Supporting Information for:

QuadraPure Cartridges for Removal of Trace Metal From Reaction Mixtures in Flow

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Experimental

General

All reagents were purchased from Aldrich and used without further purification. Solvents are standard laboratory grade and used from the drum without purification.

Cartridge experiments were run on a Biotage SP4 automated chromatography system with pre-packed QuadraPure cartridges.[1] Cartridges were fitted inside the standard compression modules but connected to the valve unit such that the flow was up the cartridge (swap the HPLC connectors around for that channel).

Microwave reactions were carried out in a Biotage Initiator 60.

GC-MS was performed on a Varian Saturn 2100T with GC 3900 containing a CP-Sil 8CB low bleed/MS 30M x 0.25 mm, 0.25 µm column.

ICP-OES Analysis

ICP–OES (Inductively Coupled Plasma Optical Emission Spectroscopy) was performed by Intertek ASG, Manchester on a Perkin Elmer Optima 3300. The samples submitted were weighed into beakers and the solvent evaporated down. The residue was then digested using nitric acid and sulphuric acid. After cooling the samples were then transferred to 25 ml volumetric flasks and made to volume with deionised water. The solutions were then analysed against known standards by ICP-OES and the results calculated.

Preliminary In-Flow scavenging of 1000 ppm palladium(II) acetate in THF

QuadraPure™ TU, 12+M Cartridge

A solution of palladium(II) acetate (2.11 g) was prepared in THF (1000 ml) which was approximately 1000 ppm with respect to palladium. Using a Biotage SP4 Flash Purification System, the palladium solution being the 'strong solvent' was connected to line 'B'. A separate flask of the 'weak solvent' THF (1250 ml) was connected to line 'A'. A 12+M flash cartridge filled with QuadraPure™ TU contained approximately 6 g of resin and had a 12 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 1 ml/min, starting with an initial 5 column volumes (60 ml) of THF to wet the resin, then 25 column volumes (300 ml) of palladium solution. The end of the gradient was programmed to another 5 column volumes (60 ml) of THF. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10 column volumes (125 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow coloured fractions. The loading of the cartridge equated to approximately 20 mg Pd/g of resin (0.19 mmol/g).

QuadraPure™ TU, 25+S Cartridge

A solution of palladium(II) acetate (2.11 g) was prepared in THF (1000 ml) which was approximately 1000 ppm with respect to palladium. Using a Biotage SP4 Flash

Purification System, the palladium solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ THF (1250 ml) was connected to line ‘A’. A 25+S flash cartridge filled with QuadraPure™ TU contained approximately 13 g of resin and had a 24 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 2 ml/min, starting with an initial 5 column volumes (120 ml) of THF to wet the resin, then 20 column volumes (480 ml) of palladium solution. The end of the gradient was programmed to another 2 column volumes (48 ml) of dichloromethane. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 12.5 column volumes (300 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow coloured fractions. The loading of the cartridge equated to approximately 23 mg Pd/g of resin (0.22 mmol/g).

QuadraPure™ TU, 40+M Cartridge

A solution of palladium(II) acetate (6.33 g) was prepared in THF (3000 ml) which was approximately 1000 ppm with respect to palladium. Using a Biotage SP4 Flash Purification System, the palladium solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ THF (1250 ml) was connected to line ‘A’. A 40+M flash cartridge filled with QuadraPure™ TU contained

approximately 67.5 g of resin and had a 132 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 8 ml/min, starting with an initial 5 column volumes (660 ml) of THF to wet the resin, then 15 column volumes (1980 ml) of palladium solution. The end of the gradient was programmed to another 2 column volumes (264 ml) of THF. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10 column volumes (1300 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow coloured fractions. The loading of the cartridge equated to approximately 19 mg Pd/g of resin (0.18 mmol/g).

Preliminary In-Flow scavenging of 1000 ppm copper(II) acetylacetonate in dichloromethane

QuadraPure™ IDA, 12+M Cartridge

A solution of copper(II) acetylacetonate (4.12 g) was prepared in dichloromethane (1000 ml) which was approximately 1000 ppm with respect to copper. Using a Biotage SP4 Flash Purification System, the copper solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ dichloromethane (1250 ml) was connected to line ‘A’. A 12+M flash cartridge filled with QuadraPure™ IDA contained approximately 6 g of resin and had a 12 ml column

volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 1 ml/min, starting with an initial 5 column volumes (60 ml) of dichloromethane to wet the resin, then 25 column volumes (300 ml) of copper solution. The end of the gradient was programmed to another 5 column volumes (60 ml) of dichloromethane. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of dichloromethane at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10 column volumes (120 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of blue coloured fractions. The loading of the cartridge equated to approximately 20 mg Cu/g of resin (0.30 mmol/g).

