Development and Execution of a Production-Scale Continuous [2+2] Photocycloaddition

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Supporting Information

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I. Details of crystallization development

Preliminary optimization efforts included dissolution of a crude reaction sample from the 500 g/day demonstration in a minimal volume of toluene or acetone at elevated temperatures followed by addition of an antisolvent and cooling (as noted). Table S1 details the results of these trials.

Table S1: Evaluation of conditions for crystallization of cyclobutane **2**.

Solvent system	Temperature	Potency (wt%)	Purity (GC area%)	Recovery	Appearance
1 V Tol. / 1 V *c*-Hex	20 °C	89	98.4	72.2%	Sticky yellow solid
1 V Tol. / 1 V *c*-Hex	10 °C	86	97.0	74%	yellow solid
2 V Tol. / 2 V *c*-Hex	10 °C	88	97.7	76.3%	yellow solid
3 V Tol. / 3 V *c*-Hex	10 °C	86	93.5	56%	yellow solid
2 V Tol. / 2 V Bu_2O	10 °C	90	91.6	49%	yellow solid
2 V Tol. / 2 V Bu_2O	20 °C	91	96.3	39.3%	yellow solid
3 V Tol. / 3 V Bu_2O	10 °C	96	98.8	49.4%	white solid
2 V Tol. / 2 V MTBE	10 °C	93	96.8	45.3%	white solid
1 V Tol. / 2 V Bu_2O	10 °C	78	86.7	55.3%	yellow solid

Solvent system	Temperature	Potency (wt%)	Purity (GC area%)	Recovery	Appearance
1 V Tol. / 2 V MTBE	10 °C	97	99.6	48.8%	white solid
1 V Tol. / 2V (i-Pr)$_2$O	10 °C	86	95.3	51.4%	Yellow solid
1 V Tol. / 1 V (i-Pr)$_2$O	10 °C	90	98.9	56.7%	Yellow solid
1 V Tol. / 1 V MTBE	10 °C	96	98.8	48.1%	White solid
0.5 V Tol. / 2 V (i-Pr)$_2$O	10 °C	96	99.5	52.3%	Yellow solid
0.5 V Tol. / 1 V (i-Pr)$_2$O	10 °C	73	76.2	71.6%	Yellow solid
0.5 V Tol. / 1 V MTBE	10 °C	93	99.1	53.5%	White solid
1 V Tol. / 2 V MTBE	–10 °C	97	96.2	62.5%	White solid
1 V Tol. / 2 V MTBE	–20 °C	92	92.8	60.1%	White solid
0.5 V Tol. / 6 V MTBE	–20 °C	89	93.0	65.8%	White solid
0.5 V Tol. / 6 V MTBE	–10 °C	97	96.1	63.7%	White solid
0.5 V Tol. / 4 V MTBE	–10 °C	94	95.2	65.7%	White solid
0. 5 V Acetone / 4 V MTBE	–10 °C	96	99.7	68.9%	White solid
0.5 V Acetone / 6 V MTBE	–10 °C	96	99.2	62.0%	White solid
3 V MTBE / 3 V MTBE	–10 °C	94	97.9	66.0%	Pale yellow solid
0.5 V Acetone / 4 V MTBE	–20 °C	94	98.2	65.2%	White solid
0.2 V Acetone / 4 V MTBE	–20 °C	95	98.4	63.0%	White solid
0.2 V Acetone / 4 V MTBE	–10 °C	93	98.1	67.2%	White solid
0.2 V Acetone / 2 V EA	–20 °C	95	95.3	59.6%	Red sticky solid
0.2 V Acetone / 2 V IPAc	–20 °C	95	98.0	72.1%	White solid
0.2 V Acetone / 4 V MTBE	–20 °C	95	97.4	68.5%	White solid
0.2 V Acetone / 4 V EA	–20 °C	97	97.9	40.2%	White solid
0.2 V Acetone / 6 V EA	–20 °C	97	97.1	38.2%	White solid
0.2 V Acetone / 4 V IPAC	–20 °C	94	97.6	64.2%	White solid
0.2 V Acetone / 6 V IPAc	–20 °C	97	98.8	51.9%	White solid

Solvent system	Temperature	Potency (wt%)	Purity (GC area%)	Recovery	Appearance
0.2 V Acetone / 4 V EA	–35 °C	97	97.2	52.8%	White solid
0.2 V Acetone / 4 V IPAc	–35 °C	97	98.5	60.4%	White solid
0.5 V Acetone / 6 V MTBE	–20 °C	91	97.9	67.3%	White solid
3 V Acetone	–30 °C	97	98.4	38.2%	White solid
0.2 V Acetone / 4 V MTBE	–30 °C	94	98.6	61.0%	White solid
0.5 V Acetone / 4 V MTBE	–30 °C	93	98.8	64.3%	White solid
1 V Acetone / 4 V MTBE	–30 °C	92	98.9	57.2%	White solid
1 V Acetone / 6 V MTBE	–30 °C	90	99.0	51.6%	White solid
1 V Acetone / 6 V MTBE	–20 °C	92	99.1	52.8%	White solid

As described in the main text, an updated isolation protocol was designed to remove the insoluble impurity responsible for the low potency of isolated solids. Tables S2 and S3 provides representative examples of this optimization effort utilizing isolation methods 1 and 2, respectively.

Table S2: Experimental data for isolation by method 1.

Method 1: Crude product was dissolved in toluene (5 L/kg) at the noted temperature and the insoluble solid was filtered. The filtrate was concentrated and then recrystallized from toluene and MTBE or cyclohexane and was filtered at the noted temperature.

Filtration temp (°C)	Product losses (%)	Solvent system	Potency (wt%)	Purity (GC area%)	Recovery
22	24	Did not proceed due to high losses			
40	3.2	2 V Tol. / 2 V *c*-Hex	92	96.8	78%
30	2.3	0.5 V Tol. / 2.5 V MTBE	95	98.3	80%
35	1.3	0.5 V Tol. / 2.5 V MTBE	95	98.3	80%
30	3.0	1 V Tol. / 2.5 V MTBE	97	98.4	80%

Table S3: Experimental data for isolation by method 2.

Method 2: Crude product was dissolved in toluene (1 L/kg) and MTBE (2.5 L/kg) at 60 °C and the insoluble solid wasfiltered. The filtrate was cooled to the noted temperature, filtered, and washed with MTBE (2 L/kg).

Filtration temp (°C)	Product losses (%)	Recrystallization temperature (°C)	Potency (wt%)	Purity (GC area%)	Recovery
60	2.3	–15	98	98.1	80%
60	2.4	–20	97	97.0	76%
60	2.4	–15	96	97.8	84%
60	2.9	–5	98	99.0	80%
60	3.4	0	98	99.1	78%

II. Analytical Methods

GC method for IPC and product purity:

Column style	HP-5, 30 m*0.32 mm*0.25 um
Temp. Program:	50°C hold for 2 min, Ramp at 20°C /min to 260°C, hold for 10 min
Injector temperature	250°C;
Detector temperature	FID Detector, 300°C;
Run time	22.5 min
Carrier gas	He
Column flow	3.0 mL/min, constant flow
Split ratio	30:1
Hydrogen flow	40 mL/min
Air flow	400 mL/min
N_2 flow	25 mL/min
Make-up gas	N_2

q-NMR for product potency:

Deuterated solvent: Acetone

Internal standard sample: 1,3,5-trimethoxybenzene