Supporting Information

A Breakthrough Method for the Accurate Addition of Reagents in Multi-step Segmented Flow Processing

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1. Experimental section and compound characterisation

1.1 General information

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX-400 spectrometer with residual $CHCl_3$ as the internal reference (δ_H = 7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX-400 or DRX-500 spectrometer with the central peak of $CDCl_3$ as the internal reference (δ_C = 77.0 ppm). DEPT 135 was used to aid in the assignment of signals in the ^{13}C NMR spectra. The multiplicity of a signal is indicated as: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, br – broad, dd – doublet of doublets, *etc*. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. ^{1}H NMR assignments were made according to the numbering applied to the compound figure.

Infrared spectra were recorded as a neat thin film on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in the parentheses refer to the relative absorbency compared to the most intense peak: w – weak, less than 40%; m – medium, 40-75%; s – strong, greater than 75%.

Melting points were obtained using an OptiMelt automated melting point system available from Stanford Research Systems calibrated against vanillin (mp 83 °C), phenacetin (mp 136 °C) and caffeine (mp 237 °C).

High resolution mass spectrometry (HRMS) was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive and negative electrospray ionisation. All reported values are within ±5 ppm of the calculated value.

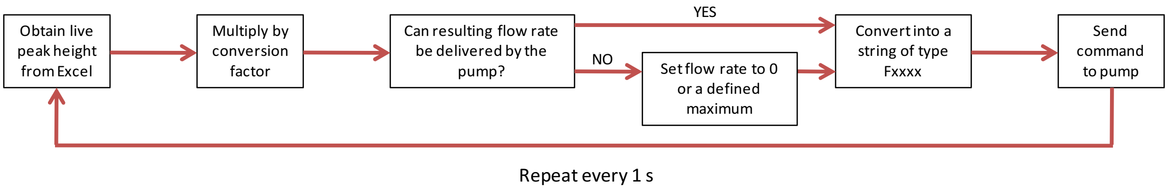
Optical rotation was measured using a Perkin-Elmer Polarimeter 343 with the sample temperature maintained at 25 °C. $[\alpha]^D_{25}$ is reported in units of 10^{-1} deg g^{-1} cm^2. Concentration is quoted in units of 0.01 g cm^{-3}.

Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. The PE used refers to the fraction boiling in the range 40-60 °C. Laboratory reagent grade solvents CH_2Cl_2, Et_2O and PE were obtained from Fischer Scientific. The CH_2Cl_2 and PE were distilled before use (CH_2Cl_2 over CaH_2). Unless otherwise stated, the quoted purity is based on ^{1}H NMR. TLC was performed on Merck 60 F254 silica gel plates and were visualised using short-wave ultra-violet light. Column chromatography was performed with a Biotage SP4 purification system using a 25 g SNAP cartridge and eluting with 20 CV of the specified solvent system. The sample was loaded onto the column by using a Biotage Samplet.

1.2 LabVIEW Details

1.2.1 LabVIEW Application

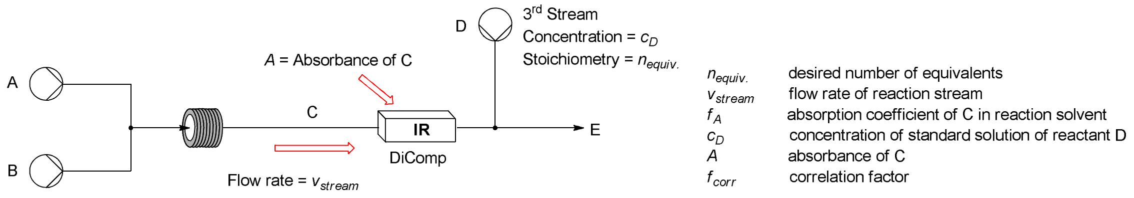
An application was written that allowed the peak height value read from a specified Excel sheet to be converted into a flow rate for a Kanuer Pump, connected to the computer by a simple RS232 serial connection.



After the peak height value had been read and multiplied by the correction factor (see section 1.2.2), the resulting integer was checked to ensure that it was not less than zero or greater than the maximum flow rate achievable by the pump (10000 μL/min for the Knauer 100) otherwise a zero, or the maximum, flow rate would be applied as appropriate. The flow rate value was then converted to an ASCII command string used to control the flow rate of the pump by appending “F” to the beginning of the number and a line feed to the end. This string was then written to the serial port that the pump was connected to. The pump responds with an “OK” string after the flow rate has been successfully set. This received data was then cleared from the read buffer to avoid a buffer overload after many iterations of the sequence. This whole process was repeated every second. To account for occasional variation in the baseline of the spectrum during the reactions, a baseline correction mechanism was introduced. The baseline was monitored at a wavelength that was not affected by the compounds present in the reaction and this value subtracted from the peak height of the intermediate compound of interest, to create an absorbance “threshold”.

