

**Automated On-demand Titration of Organometallic Reagents in
Continuous Flow**

Supporting Information

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A. Materials, Methods, and General Considerations

For the performed titrations, all glassware was dried in a 120 °C oven overnight and cooled in a desiccator prior to use. All volumetric glassware, syringes, tubing, and connectors were dried in a vacuum oven overnight at 40 °C and cooled in a desiccator prior to use. Manipulations of all air-sensitive reagents were carried out using standard Schlenk technique. All solvents were degassed by sparging with nitrogen and dried by passage through a column of activated alumina on an SG Water solvent purification system. *N*-Pivaloyl Toluidine (99%) (CAS# 61495-04-3)¹ was purchased from Acros Organics and used as is. Salicylaldehyde Phenylhydrazone (CAS# 614-65-3)² and 4-phenylbenzylidene benzylamine (CAS# 118578-71-5)³ were prepared according to their corresponding literature preparations and dried overnight in a vacuum oven at 40 °C. Hexylmagnesium bromide (CAS# 3761-92-0) was obtained as a 1M solution (20%) in tetrahydrofuran (THF) from TCI America and was used as is. Potassium bis(trimethylsilyl)amide (1M in THF) (CAS# 40949-94-8) and methylmagnesium bromide (3.0M in Et₂O) (CAS# 75-16-1) solutions were obtained from Sigma-Aldrich in Sure/Seal™ packaging and were diluted to their recorded concentrations prior to use. All other reagents were purchased from Sigma-Aldrich in Sure/Seal™ packaging and used as is.

B. Equipment Details

Pumps: Harvard Apparatus PHD ULTRA™ infuse only (item# 70-3005) and infuse/withdraw (item# 70-3007) pumps were used containing Harvard Apparatus 8 mL stainless steel syringes with 1/16 inch SWAGELOCK® (item# 70-2267) were used to pump all reagent solutions. The pumps were used as is utilizing the preloaded manufacturing specifications for the 8 mL stainless steel syringe and no further calibration performed.

UV/Vis spectrometer: For all experiments the following equipment was used.

- Avantes AvaSpec-ULS2048-USB2-UA-50 spectrometer
- AvaLight-DHC full-range compact light source
- FC-UV400-2-BX-SR fiber optic cables
- Avantes ¼ inch flow cell

- Modified to include a 3 inch length of quartz tubing (1/8 inch O.D., I.D.)
- AvaSoft 7 – Full version
- LabVIEW – Main VI
 - Modified to include light and dark reference for conversion of scope to absorbance

Tubing and Connections: All tubing and connections were obtained from IDEX health & Science and was used as is.

- PFA (perfluoroalkoxy alkane) tubing 1/16 inch O.D. x 0.03 inch I.D. (part# 1514L)
- PEEK (polyether ether ketone) connectors:
- Y Assembly 1/4-28 0.02 inch (part# P-512)
- Standard Union Tefzel™ 1/4-28 (part# P-623)
- Check Valve Inlet 1/4-28 Male x 1/4-28 female (part# CV-3301)
- Super Flangeless™ Nut PEEK, Short, 1/4-28 Flat-Bottom, for 1/16 inch O.D. Natural (part # LT-115X)
- Super Flangeless™ Ferrule w/SST Ring, Tefzel™ (ETFE), 1/4-28 Flat-Bottom, for 1/16 inch O.D. Yellow (part# P-259X)
- BPR Assembly – biocompatible (part# P-791 (20 psi), P-785 (40 psi), P-786 (75 psi))

Computer: A Lenovo Thinkpad 11e (3rd Gen) laptop with the following specifications was used for automation.

- OS: Microsoft Windows 10 Home
- System Type: x64
- Processor: Intel Celeron CPU N3150 @ 1.6GHz, 4 Core Processor
- Physical Memory (RAM): 8.00 GB

Software: For all automation and analysis the following programs were utilized.

- Microsoft Excel 2013
- National Instruments LabVIEW 2015 (32-bit)

C. LabVIEW Virtual Instrument (VI) Development

For automation of the syringe pumps and UV/Vis spectrometer, VIs were obtained from Harvard Apparatus and Avantes, respectively. Harvard Apparatus VIs were used without modification. In order to obtain and export absorbance data directly from the spectrometer modifications to the Avantes VI were made (Figure S1). All other components of the finalized VI were native to LabVIEW.

As mentioned, the VI provided by Avantes (“AVS_main”) exports data in scope format which provides the relative intensity of the light source. In order to convert this value into an absorbance reading the following equation was utilized.

$$A_{\lambda} = -\log\left(\frac{S_{\lambda} - D_{\lambda}}{L_{\lambda} - D_{\lambda}}\right)$$