QuadraPure™ IDA, 25+S Cartridge

A solution of copper(II) acetylacetonate (4.12 g) was prepared in dichloromethane (1000 ml) which was approximately 1000 ppm with respect to copper. Using a Biotage SP4 Flash Purification System, the copper solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ dichloromethane (1250 ml) was connected to line ‘A’. A 25+S flash cartridge filled with QuadraPure™ IDA contained approximately 13 g of resin and had a 24 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 2 ml/min, starting with an initial 5 column volumes (120 ml) of dichloromethane to wet the resin, then 15 column volumes (360 ml) of copper solution. The end of the gradient was programmed to another 1 column volume (24 ml) of dichloromethane. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of dichloromethane at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 12.5 column volumes (300 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of blue coloured fractions. The loading of the cartridge equated to approximately 21 mg Cu/g of resin (0.33 mmol/g).

QuadraPure™ IDA, 40+M Cartridge

A solution of copper(II) acetylacetonate (20.6 g) was prepared in dichloromethane (5000 ml) which was approximately 1000 ppm with respect to copper. Using a Biotage SP4 Flash Purification System, the copper solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ dichloromethane (1250 ml) was connected to line ‘A’. A 40+M flash cartridge filled with QuadraPure™ IDA contained approximately 67.5 g of resin and had a 132 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 8 ml/min, starting with an initial 5 column volumes (660 ml) of dichloromethane to wet the resin, then 30 column

volumes (3960 ml) of copper solution. The end of the gradient was programmed to another 2 column volumes (264 ml) of dichloromethane. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of dichloromethane at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10 column volumes (1300 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of blue coloured fractions. The loading of the cartridge equated to approximately 19 mg Cu/g of resin (0.3 mmol/g).

Preliminary In-Flow scavenging of 500 ppm iron(III) chloride in THF

QuadraPure™ AMPA, 12+M Cartridge

A solution of iron(III) chloride (3.16 g) was prepared in THF (1000 ml) which was approximately 500 ppm with respect to iron. Using a Biotage SP4 Flash Purification System, the iron solution being the ‘strong solvent’ was connected to line ‘B’. A separate flask of the ‘weak solvent’ THF (1250 ml) was connected to line ‘A’. A 12+M flash cartridge filled with QuadraPure™ AMPA contained approximately 6 g of resin and had a 12 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 1 ml/min, starting with an initial 2 column volumes (24 ml) of THF to wet the resin, then 25 column volumes (300 ml) of iron solution. The end of the gradient was programmed to another 2 column volumes (24 ml) of THF. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10 column volumes (120 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow coloured fractions. The loading of the cartridge equated to approximately 10 mg Fe/g of resin (0.18 mmol/g).

QuadraPure™ AMPA, 25+S Cartridge

A solution of iron(III) chloride (3.16 g) was prepared in THF (1000 ml) which was approximately 500 ppm with respect to iron. Using a Biotage SP4 Flash Purification System, the iron solution being the 'strong solvent' was connected to line 'B'. A separate flask of the 'weak solvent' THF (1250 ml) was connected to line 'A'. A 25+S flash cartridge filled with QuadraPure™ AMPA contained approximately 13 g of resin and had a 24 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 2 ml/min, starting with an initial 4 column volumes (96 ml) of THF to wet the resin, then 20 column volumes (480 ml) of iron solution. The end of the gradient was programmed to another 2 column volumes (48 ml) of THF. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 16.5 column volumes (400 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow

coloured fractions. The loading of the cartridge equated to approximately 15 mg Fe/g of resin (0.27 mmol/g).

QuadraPure™ AMPA, 40+M Cartridge

A solution of iron(III) chloride (9.48 g) was prepared in THF (3000 ml) which was approximately 500 ppm with respect to iron. Using a Biotage SP4 Flash Purification System, the iron solution being the 'strong solvent' was connected to line 'B'. A separate flask of the 'weak solvent' THF (1250 ml) was connected to line 'A'. A 40+M flash cartridge filled with QuadraPure™ AMPA contained approximately 68 g of resin and had a 132 ml column volume. UV detector collection wavelength was set to 232 nm, and the monitor wavelength 320 nm.

A gradient was programmed at a fixed flow rate of 8 ml/min, starting with an initial 4 column volumes (528 ml) of THF to wet the resin, then 15 column volumes (1980 ml) of iron solution. The end of the gradient was programmed to another 2 column volumes (264 ml) of THF. The programme was set to collect all fractions (51 ml each).