1.2.2 Relationship between peak height and flow rate

Many factors need to be taken into account to link the peak height observed in the IR (A) to the flow rate of a third stream. The concentration of component C, in the spectrometer can be calculated by $c_C = f_A \cdot A$ where f_A is the absorption coefficient and A is the IR absorbance that is read out in real time (Scheme 1). f_A is predetermined by performing a concentration screen of C in the reaction solvent.



Scheme SI1. Parameters required for the calculation of the third stream flow rate.

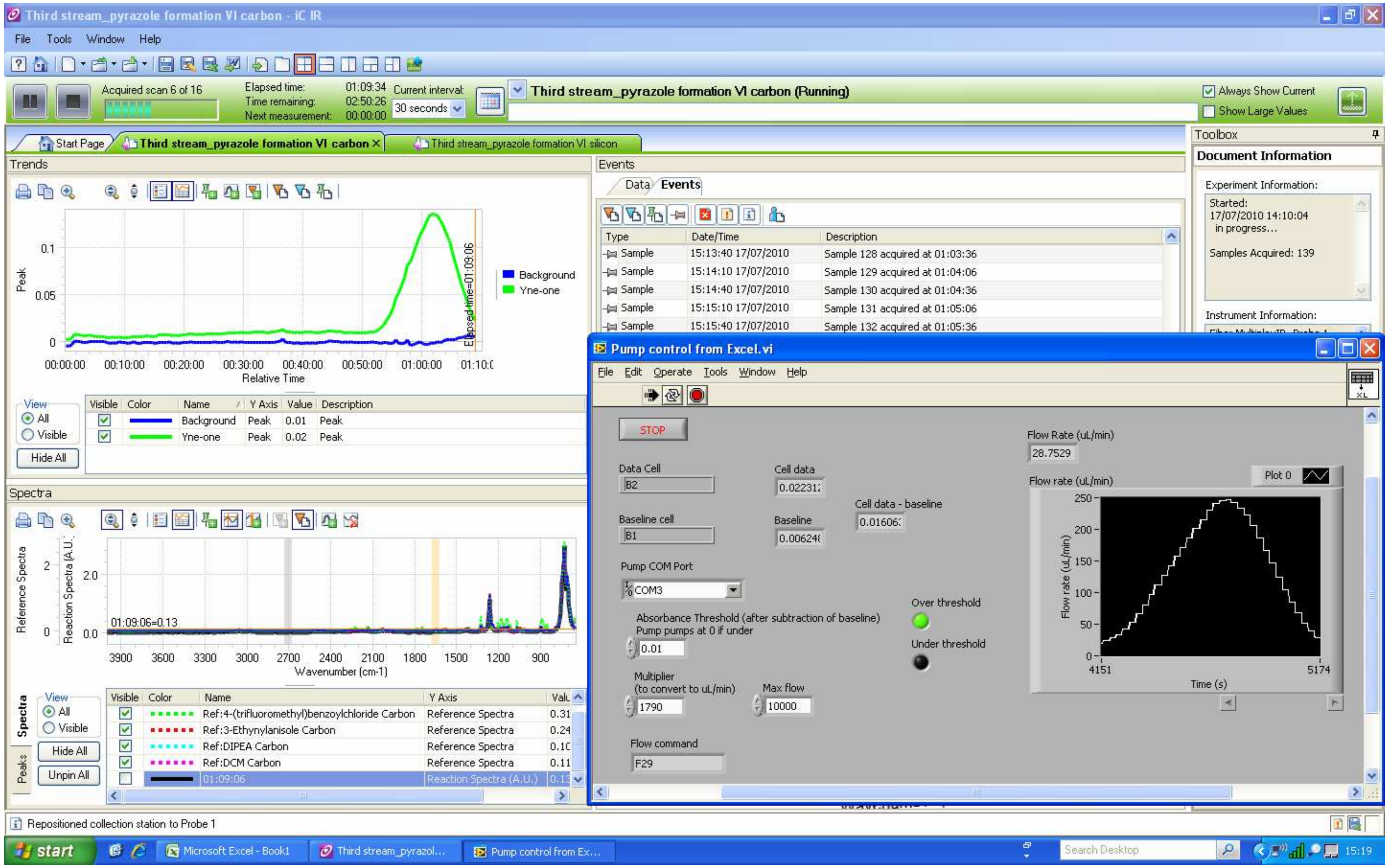
The required flow rate of the stream of D also depends upon three other factors: The flow rate of C exiting the first step (v_{stream}); the concentration of the solution of D (c_D) and the desired stoichiometry between the two reagents ($n_{equiv.}$). Taking these parameters into account, the flow rate of the third stream (v_{pump}) is found to be:

$$v_{pump} = \frac{n_{equiv.}\, v_{stream}\ f_A}{c_D} A \qquad (1)$$

$$= f_{corr.} A \qquad (2)$$

The value of f_{corr} is therefore the multiplier used in the LabVIEW program to calculate the required flow rate.