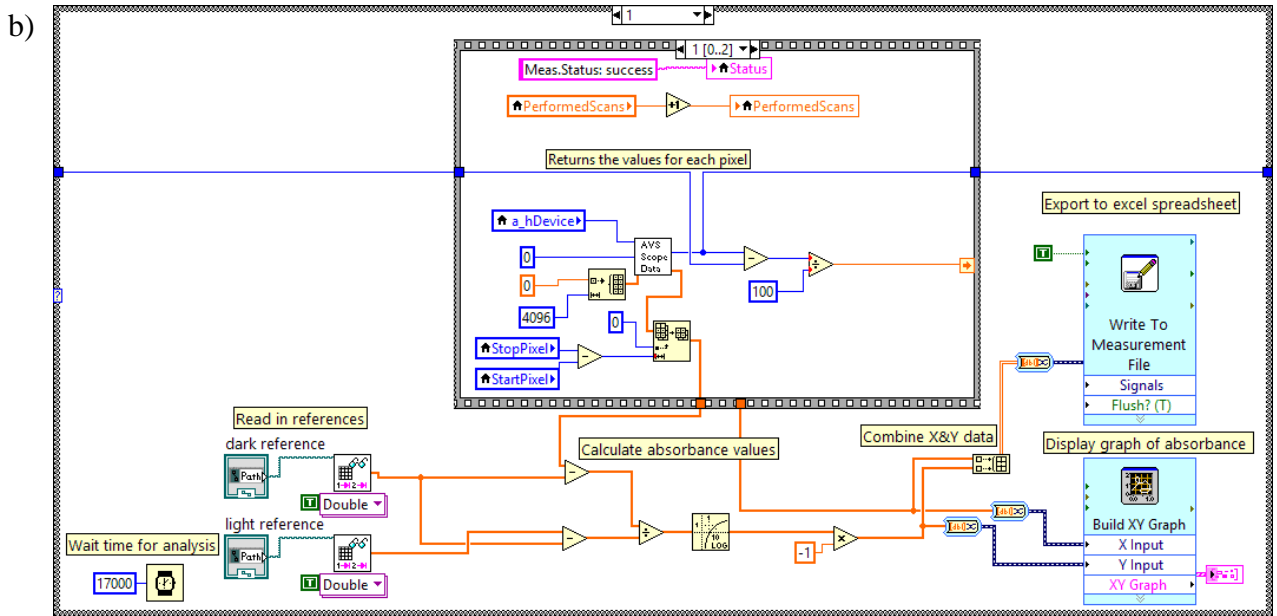
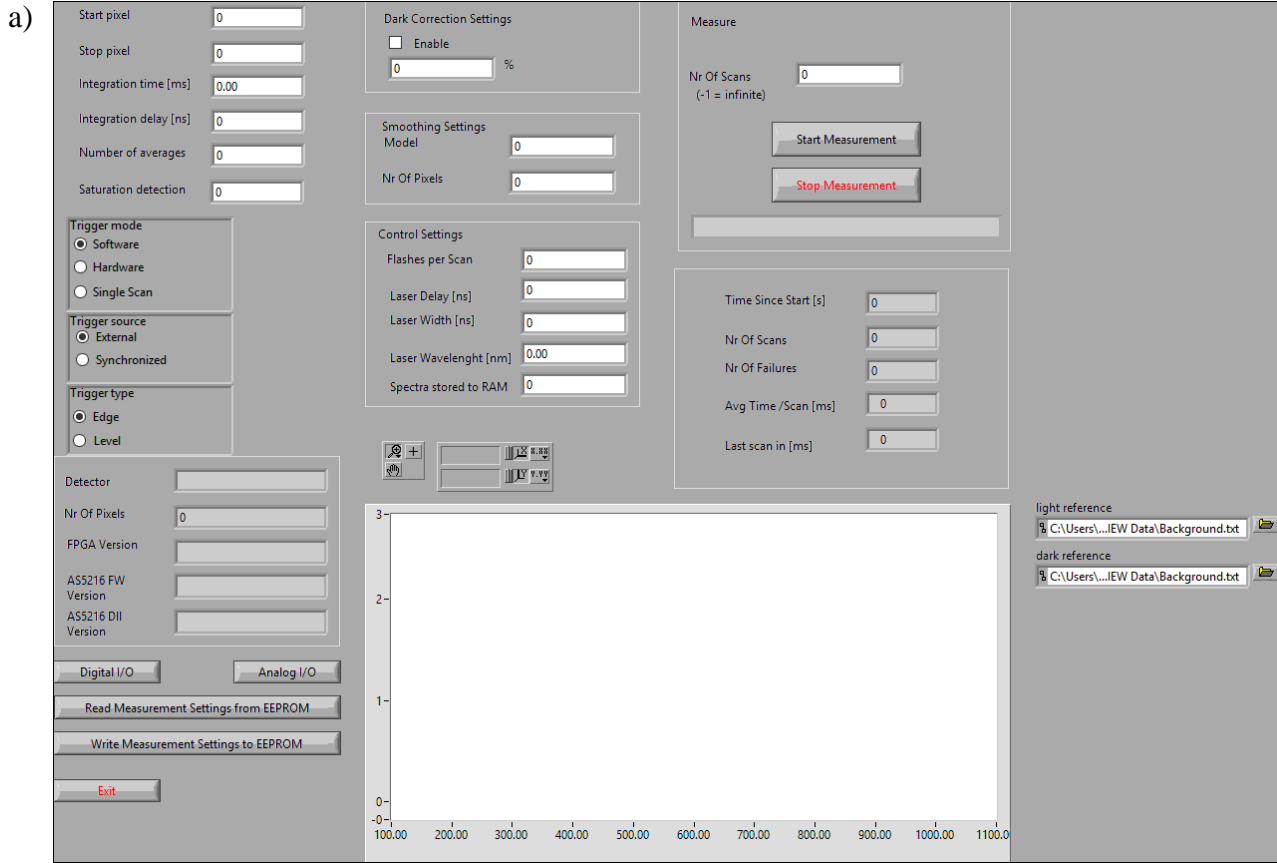
Where: S_{λ} = *Sample intensity at λ*

D_{λ} = *Dark Intensity at λ*

L_{λ} = *Light Intensity at λ*

Within the VI itself, this was accomplished by addition of inputs for light and dark reference values. The light and dark reference files, formatted as *.txt files are input by the user (Figure S2a) and read in via the “Read Delimited Spreadsheet.vi” found in LabVIEW. The equation above is then utilized to calculate absorbance values using the combined scope, light, and dark reference data. These values are then fed into the Y-input of a “Build XY Graph Express VI.” The X-values are input directly from the spectrometer without modification as is found in the original AVS_Main.vi. To export this data, the X and Y data was also combined using a “Build Array” function and fed into a “Write to Measurement File Express VI” configured to save to a *.xlsx file at a user set location. The wait time between data acquisition was set to 17 seconds by placing a “Wait (ms)” function within the case structure related to data acquisition within AVS_Main.vi (Figure S2b).

Figure S2. Modified Front Panel and Block Diagram of AVS_main.vi



(a) Front panel (user interface). (b) Zoomed view of modifications made to AVS_main.vi.

With a VI for exporting the spectrometer data constructed. The complete VI for automation could be constructed. First, subVIs from the native Harvard Apparatus pump Vis were introduced to input the location, communication rate, and syringe size of the titrant and organometallic reagents pumps (Figure S3). Based on the reactor size, flow rate of the titrant, and concentration range of the organometallic reagent set by the user, a flow rate for the organometallic reagent pump is calculated based on the equation provided below.

$$flow\ rate_{organometallic} = \frac{\left(\frac{[titrant] \times flow\ rate_{titrant}}{[organometallic]_{Upper}} + \frac{[titrant] \times flow\ rate_{titrant}}{[organometallic]_{Lower}} \right)}{2}$$

All of this data is sent to the pumps and enters the “Initiate” case of the search function case structure (Figure S4). Within this is an event structure which will not start the system until the user presses the “Infuse” button. Once pressed, the pumps will begin flowing and the data is passed into the “Wait” case structure (Figure S5) Here, the system will wait three residence times for equilibration to be complete, at which point the data is passed into the “Check for signal” case structure. The system will then check the spreadsheet and cell, as defined by the user, for the desired value (absorbance in this particular case) and compare that value to a threshold value (set by the user) to determine whether a signal is present or not (Figure S6). Depending on whether a signal is observed or not the data is then sent to either the “Step Down” or “Step Up” case structure, respectively (Figure S7, Figure S8). Here a new flow rate is calculated based on the equation below. To achieve this a “Feedback Node” function is utilized to store the flow rate used in the last iteration (Figure S3). By default this value is initially set to be the flow rate corresponding to the lowest concentration within the set range. Following this calculation the new flow rate of organometallic is sent to the pump and the data once again enters the “Wait” case structure. This process of calculating a flow rate, waiting for equilibration, and checking for signal is repeated a total of 6 times. With each iteration the system information (Boolean signal data and absorbance value) are also sent to an array (Figure S9) and displayed on the user interface to allow the system to be monitored throughout. Once six iterations are complete, the system checks the final signal, calculates the concentration (Figure S9), and stops the pumps. If the final signal is yes the current flow rate and the last flow rate at which no signal was observed are used to calculate the final concentration. Conversely if the final signal is no, the last yes value is utilized. To do this, the

system searches the array of the iteration data for the appropriate value (depending on what the final signal is) and reads in the appropriate data. In either case, the final concentration is calculated as shown below. Within the SI, the two values utilized to perform this calculation are highlighted within the results of each titration.

$$[\text{organometallic}] = \frac{\left(\frac{\text{flow rate}_{\text{current}} + \text{flow rate}_{\text{last Y (or N)}}}{2} \right)}{[\text{titrant}] \times \text{flow rate}_{\text{titrant}}}$$

