (g) A. Alhifthy, B. L. Harris, L. Goerigk, J. M. White, S. J. Williams, Structure–reactivity correlations of the abnormal Beckmann reaction of dihydrolevoglucosenone oxime. *Org. Biomol. Chem.* **2017**, *15*, 10105. (h) R. A. Milesescu, A. Zhenova, M. Vastano, R. Gammons, S. Lin, C. Lau, J. H. Clark, C. R. McElroy, A. Pellis, Polymer chemistry applications of cyrene and its derivative Cygnet 0.0 as safer replacements for polar aprotic solvents. *ChemSusChem* **2021**, *14*, 1.

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