1.2.3 Screen shot of LabVIEW application



Acquired scan 6 of 16

Elapsed time: 01:09:34
Time remaining: 02:50:26
Next measurement: 00:00:00
Current interval: 30 seconds

Third stream_pyrazole formation VI carbon (Running)

☑ Always Show Current
☐ Show Large Values

View: ● All ○ Visible

Visible	Color	Name	Y Axis	Value	Description
☑		Background	Peak	0.01	Peak
☑		Yne-one	Peak	0.02	Peak

Events

Type	Date/Time	Description
Sample	15:13:40 17/07/2010	Sample 128 acquired at 01:03:36
Sample	15:14:10 17/07/2010	Sample 129 acquired at 01:04:06
Sample	15:14:40 17/07/2010	Sample 130 acquired at 01:04:36
Sample	15:15:10 17/07/2010	Sample 131 acquired at 01:05:06
Sample	15:15:40 17/07/2010	Sample 132 acquired at 01:05:36

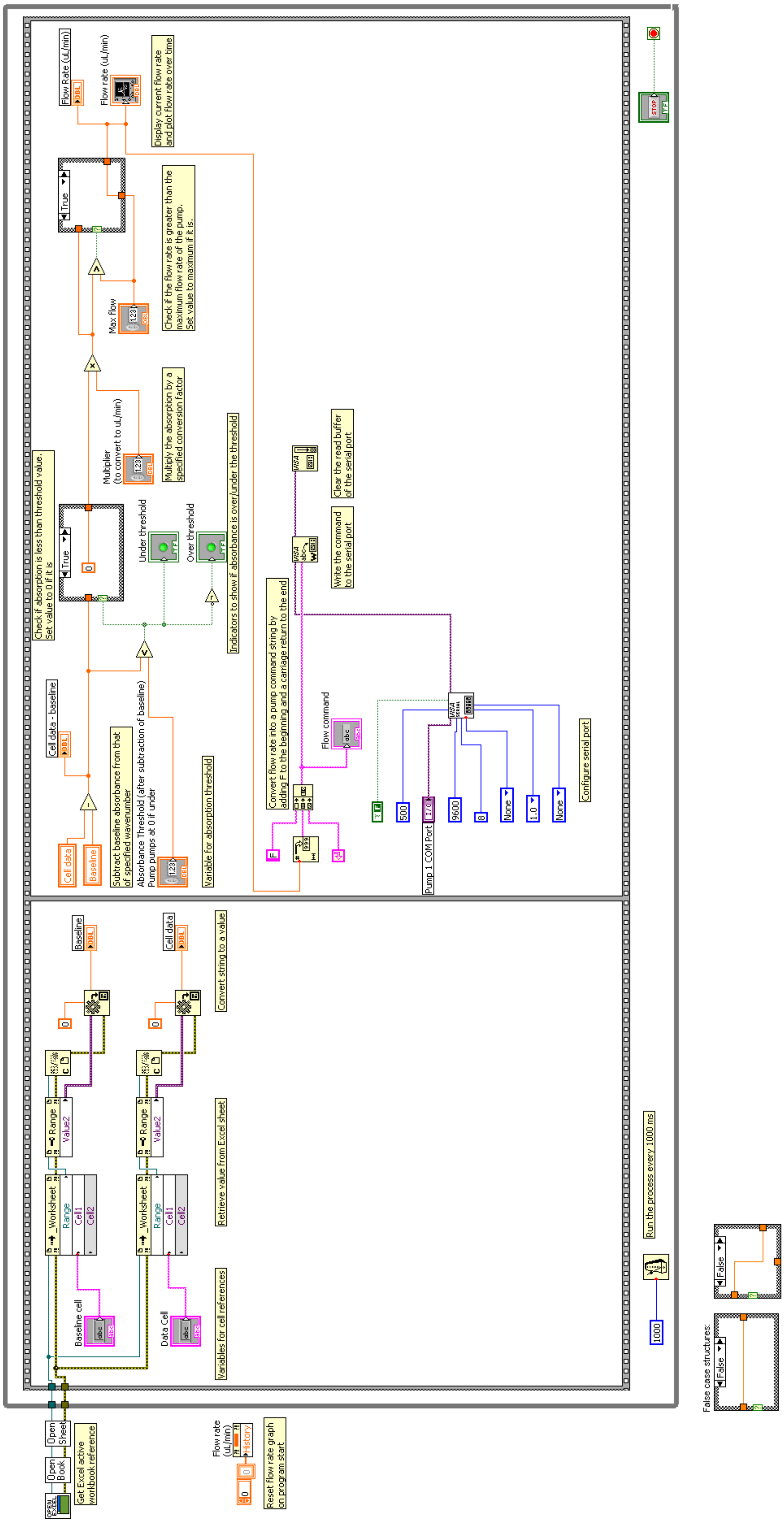
Experiment Information:
Started:
17/07/2010 14:10:04
in progress...
Samples Acquired: 139