Figure S3. Block Diagram of Finished.vi

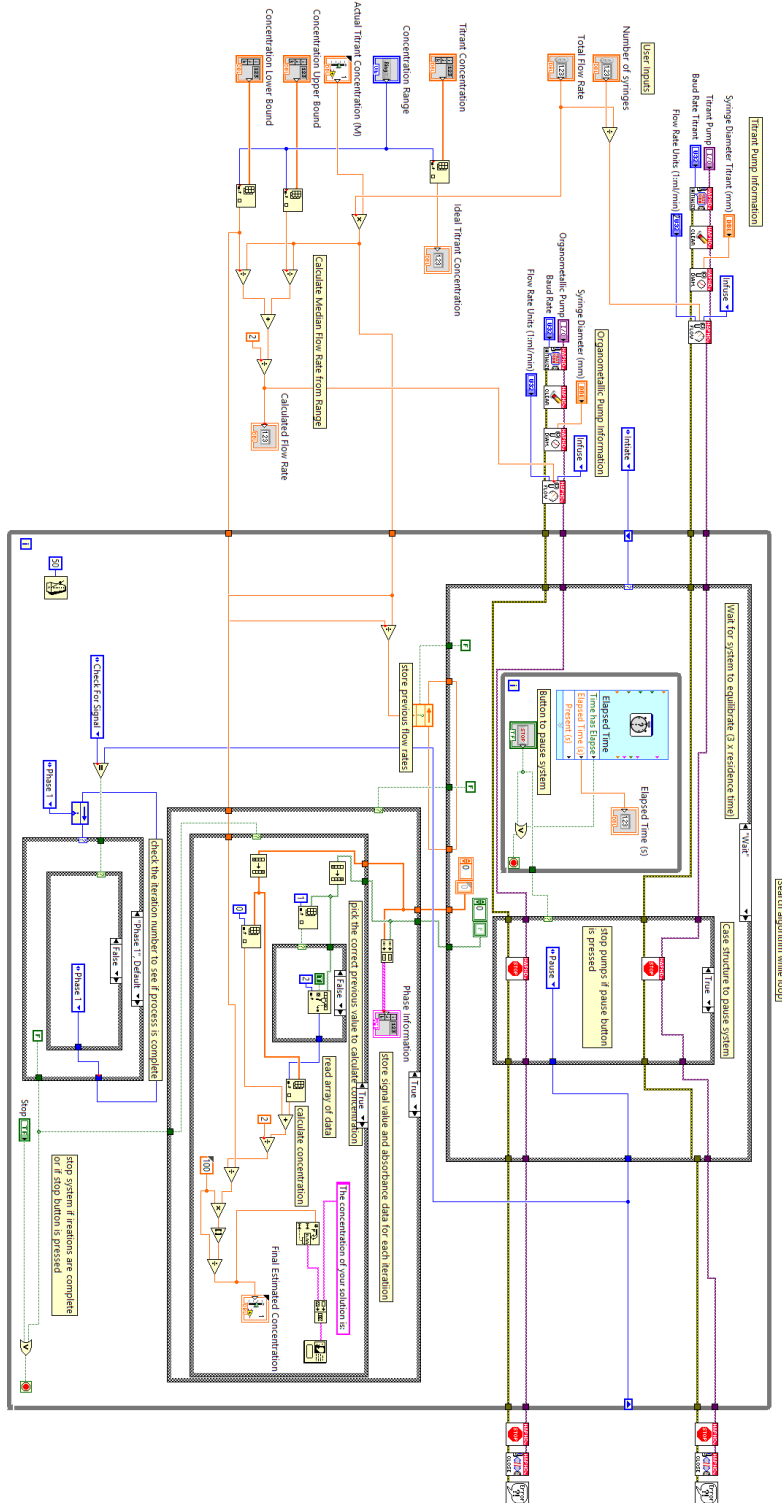


Figure S4. "Initiate" Case Structure

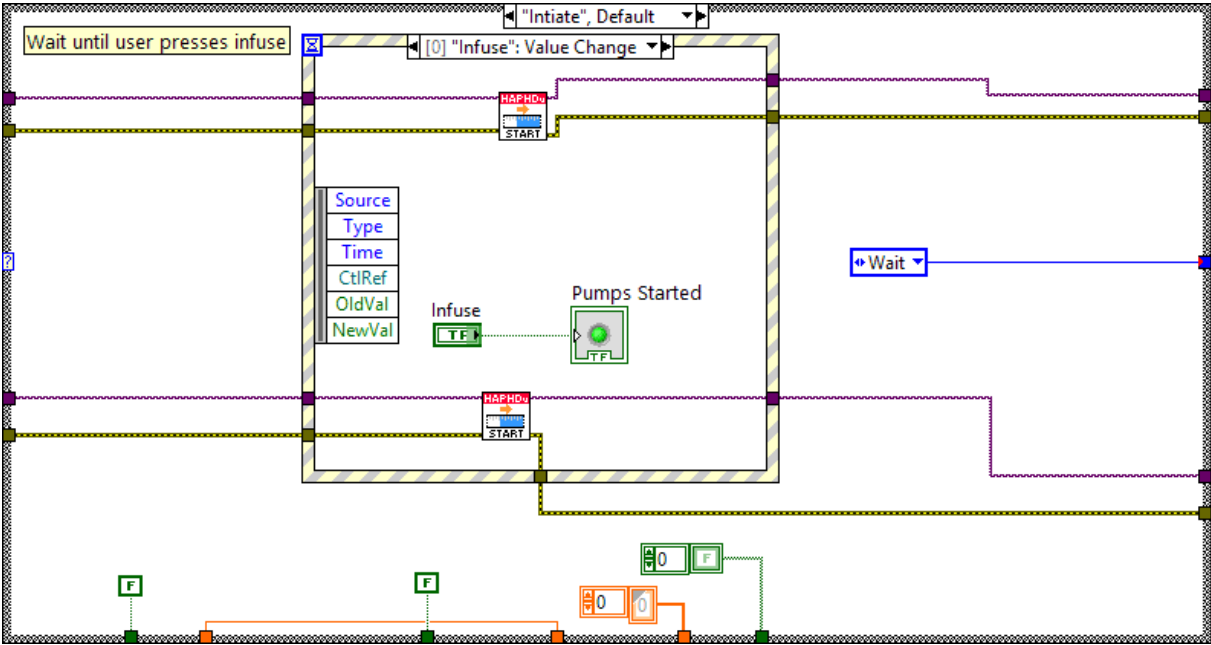


Figure S5. "Wait" Case Structure

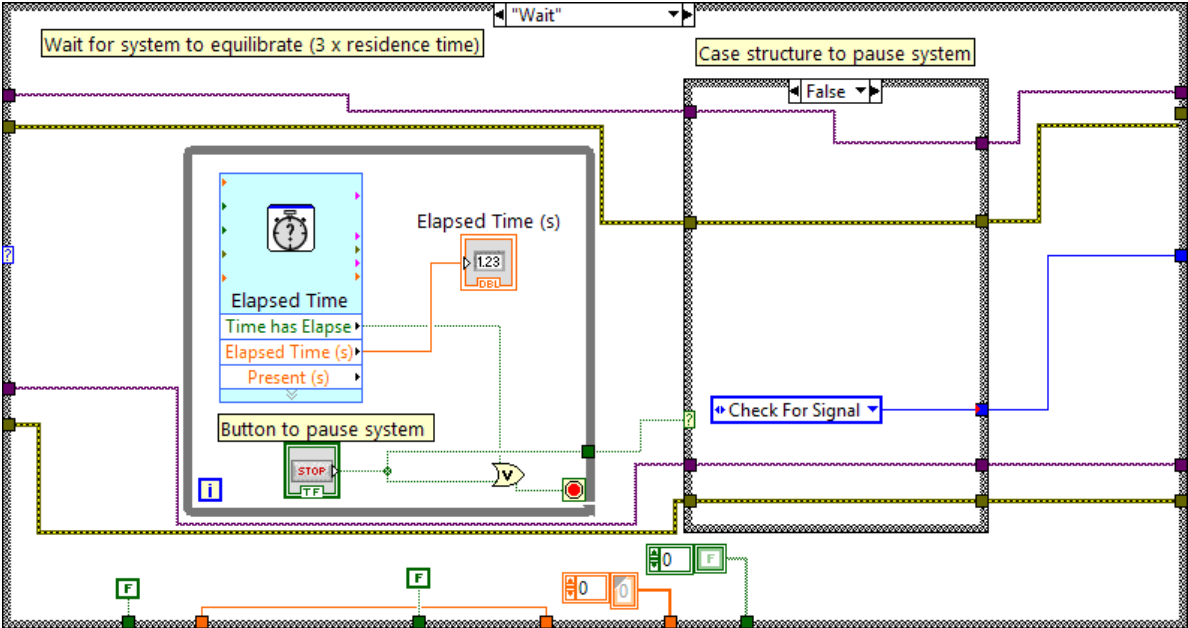


Figure S6. "Check For Signal" Case Structure

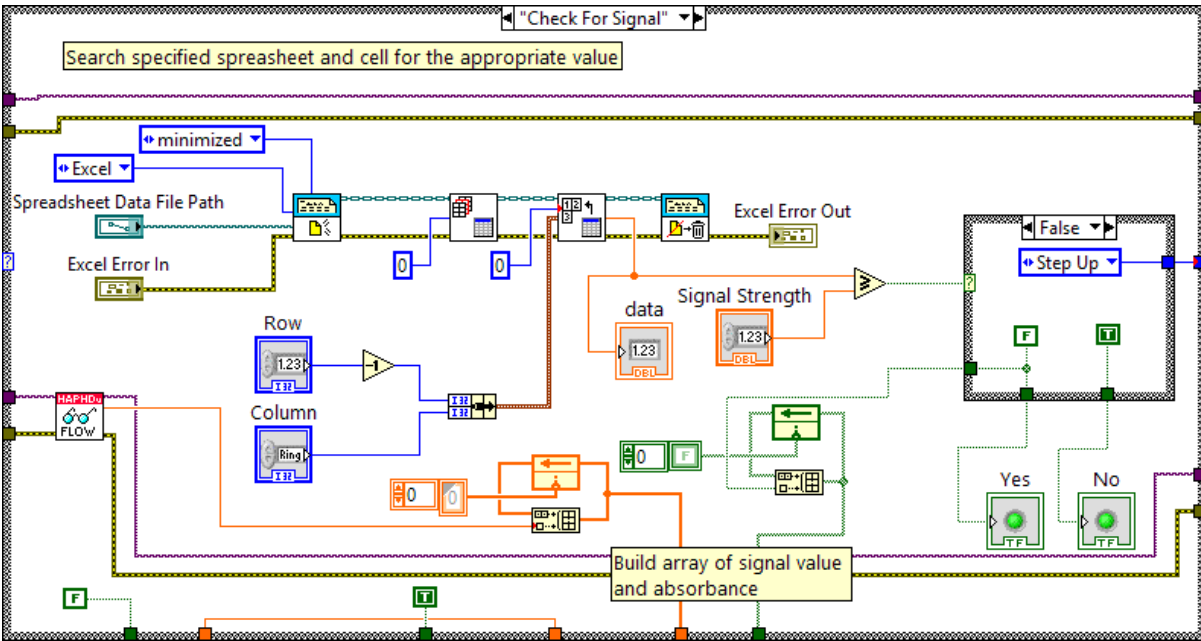


Figure S7. "Step Up" Case Structure

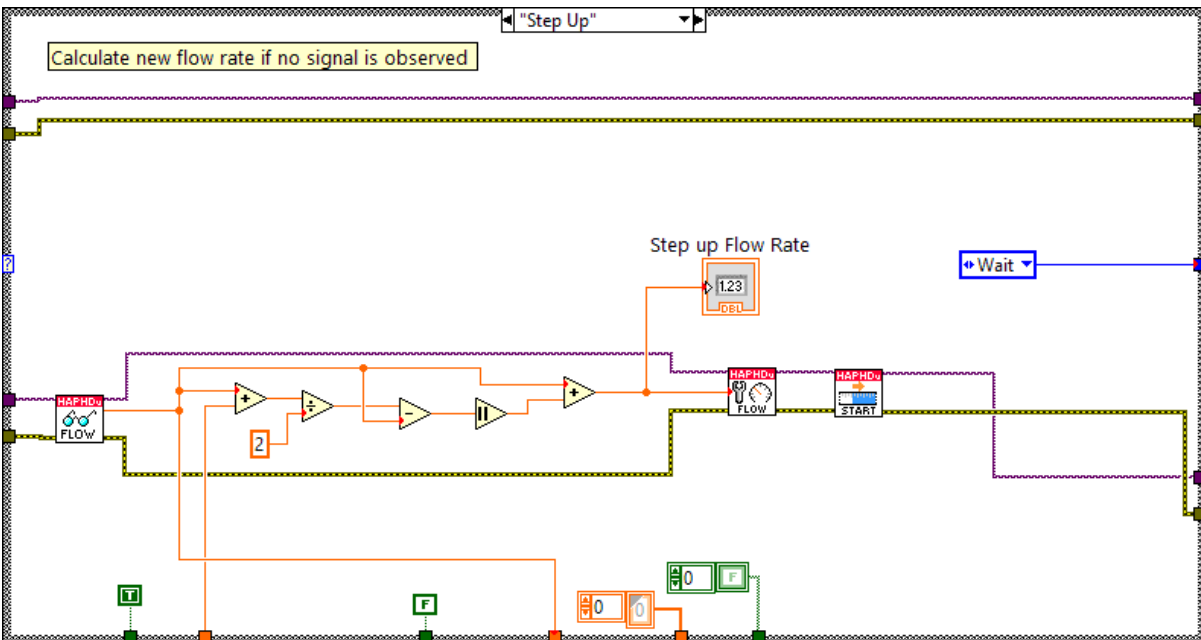


Figure S8. "Step Down" Case Structure

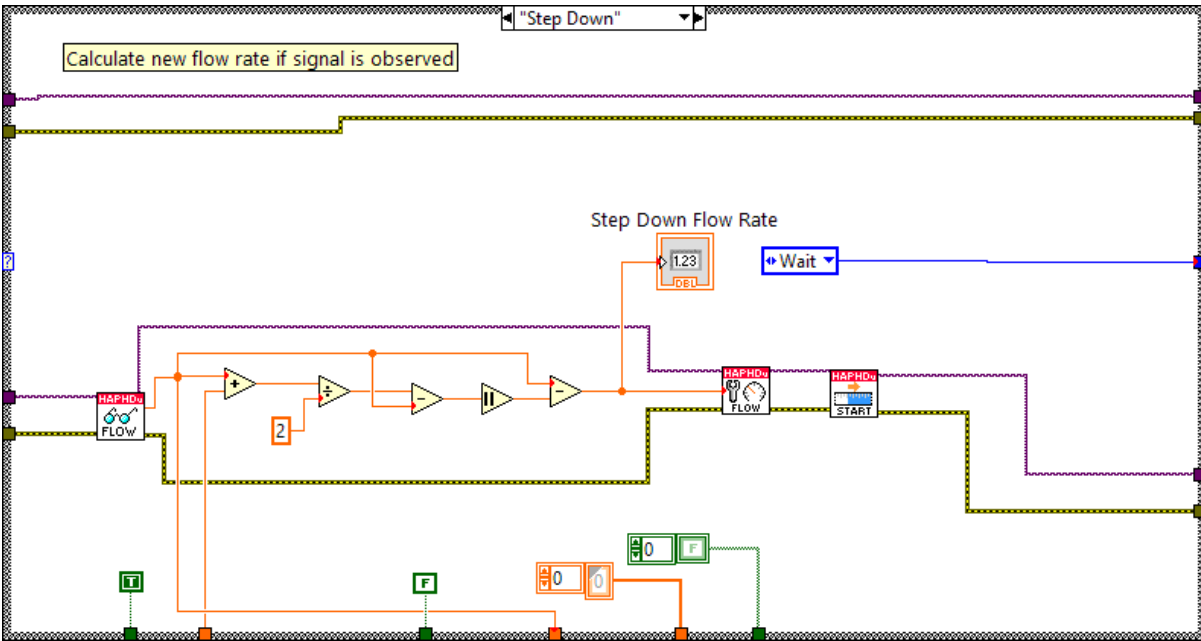