The Biotage unit was first primed with a 50 ml portion of THF at a flow rate of 20 ml/min to remove air bubbles, bypassing the column. The program was then run giving a breakthrough point at 10.5 column volumes (1400 ml), depicted by a sharp increase in gradient on the UV trace, and also visually by the appearance of yellow coloured fractions. The loading of the cartridge equated to approximately 10 mg Fe/g of resin (0.18 mmol/g).

Acknowledgements

We thank Biotage (www.biotage.com) for packing of cartridges.

References and Notes

(1) Available through Reaxa Ltd., (www.reaxa.com).

(2) Based on procedure in: Newman, M. S. *Org. Synth.,* **1941**, *21*, 89-91.

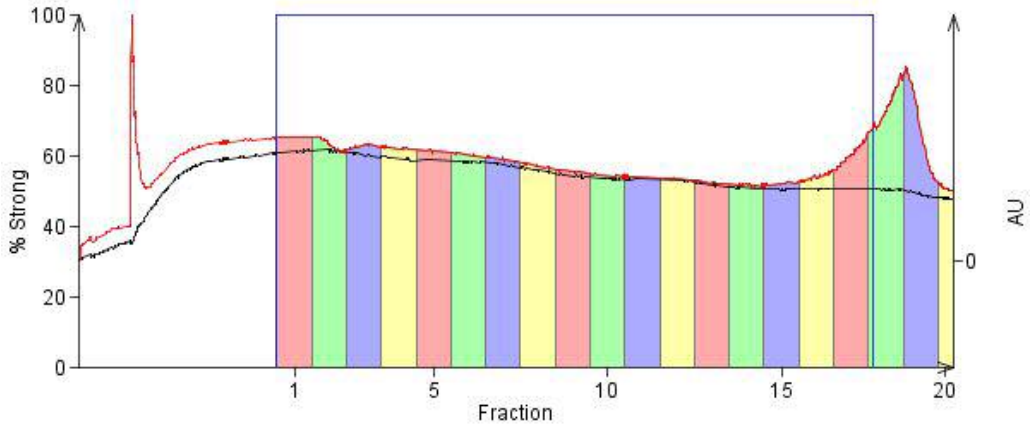
(3) www.biotage.com/DynPage.aspx?id=22001 *(accessed October 2006)*.

(4) Christoffers, J. *Org. Synth.,* **2002**, *78*, 249-251.

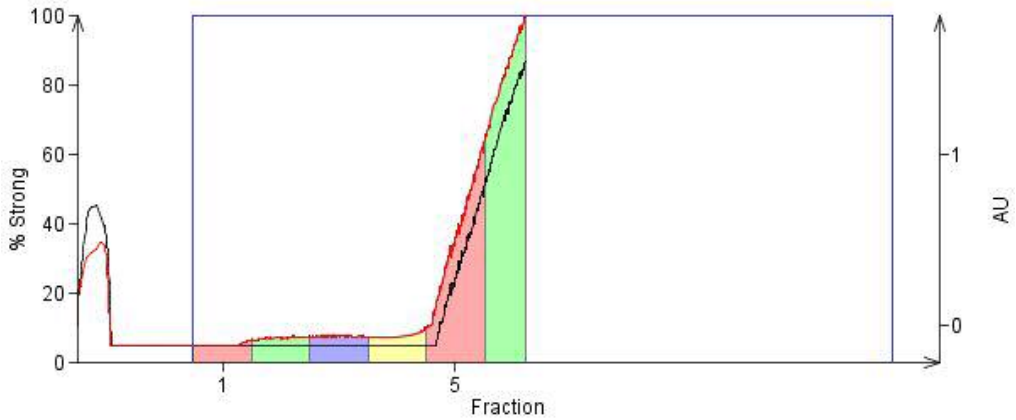
(5) Ireland R. E.; Bey, P. *Org. Synth.,* **1973**, *53*, 63-65.