Visible	Color	Name	Y Axis	Valu
☑		Ref:4-(trifluoromethyl)benzoylchloride Carbon	Reference Spectra	0.31
☑		Ref:3-Ethynylanisole Carbon	Reference Spectra	0.24
☑		Ref:DIPEA Carbon	Reference Spectra	0.10
☑		Ref:DCM Carbon	Reference Spectra	0.11
☐		01:09:06	Reaction Spectra (A.U.)	0.1

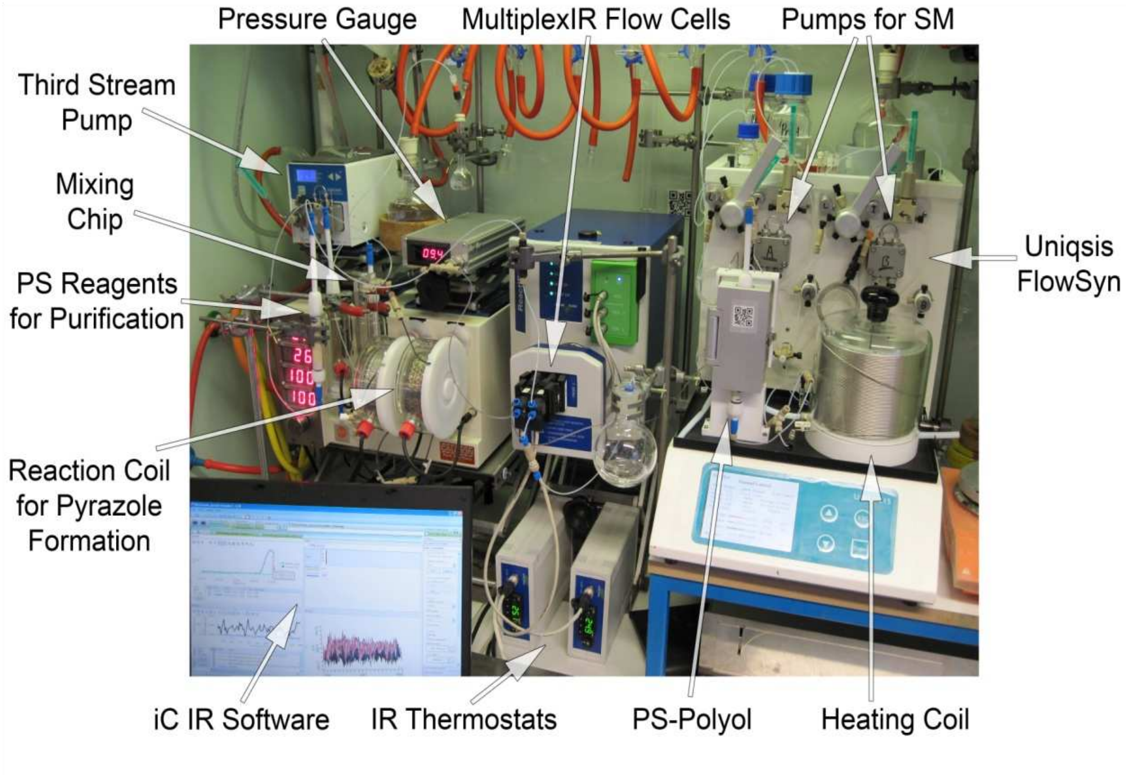
Repositioned collection station to Probe 1

Data Cell: B2
Cell data: 0.02231
Baseline cell: B1
Baseline: 0.00624
Cell data - baseline: 0.01606
Pump COM Port: COM3
Absorbance Threshold (after subtraction of baseline) Pump pumps at 0 if under: 0.01
Multiplier (to convert to uL/min): 1790
Max flow: 10000
Flow command: F29
Flow Rate (uL/min): 28.7529