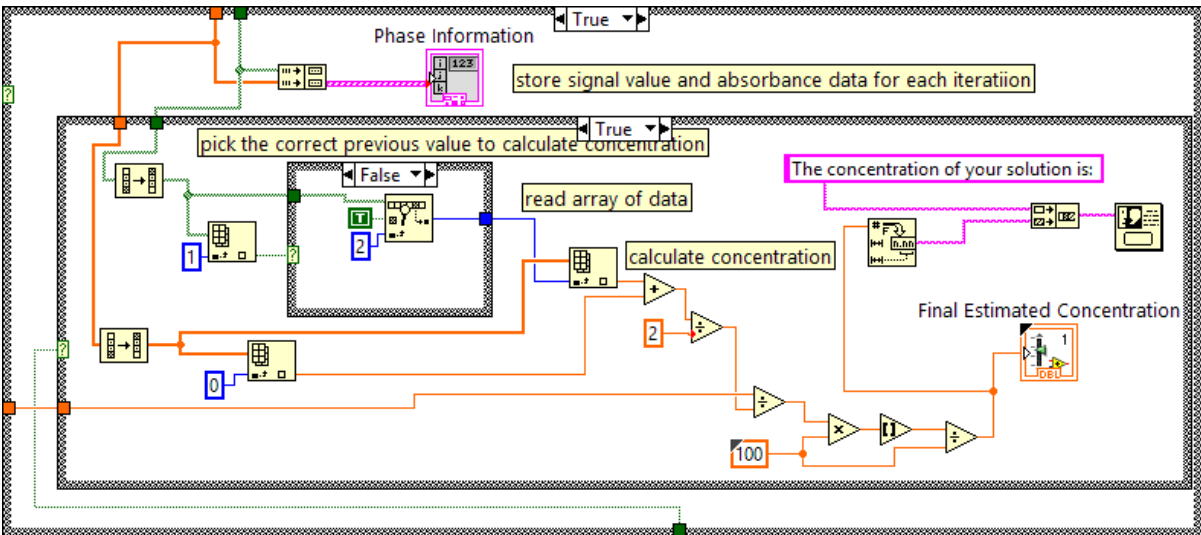
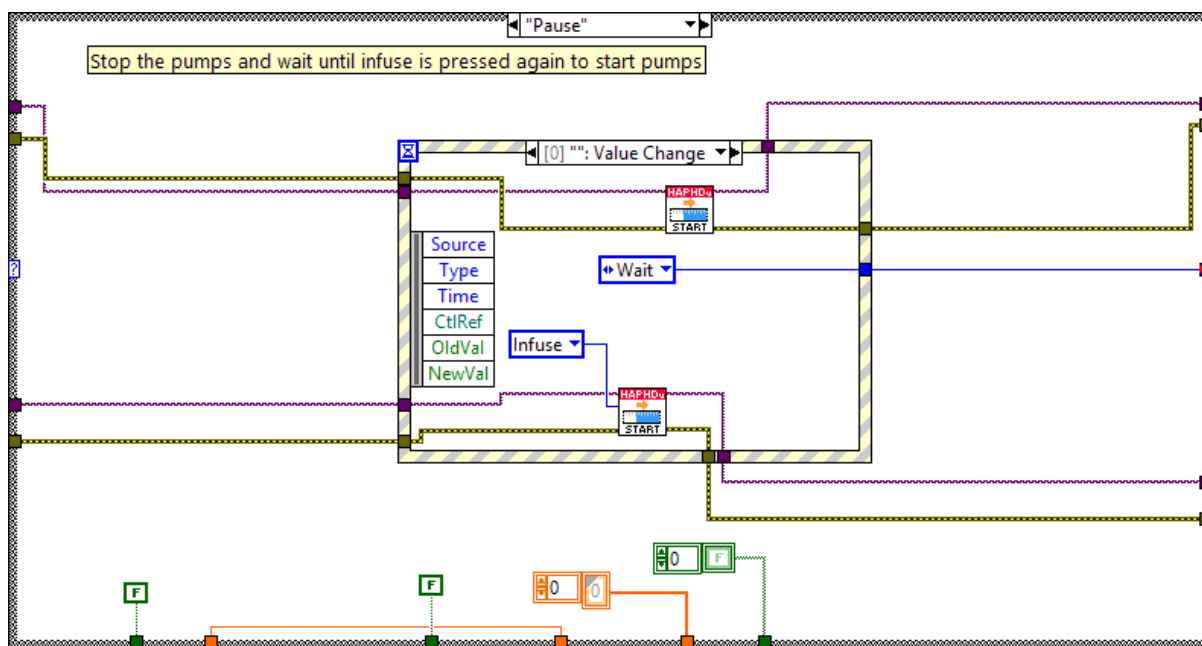


Figure S9. Phase Information Array and Final Concentration Calculation Case Structure



For the convenience of the user, several additional safety features were built into the system. If for any reason the system needs to be stopped, e.g. a pump stalls, the system leaks, a syringe breaks, the “Pause” button on the user interface can be used to stop all of the pumps (Figure S10). If the issue is minor and the user would like to continue the titration from its current iteration, the “Infuse” button can be pressed again to start the system again. If the user would like to shut down the system entirely, the “Stop” button may be pressed. Both of these features help mitigate some of the hazards associated with utilizing the sometimes hazardous and pyrophoric organometallic species as well as provide the flexibility to make minor adjustments to the system without losing all of the data.