Appendix 1

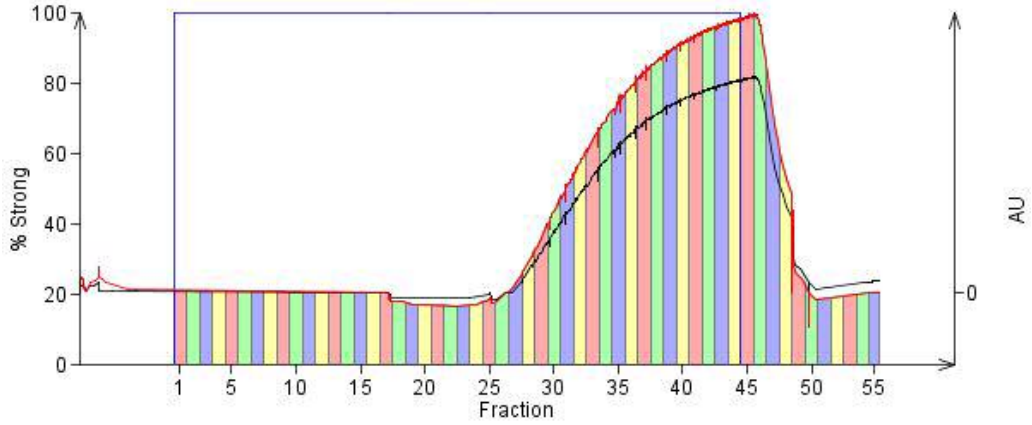
UV Trace of Breakthrough Curves



breakthrough curve of $Pd(OAc)_2$ in THF (1000 ppm) through QuadraPure TU cartridge



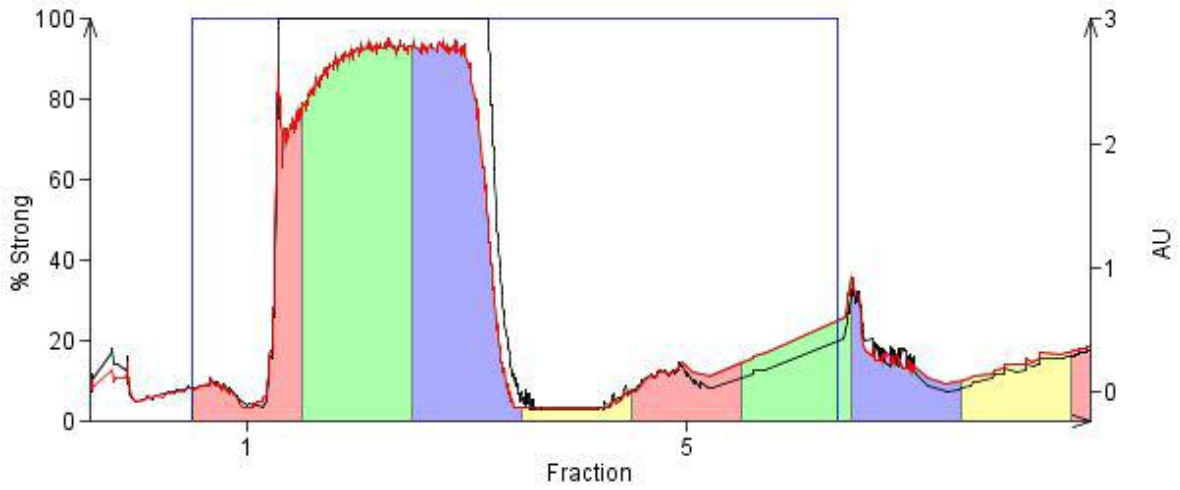
breakthrough curve of $Cu(acac)_2$ in DCM (1000 ppm) through QuadraPure IDA cartridge



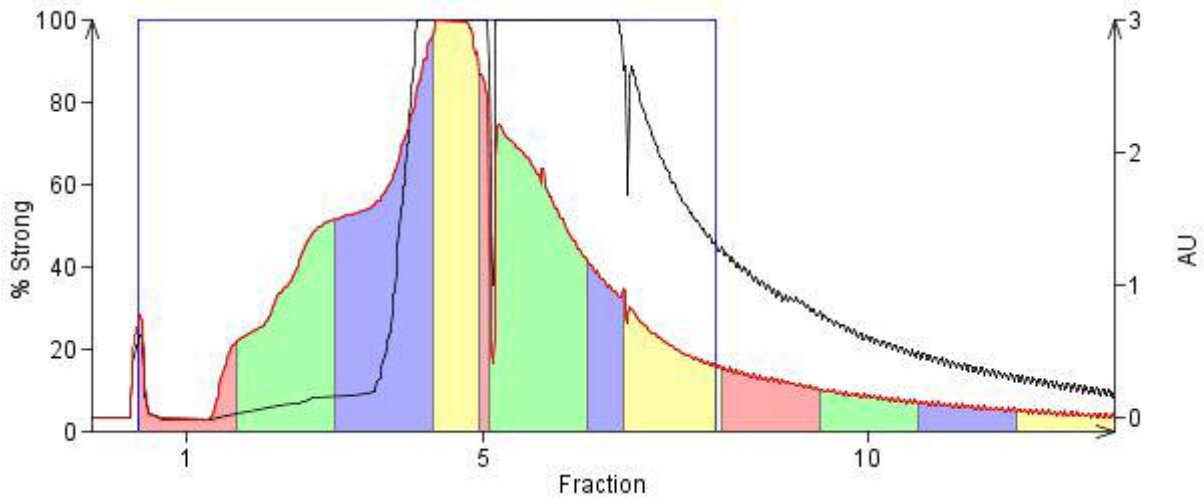
breakthrough curve of $FeCl_3$ in THF (500 ppm) through QuadraPure AMPA cartridge