1.2.4 LabVIEW Block Diagram



1.2.5 Photograph of reaction set-up



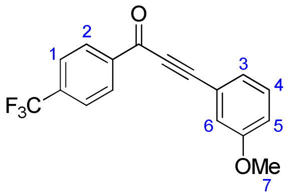
1.3 Pyrazole formation

1.3.1 General Procedure for the preparation of pyrazoles

A solution (2 mL) of $Pd(OAc)_2$ (4.5 mg, 20.0 µmol) and DIPEA (418 µL, 2.40 mmol) in CH_2Cl_2 was loaded into a sample loop (2 mL) on a Uniqsis FlowSyn. A solution (2 mL) of a terminal alkyne (2.00 mmol) and an acid chloride (2.40 mmol) was loaded into a second sample loop (2 mL). The two sample loops were switched in-line into streams of CH_2Cl_2 each flowing at 0.25 mL/min and mixed in a T-piece. The output of the T-piece was directed into the FlowSyn heating coil (20 mL, 80 °C) then into a 10 mm diameter Omnifit column filled with PS-Polyol resin (2.24 mmol/g, 3,00 g, 6.7 mmol) followed by a 250 psi BPR. The flow stream was then directed through a pressure sensor followed by the Mettler-Toledo ReactIR^{TM} 45m diamond flow cell and an Aldrich borosilicate glass microreactor. A Knauer Smartline Pump 100, pre-primed with a solution of methylhydrazine in EtOH (1.5 M, 20 mL), was connected through a 75 psi BPR to the second input of the glass mixing chip. Using the iC IR software, the absorption at the specified product and baseline (2705 cm^{-1}) frequencies were set to output to Microsoft Excel. The Knauer pump was controlled through an RS232 serial cable using a LabVIEW VI from the Microsoft Excel spreadsheet to automatically dispense the methylhydrazine solution. The output stream of the mixing chip was then passed through a reactor coil (20 mL) held at 40 °C using a Vapourtec R4 heating unit. The stream was then directed into a series of 10 mm diameter Omnifit columns filled with $CaCO_3$ (3 g, 30 mmol), QP-SA (5 g, 15 mmol), QP-TU (2 g, 6 mmol) and silica gel (8 cm). The output was then passed through a 100 psi BPR followed by the second ReactIR^{TM} 45m flow cell and a 40 psi BPR. The product was manually collected when IR absorption of the product was detected and the resulting solution left to stand at rt overnight to allow crystallisation of the product.

1.3.2 Compound characterisation

3-(3-Methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one.



Prepared according to the general procedure, then purified by column chromatography (4:1 PE/Et_2O) to give the title compound (389 mg, 64%, >95% purity) as yellow crystals.

Mp 60-64 °C. R_f 0.35 (4:1 PE/Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (2 H, d, J = 8.2 Hz, H-2), 7.79 (2 H, d, J = 8.2 Hz, H-1), 7.38-7.27 (2 H, m, H-3 and H-4), 7.20 (1 H, d, J = 2.3 Hz, H-6), 7.06 (1 H, ddd, J = 8.2, 2.5, 0.9 Hz, H-5), 3.85 (3 H, s, H-7) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.62 (C), 159.45 (C), 139.27 (C), 135.09 (C, q, J = 32.7 Hz), 129.85 (CH), 129.74 (CH), 125.64 (CH, q, *J* = 3.7 Hz), 125.63 (CH), 123.49 (C, q, *J* = 272.9 Hz), 120.49 (C), 117.85 (CH), 117.65 (CH), 94.36 (C), 86.18 (C), 55.34 (CH_3) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 2970 (w, C–H), 2194 (m, C≡C), 1637 (s, C=O), 1574 (m, C=C), 1320 (s, C–F), 1233 (s, C–O) cm^{-1}. HRMS (ESI): calculated for $C_{17}H_{12}F_3O_2$, $[M + H]^+$, 305.0789; found 305.0802; Δ = 4.3 ppm.

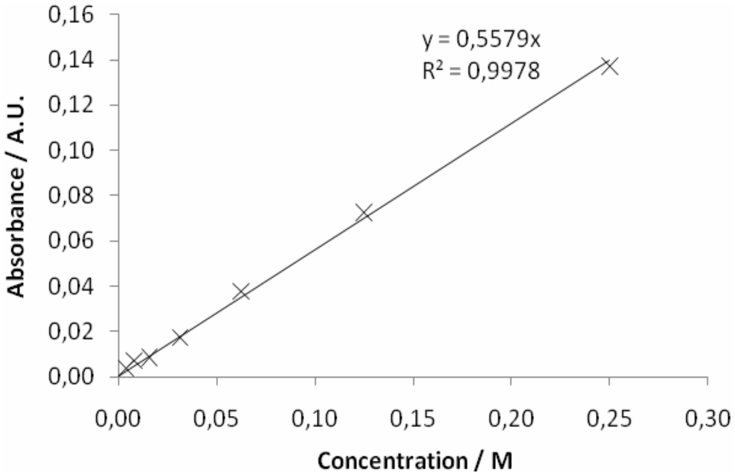
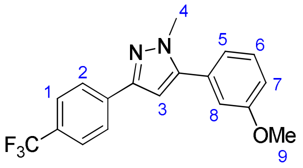


Figure SI1. Determination of the correlation factor for 3-(3-Methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one.