Figure S10. “Pause” Case Structure

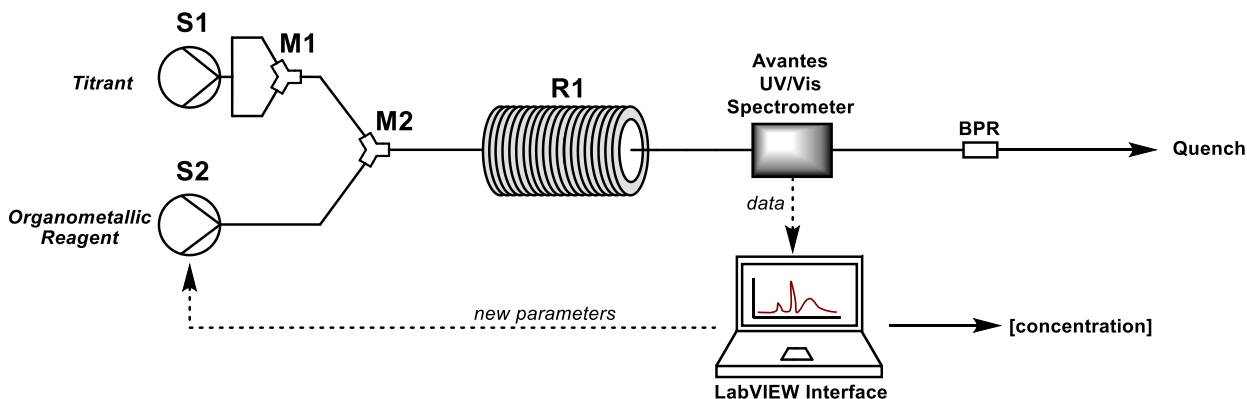


D. General Procedure for Performing Automated Continuous Flow Titrations

As shown in the Figure 1 and Figure S11, two Harvard Apparatus PHD Ultra pumps were used to deliver the titrant and organometallic reagent solutions. Typically one Harvard Apparatus 8 mL stainless steel syringe was used to deliver the organometallic reagent (S2) solution and two

were utilized to deliver the titrant (S1). Two polyether ether ketone (PEEK) Y-mixers (M1, M2), one perfluoroalkoxy alkane (PFA) tubing reactor (R1), one Avantes UV/Vis spectrometer, and one back pressure regulator (BPR) were used to construct the reactor system. The pumps and the UV/Vis spectrometer were all connected to the laptop using a USB hub. The titrant solution from S1 was mixed with the organometallic reagent solution from S2 via a Y-mixer (M2) and the reaction solution then entered R1 (1/16" OD × 0.03" ID, length = 68 7/8", volume = 0.798 mL). The stream exiting R1 then passed through the UV/Vis cell and the BPR (20 psi or 40 psi) before being quenched using a dry ice / isopropanol bath.

Figure S11. Continuous Flow Diagram of Automated Titration System



To perform a titration the titrant solution was first prepared by weighing out the titrant in a volumetric flask and purging the head through several vacuum/backfill cycles on a Schlenk line with N₂. The titrant was then dissolved in the appropriate solvent and diluted to the mark. This solution was directly withdrawn from the flask using a Harvard Apparatus 8mL stainless steel syringe and placed within the corresponding pump. The organometallic reagent solution was drawn directly from the commercial bottle using a stainless steel syringe and subsequently connected to the titration system. Prior to this, the entire reaction line was purged with THF.

Within LabVIEW, background light and dark spectra were saved using the AVS_main.vi. The file paths for these spreadsheets were then entered into the AVS_main_background_subtract.vi and the spectrometer was turned on. All of the system's parameters were then entered into the "Finished VI" and the titration was commenced by pressing the "Infuse" button in the software.

E. General Procedure for Batch Titrations

In three separate 1 dram vials the desired titrant was weighed out and a stir bar was added. The vial was subsequently capped and the headspace was purged through several vacuum/backfill cycles with N₂. 1mL of the appropriate solvent was then added to the vial. Using a 1 mL HGS syringe, the organometallic reagent solution was withdrawn from the commercial bottle and the starting volume was recorded. The organometallic reagent was then added dropwise to the titrant solution until the endpoint was observed visually and the final volume of the syringe was recorded. The difference in these volumes was then used to calculate the concentration of the commercial solution. This process was repeated for each of the titrant solutions and the final concentration (an average of the three runs) and its standard deviation were calculated.

F. Using the Withdraw Feature of the Harvard Apparatus Syringe Pump

A syringe was placed atop the syringe holder and held in place firmly by the syringe barrel clamp. The syringe barrel was completely depressed and the end was attached firmly to the pusher block. The syringe was disconnected from the system and attached to a stainless steel needle. The pumps were then oriented vertically prior to inserting the needle through the septum of the reagent bottle. The organometallic reagent was then withdrawn, utilizing the user interface of the syringe pump, until the desired volume was reached. Subsequently, the pumps were advanced using the syringe pump user interface (while still vertical) until no further bubbles were observed exiting the tubing. The needle was then removed from the reagent line and reattached to the system before starting the titration procedure.

G. Optimization of Titrations in Continuous Flow

The optimization of the flow titration was carried out using *N*-Pivaloyl Toluidine (0.46M in THF) and *n*-Butyllithium (1.6M in hexane) as model substrates (Table S1). Each titration was carried out according to the general procedure described in section E. Different reactor and mixing types were tested at variable flow rates to give a color change which was observed visually at the terminus of the specific reactor being utilized.

The flow rate of the indicator solution was kept consistent at 0.240 mL/min throughout all runs and reactor types. Of the three different flow rates analyzed a $t_R = 2.5$ minutes produced the most consistent results. Attempts to decrease the required residence time by using either a helical static mixer or packed bed reactor showed no benefit over standard PFA tubing. In fact, titrations using static mixing led to reproducibility issues. Therefore we chose to use PFA tubing combined with a Y-mixer in all titrations due to better reproducibility, lower cost, and ease of assembly. We also moved forward with a 2.5 minute residence time in favor of further optimization, to offer enough mixing time when utilizing different indicators (see below for further discussion).

Table S1. Optimization of Titrations in Flow

Entry	Reactor, Mixing	Residence Time (min)	Result
1	PFA Tubing, Y-mixer	1.3	Inconsistent color change
2	PFA Tubing, Y-mixer	1.8	Inconsistent color change
3	PFA Tubing, Y-mixer	2.5	Consistent, reproducible (1.620 ± 0.012M)
4	PFA Tubing, Y-mixer, 2.5 in. helical static mixer	1.3	Inconsistent
5	PFA Tubing, Y-mixer, 2.5 in. helical static mixer	1.8	Inconsistent
6	PFA Tubing, Y-mixer, 2.5 in. helical static mixer	2.5	Not reproducible
7	Y-mixer, packed bed	1.3	Inconsistent
8	Y-mixer, packed bed	1.8	Inconsistent
9	Y-mixer, packed bed	2.5	Not reproducible between packed beds

Table S1 Legend:

Inconsistent = color change (colorless to yellow) was not consistent over 1 residence time.