red line 232 nm, black line 320 nm

Suzuki Coupling Palladium Clean-Up



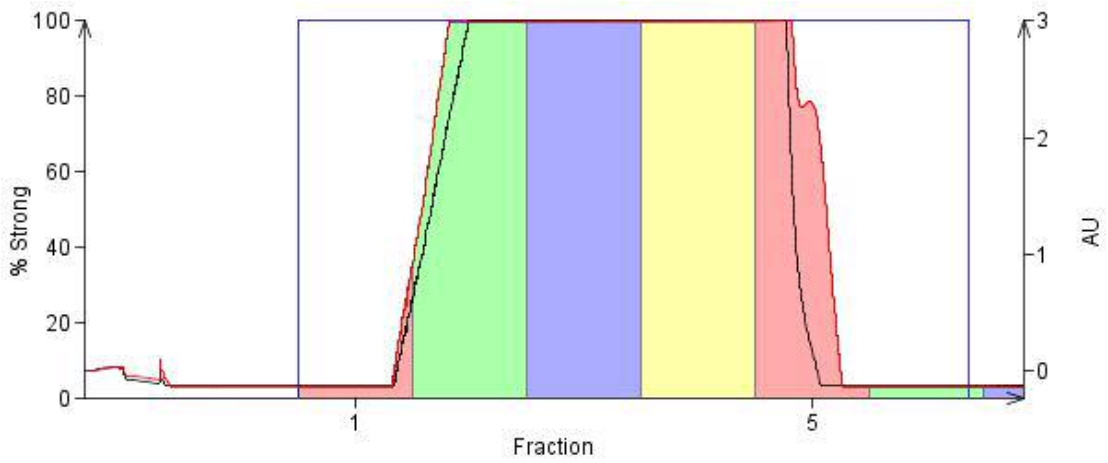
trace of product flow through QuadraPure TU cartridge



trace of product flow through Biotage AC carbon cartridge

red line 232 nm, black line 254 nm

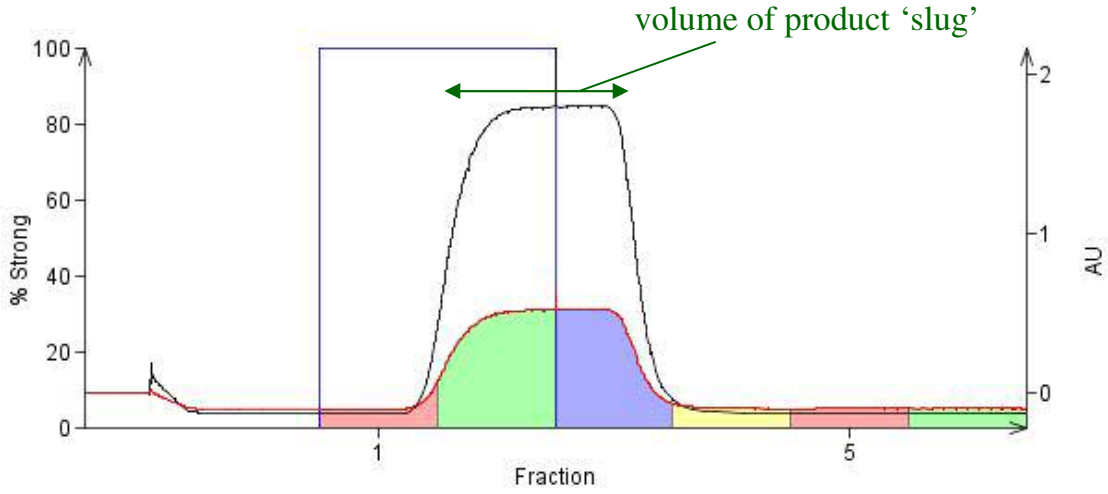
Sonogashira Palladium and Copper Clean-Up



trace of product flow through QuadraPure TU cartridge

red line 232 nm, black line 254 nm

Michael Addition Iron Clean-Up



trace of product flow through QuadraPure AMPA cartridge

red line 220 nm, black line 254