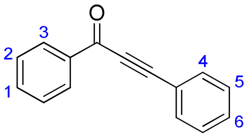
5-(3-Methoxyphenyl)-1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (5a)



Prepared according to the general procedure using 3-ethynylanisole (254 µL, 2.0 mmol) and 4-(trifluoromethyl)benzoyl chloride (501 mg, 2.4 mmol). The ynone intermediate was monitored at 1648 cm^{-1}. The title compound (459 mg, 69%, >95% purity) was collected as orange crystals.

Mp 71-73 °C. R_f 0.10 (4:1 PE/Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (2 H, d, *J* = 8.2 Hz, H-2), 7.66 (2 H, d, *J* = 8.2 Hz, H-1), 7.40 (1 H, dd, *J* = 8.9 and 7.6 Hz, H-6), 7.04 (1 H, ddd, *J* = 7.6, 1.5 and 1.0 Hz, H-5), 7.01-6.98 (2 H, m, H-7 and H-8), 6.65 (1 H, s, H-3), 3.95 (3 H, s, H-4), 3.87 (3 H, s, H-9) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.68 (C), 148.86 (C), 145.20 (C), 136.75 (C), 131.41 (C), 129.78 (CH), 129.25 (C, q, *J* = 32.3 Hz), 125.51 (CH), 125.50 (CH, q, *J* = 3.8 Hz), 124.27 (C, q, *J* = 271.9 Hz), 120.96 (CH), 114.50 (CH), 114.02 (CH), 103.57 (CH), 55.23 (CH_3), 37.62 (CH_3) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 2837 (w, C–H), 2549 (w, C–H), 1693 (s, C=N), 1583 (m, C=C), 1428 (m, C=C), 1321 (s, C–F), 1286 (s, C–O) cm^{-1}. HRMS (ESI): calculated for $C_{18}H_{16}F_3N_2O$, $[M + H]^+$, 333.1215; found 333.1221; Δ = 1.8 ppm.

1,3-Diphenylprop-2-yn-1-one[1]



Prepared according to the literature procedure, then purified by column chromatography (4:1 PE/Et_2O) to give the title compound (247 mg, 60%, >95% purity) as a brown solid.

Mp 44-46 °C. R_f 0.36 (4:1 PE/Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (2 H, dd, *J* = 8.4 and 1.3 Hz, H-3), 7.69 (2 H, dd, *J* = 8.3 and 1.4 Hz, H-4), 7.64 (1 H, tt, *J* = 7.4 and 1.3 Hz, H-1), 7.54-7.46 (3 H, m, H-2 and H-6), 7.44-7.40 (2 H, m, H-5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.95 (C), 136.88 (C), 134.06 (C), 133.02 (CH), 130.75 (CH), 129.53 (CH), 128.65 (CH), 128.58 (CH), 120.11 (CH), 93.06 (C), 86.87 (C) ppm. IR: $\tilde{\nu}_{max}$ = 3069 (w, C–H), 2202 (s, C≡C), 1641 (s, C=O), 1600 (m, C=C), 1581 (m, C=C), 1495 (m, C=C) cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{10}ONa$, $[M + Na]^+$, 229.0635; found 229.0641; Δ = 2.6 ppm.

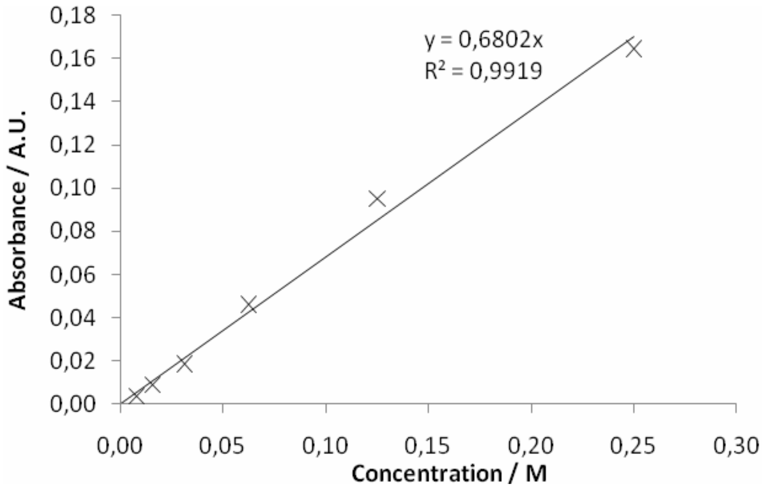


Figure SI2. Determination of the correlation factor for 1,3-Diphenylprop-2-yn-1-one.