Not reproducible = variability between 3 separate runs of the titration.

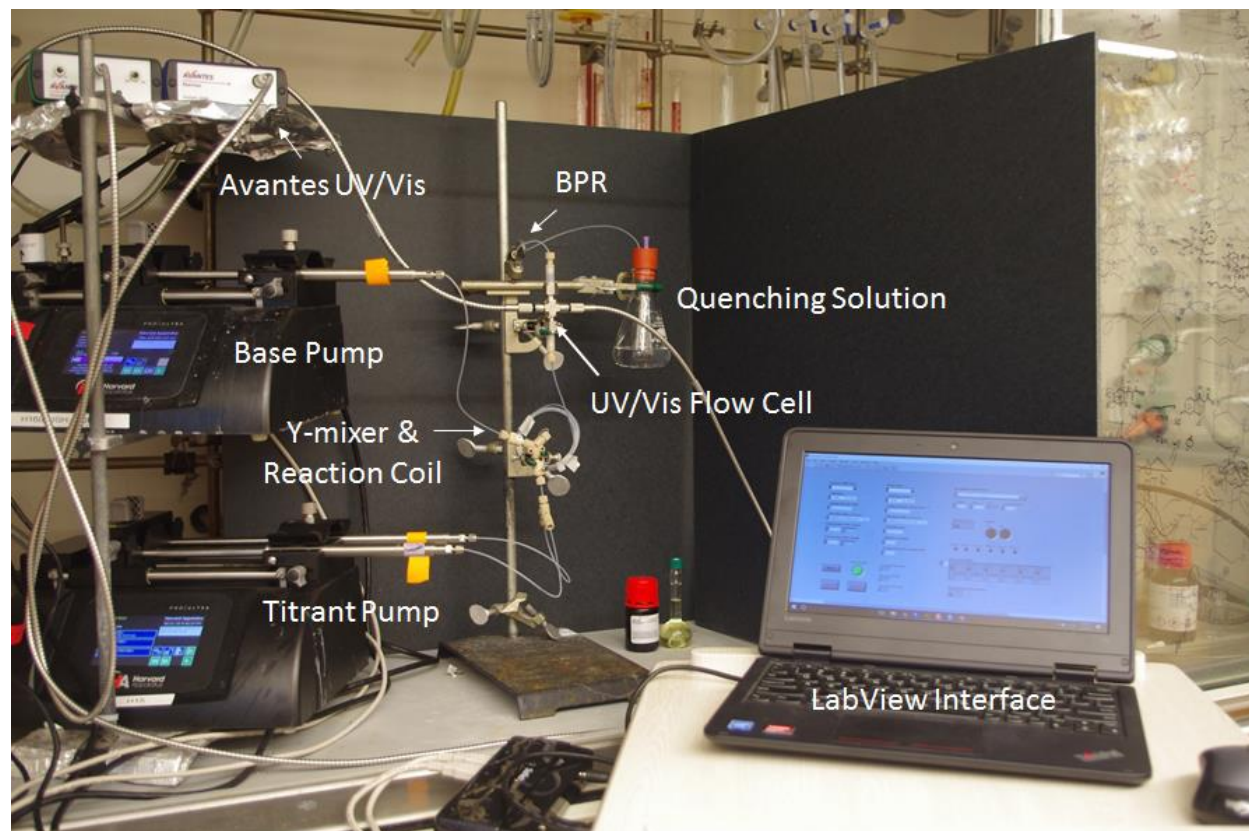
Reactors used:

- 1) Y-mixer + PFA tubing as described in the general procedure
- 2) Stamixco, HT: helical static mixer (PTFE Teflon®, length = 2.5 inch, diameter = 0.067 inch; placed within PFA tubing O.D. = 1/8 inch, I.D. = 0.065 inch, length 2.5 inches.) + PFA tubing.
- 3) Packed bed: Type 316 stainless steel tubing, packed with type 304-L stainless steel powder (STREM # 93-2697)

With the desired flow system developed, we now needed to determine the proper titration ranges that can be titrated using this system. Ideally, a one size fits all for organometallic concentration ranges is desired, but the current system is regulated by two constraints. First, for ease of use we have chosen to keep the indicator concentration and flow rate constant while changing the flow rate of the base. For most consistent results we determined that the ratio of flow rates between indicator and base solutions be <7:1, respectively. Second, to remain within the desired residence time ($t_R = 2.5$ minutes) we would be limited to a particular concentration range. The software takes these ranges into consideration and is described further in section C of the SI.

H. Image of Continuous Flow Titration System

Figure S12. Flow Titration Set Up.



I. Titration Results for *N*-Pivaloyl Toluidine

n-BuLi

Commercial Source: 1.6 M *n*-BuLi in Hexanes

Titration Solution: 0.46 M (2.2223 g in 25 mL THF)

Titration Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.2 M to 2.4 M

Signal monitored: 450 nM @ > 0.3 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	65.0	N
2	78.5	Y
3	71.8	Y
4	68.5	Y
5	66.9	N
6	67.7	Y

Final concentration: 1.62 M

2nd separate syringe of titrant:

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	65.0	N
2	78.5	Y
3	71.8	Y
4	68.5	Y
5	66.9	N
6	67.7	Y

Final concentration: 1.62 M

3rd separate syringe of *n*-BuLi:

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	65.0	N
2	78.5	Y
3	71.8	Y
4	68.5	Y
5	66.9	N
6	67.7	Y

Final concentration: 1.62 M

Batch Results

Entry	Titrant (mg)	<i>n</i>-BuLi (mL)	[<i>n</i>-BuLi] (M)
1	113.4	0.360	1.63
2	108.8	0.350	1.61
3	134.4	0.430	1.62

Final Concentration: 1.62 M ± 0.01 M

***s*-BuLi**

Commercial Source: 1.4 M *s*-BuLi in Cyclohexane

Titrant Solution: 0.38 M (1.8348 g in 25 mL THF)

Titrant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ -10 °C to 0 °C

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.2 M to 2.4 M

Signal monitored: 450 nM @ > 0.30 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	N
2	77.9	Y
3	71.3	Y
4	68.0	Y
5	66.4	Y
6	65.6	N

Final concentration: 1.40 M

Batch Results

Entry	Titrant (mg)	<i>s</i> -BuLi (mL)	[<i>s</i> -BuLi] (M)
1	88.3	0.320	1.43
2	89.9	0.325	1.43
3	91.4	0.335	1.41

Final Concentration: 1.42 M ± 0.01 M

t-BuLi

Commercial Source: 1.7 M *t*-BuLi in Pentanes

Titrant Solution: 0.38 M (1.8348 g in 25 mL THF)

Titrant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ -10 °C to 0 °C

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.2 M to 2.4 M

Signal monitored: 450 nM @ > 0.30 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	Y
2	51.3	N
3	58.0	Y
4	54.7	N
5	56.3	N
6	57.1	Y

Final concentration: 1.58 M

Batch Results

Entry	Titant (mg)	<i>t</i> -BuLi (mL)	[<i>t</i> -BuLi] (M)
1	95.3	0.320	1.54
2	93.0	0.330	1.45
3	94.0	0.300	1.62

Final Concentration: 1.54 M ± 0.08 M

J. Titrations with 2-Hydroxybenzaldehyde Phenylhydrazone

n-BuLi

Commercial Source: 1.6 M *n*-BuLi in Hexanes

Titant Solution: 0.38 M (2.0681 g in 25 mL THF, 0.8073 g in 10 mL, and 0.4004 g in 5 mL)

Titant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.2 M to 2.4 M

Signal monitored: 500 nM @ > 1.4 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.4	Y
2	51.1	N
3	57.7	Y
4	54.4	N
5	56.1	N
6	57.0	Y

Final concentration: 1.59 M

2nd separate syringe of titrant ([titrant] adjusted, see above):

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	66.3	Y
2	52.7	N
3	59.5	Y
4	56.1	N
5	57.8	N
6	58.6	Y

Final concentration: 1.59 M

3rd separate syringe of *n*-BuLi:

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	66.3	Y
2	52.7	N
3	59.5	Y
4	56.1	N
5	57.8	N
6	58.6	Y

Final concentration: 1.59 M

Batch Results

Entry	Titrant (mg)	<i>n</i>-BuLi (mL)	[<i>n</i>-BuLi] (M)
1	96.6	0.280	1.62
2	97.8	0.285	1.61
3	99.0	0.345	1.48
4	110.9	0.370	1.55

Final Concentration: 1.57 M ± 0.06 M

***i*-PrMgBr**

Commercial Source: 2.0 M *i*-PrMgBr in THF

Titration Solution: 0.38 M (2.0097 g in 25 mL THF)

Titration Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.0 M to 2.4 M

Signal monitored: 500 nM @ > 1.4 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.4	Y
2	51.1	Y
3	44.5	Y
4	41.2	N
5	42.8	N
6	43.6	N

Final concentration: 2.06 M

Batch Results

Entry	Titrant (mg)	<i>i</i> -PrMgBr (mL)	[<i>i</i> -PrMgBr] (M)
1	101.0	0.230	2.07
2	96.1	0.230	1.97
3	103.9	0.240	2.04

Final Concentration: 2.03 M ± 0.05 M

PhMgBr

Commercial Source: 2.0 M PhMgBr in THF

Titrant Solution: 0.38 M (2.0097 g in 25 mL THF)

Titrant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 1.0 M to 2.4 M

Signal monitored: 500 nM @ > 1.0 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.4	Y
2	51.1	Y
3	44.5	Y
4	41.2	N
5	42.8	N
6	43.6	N

Final concentration: 2.06 M

Batch Results

Entry	Titrant (mg)	PhMgBr (mL)	[PhMgBr] (M)
1	113.7	0.260	2.06
2	109.1	0.250	2.05
3	120.4	0.275	2.06

Final Concentration: 2.06 M ± 0.01 M

n-C₆H₁₃MgBr

Commercial Source: 1.0 M (20%) *n*-C₆H₁₃MgBr in THF

Titrant Solution: 0.19 M (1.0082 g in 25 mL THF)

Titrant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 0.5 M to 1.2 M

Signal monitored: 500 nM @ > 0.3 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	65.3	Y
2	51.9	Y
3	45.2	N
4	48.5	Y
5	46.9	Y
6	46.1	N

Final concentration: 1.01 M

Batch Results

Entry	Titrant (mg)	<i>n</i> -C ₆ H ₁₃ MgBr (mL)	[<i>n</i> -C ₆ H ₁₃ MgBr] (M)
1	43.0	0.205	0.988
2	44.8	0.220	0.959
3	43.2	0.210	0.969

Final Concentration: 0.97 M ± 0.02 M

MeMgBr

Commercial Source: 1.0 M (diluted from commercial 3.0 M MeMgBr in Et₂O)

Titrant Solution: 0.192 M (1.0211 g in 25 mL THF)

Titrant Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 40 psi

Concentration Range: 0.5 M to 1.2 M

Signal monitored: 500 nM @ > 0.3 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	63.9	Y
2	50.7	Y
3	44.1	N
4	47.4	N
5	49.0	N
6	49.8	Y

Final concentration: 0.90 M

Batch Results

Entry	Titrant (mg)	MeMgBr (mL)	[MeMgBr] (M)
1	51.5	0.240	1.011
2	47.2	0.230	0.967
3	47.3	0.235	0.949

Final Concentration: 0.97 M \pm 0.02 M

K. Titration Results for 4-Phenylbenzylidene Benzylamine

LDA

Commercial Source: 1.0 M LDA in THF/Hexanes

Titration Solution: 0.19 M *s*-BuOH (0.871 mL in 50 mL *p*-Xylenes with 502.9 mg indicator)

Titration Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 0.5 M to 1.2 M

Signal monitored: 580 nM @ > 2.0 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	Y
2	51.3	Y
3	44.6	Y
4	41.3	N
5	43.0	N
6	43.8	N

Final concentration: 1.03 M

2nd separate syringe of titrant:

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	Y
2	51.3	Y
3	44.6	N
4	47.9	Y
5	46.2	Y
6	45.4	Y

Final concentration: 1.01 M

3rd separate syringe of LDA:

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	Y
2	51.3	Y
3	44.6	Y
4	41.3	N
5	43.0	N
6	43.8	N

Final concentration: 1.03 M

Batch Results

Entry	Titration Soln. (mL)	LDA (mL)	[LDA] (M)
1	1.2	0.220	1.04
2	1.2	0.225	1.01
3	1.2	0.215	1.06

Final Concentration: 1.04 M ± 0.02 M

NaHMDS

Commercial Source: 1.0 M NaHMDS in THF

Titration Solution: 0.19 M *s*-BuOH (0.44 mL in 25 mL *p*-Xylenes with 250 mg indicator)

Titration Flow Rate: 0.240 mL/min

Reactor: 0.798 mL @ rt

Equilibration time: 7.5 min (450 s)

System Pressure: 20 psi

Concentration Range: 0.5 M to 1.2 M

Signal monitored: 450 nM @ > 0.30 au threshold

Flow Results

Phase	Flow rate (uL/min)	Signal (Y/N)
1	64.6	Y
2	51.3	Y
3	44.6	N
4	47.9	Y
5	46.2	N
6	47.0	Y

Final concentration: 0.96 M

Batch Results

Entry	Titrant Soln. (mL)	NaHMDS (mL)	[NaHMDS] (M)
1	1.2	0.240	0.95
2	1.2	0.230	0.99
3	1.2	0.230	0.99

Final Concentration: 0.98 M ± 0.02 M

¹ Suffert, J. Simple Direct Titration of Organolithium Reagents Using *N*-pivaloyl-*o*-toluidine and/or *N*-pivaloyl-*o*-benzylaniline. *J. Org. Chem.* **1989**, *54*, 509-510.

² Love, B. E.; Jones, E. G. The Use of Salicylaldehyde Phenylhydrazine as an Indicator for the Titration of Organometallic Reagents. *J. Org. Chem.* **1999**, *64*, 3755-3756.

³ Duhamel, L.; Plaquevent, J. C. A Method for Simple Titration of Organolithium Reagents in Ethers or Hydrocarbons Using Metalation of *N*-Benzylidenebenzylamine as Colored Reaction. *J. Org. Chem.* **1979**, *44*, 3404-3405.