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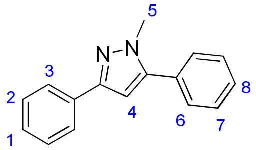
[1] I. R. Baxendale, S. C. Schou, J. Sedelmeier, S. V. Ley, *Chem. Eur. J.*, 2010, **16**, 89-94.

1-Methyl-3,5-diphenyl-1*H*-pyrazole (5b)[1]



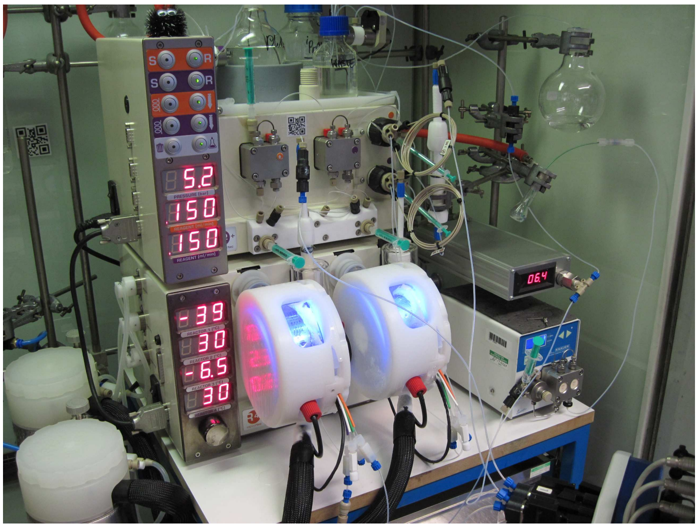
Prepared according to the general procedure using phenylacetylene (220 µL, 2.0 mmol) and benzoyl chloride (279 µL, 2.4 mmol). The ynone intermediate was monitored at 1640 cm^{-1}. The title compound (337 mg, 72%, >95% purity) was collected as pale brown crystals.

Mp 56-58 °C. R_f 0.12 (4:1 PE/Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (2 H, d, J = 8.4 Hz, H-3), 7.52-7.38 (7 H, m, H-1, H-2, H-6 and H-7), 7.31 (1 H, t, J = 7.4 Hz, H-8), 6.62 (1 H, s, H-4), 3.95 (3 H, s, H-5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.44 (C), 145.03 (C), 133.34 (C), 130.60 (C), 128.69 (CH), 128.67 (CH), 128.58 (CH), 128.51 (CH), 127.58 (CH), 125.48 (CH), 103.19 (CH), 37.53 (CH_3) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 3061 (w, C–H), 2562 (w, C–H), 1687 (s, C=N), 1484 (m, C=C), 1451 (m, C=C), 1274 (s, C–N) cm^{-1}. HRMS (ESI): calculated for $C_{16}H_{15}N_2$, $[M + H]^+$, 235.1270; found 235.1273; Δ = 1.3 ppm.

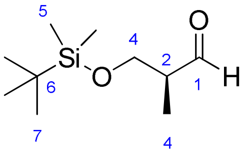
1.5 Reduction and crotylation

A solution (1 mL) of (*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (1 mmol) in toluene was loaded into a sample loop (1 mL) on a Vapourtec R2+/R4. A solution (1 mL) of DIBAL-H (1 mmol) in toluene (1 M) was loaded into a second sample loop (1 mL). The two sample loops were switched in-line into streams of toluene each flowing at 0.15 mL/min and mixed in a cooled T-piece within a Vapourtec low temperature coil held at –78 °C. The output of the coil was then directed into a 10 mm diameter Omnifit column filled with PS-Polyol resin (2.24 mmol/g, 2.5 g, 5.60 mmol) and a 1 cm plug of silica gel. The flow stream was then passed through the Mettler-Toledo ReactIR^{TM} 45m diamond flow followed by a 75 psi back pressure regulator into the first input of a second cooled T-piece. A Knauer Smartline Pump 100, pre-primed with a solution of boronate **7** in toluene (1.5 M), was connected through a 75 psi BPR to the second input of the T-piece. Using the iC IR software, the absorption at the specified product (1737 cm^{-1}) and baseline (2705 cm^{-1}) frequencies were set to output to Microsoft Excel. The Knauer pump was controlled through an RS232 serial cable using a LabVIEW VI from the Microsoft Excel spreadsheet to automatically dispense the boronate solution. The output stream of the T-piece was then passed through a second cooled coil held at –40 °C. The stream was then directed into a 10 × 15 mm diameter Omnifit column filled with PS-Polyol resin (2.24 mmol/g, 5 g, 11.2 mmol) The output was then passed through the second ReactIR^{TM} 45m flow cell and a 40 psi BPR. The product was manually collected when IR absorption of the product was detected.

Photograph of set-up (temperatures displayed are NOT the reaction temperatures):



(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal[2]



Prepared according to the general procedure with collection after the first column of PS-polyol resin and silica gel to yield the title compound as colourless oil. (176 mg, 88%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (1 H, d, *J* = 1.6 Hz, H-1), 3.84 (1 H, dd, *J* = 5.2, 10.2 Hz, H-4_A), 3.79 (1 H, dd, *J* = 6.3, 10.2 Hz, H-4_B), 2.55 – 2.46 (1 H, m, H-2), 1.07 (3 H, d, *J* = 7.0 Hz, H-4), 0.86 (6 H, s, H-5), 0.04 (9 H, s, H-7) ppm.

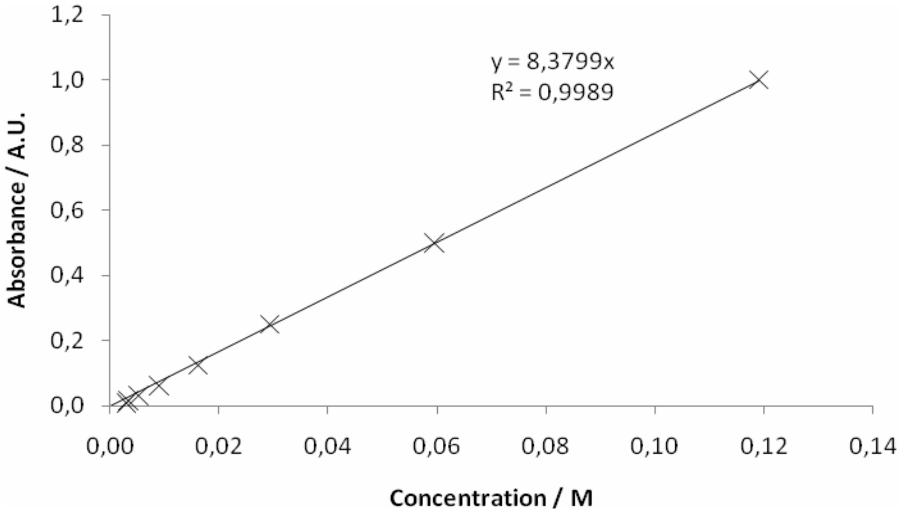
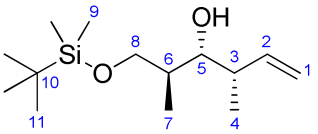


Figure SI3. Determination of the correlation factor for (*S*)-3-(tert-butyldimethylsilyloxy)-2-methylpropanal.

(2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhex-5-en-3-ol (8) [3]



Prepared according to the general procedure and evaporated to dryness to give olefin **8** as colourless oil (202 mg, 78%).

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[2] J. A. Marshall, B. A. Johns, *J. Org. Chem.*, 1998, **63**, 7885–7892.

[3] P. V. Ramachandran, A. Srivastava, D. Hazra, *Org. Lett.*, 2007, **9**, 157-160.

$[\alpha]_D^{25}$ = +6.4 (*c* 2.00, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.84 (1 H, ddd, *J* = 7.3, 10.4, 17.5 Hz, H-2), 5.05-5.02 (2 H, m, H-1), 3.82 (1 H, dd, *J* = 3.9, 9.9 Hz, H-8_A), 3.61 – 3.55 (1 H, m, H-8_B), 3.38 (1 H, dt, *J* = 4.6, 6.7 Hz, H-5), 2.35 – 2.27 (1 H, m, H-3), 1.82 – 1.73 (1 H, m, H-6), 1.03 (3 H, d, *J* = 6.8 Hz, H-4), 0.89 (3 H, d, *J* = 7.1 Hz, H-7), 0.87 (9 H, s, H-11), 0.05 (6 H, d, *J* = 2.1 Hz, H-9) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.47 (CH), 113.88 (CH_2), 79.60 (CH), 67.98 (CH_2), 41.26 (CH), 36.62 (CH), 25.85 (C), 18.14 (CH_3), 14.10 (CH_3), 13.40 (CH_3), –5.61 (CH_3), –5.64 (CH_3) ppm. IR (ATR): $\tilde{\nu}_{max}$ = 3510 (br, O–H), 2929 (w, C–H), 2858 (w, C–H), 1463 (m, C=C), 1253 (m, C–O), 1075 (s, Si–O) cm^{-1}.