CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902396

Propargyl Amine Synthesis Catalysed by Gold and Copper Thin Films by Using Microwave-Assisted Continuous-Flow Organic Synthesis (MACOS)

Gjergji Shore,[a] Woo-Jin Yoo,[b] Chao-Jun Li,*[b] and Michael G. Organ*[a]

Abstract: An effective multi-component reaction (MCR) protocol has been developed for the construction of propargyl amines from aldehydes, amines and terminal alkynes by using microwave-assisted continuous-flow organic synthesis (MACOS). The process is catalysed by thin films of either copper or gold that achieve temperatures in excess of 900 °C when irradiated with low levels of microwave power. The process works equally well for premixed solutions of the three starting materials, or as three separate streams, which improves the combinatorial efficiency of the method. The process tolerates a wide variety of functional groups and heterocycles, and conversion over these diverse substrates ranges from 70–90 %.

Keywords: amines · copper · gold · microwave chemistry · thin films

Introduction

Microwave-assisted organic synthesis (MAOS) has become an important tool in the hands of synthetic organic chemists in the recent years. Some of the advantages of MAOS over conventional heating methods (e.g., oil baths) include a significant reduction of reaction times and the generation of cleaner product mixtures.[1] However, batch-reactor MAOS requires that transformations be conducted in sealed, high-pressure vials; this necessitates the manual handling of each individual transformation that slows down the overall synthetic process. Over the last five years, the development of microwave-assisted continuous-flow organic synthesis (MACOS) has also rapidly progressed.[2,3] Continuous-flow technology also offers numerous advantages over traditional batch reactors.[4] A synthetic process can be rapidly optimised because the results of any set of reaction parameters can be assessed from the first drop of eluent. Every subsequent drop of product should be the same over time, which is not the case with batch reactions. The physical separation of reactive intermediates from the starting materials (and products) until the point of contact at the start of the flow tube minimises side reactions. Continuous removal of products from the reaction zone limits the formation of by-products owing to prolonged unnecessary exposure to heat, catalysts or other reaction-promoting elements. The potential to couple in-line analysis into a continuously moving flow stream allows for instantaneous changes to reaction conditions for process optimisation, and once ideal conditions have been achieved, larger quantities of product can be obtained by flowing reactions for longer and/or in parallel tubes without the need for time-consuming, scale-up process optimisation.

We have demonstrated that homogeneous reaction mixtures flowed through capillary-size glass reactors while being constantly irradiated with microwave irradiation can lead to excellent conversions. This can be done by flowing premixed solutions through a single lead into the reactor or by flowing the reactants into the reactor through separate inlets where they mix under microwave radiation.[5] More recently we have shown that coating the glass capillary reactors with thin layers of metals can tremendously accelerate flowed reactions.[6] This rate acceleration can be a result of direct catalysis by the thin film itself, the extremely high temperatures achieved by microwaving the film or by a combination of the two. Pd thin films have been shown to be capable of catalysing Suzuki–Miyaura and Heck reactions,[6a] whereas gold films can very efficiently catalyse hydrosilylation and benzannulation reactions.[6b,c] All of these trans-

[a] G. Shore, Prof. M. G. Organ
Department of Chemistry, York University
4700 Keele Street, Toronto, ON, M3J 1P3 (Canada)
Fax: (+1) 416-736-5936
E-mail: organ@yorku.ca

[b] Dr. W.-J. Yoo, Prof. C.-J. Li
Department of Chemistry, McGill University
801 Sherbrooke Street West
Montreal, Quebec, H3A2K6 (Canada)
Fax: (+1) 514-398-3797
E-mail: cj.li@mcgill.ca

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902396.

formations proceed without any additional catalyst being added to the reaction mixture. In the absence of microwave irradiation, none of these reactions proceeded, indicating that heating supplied by the thin films under microwave irradiation plays a fundamental role in the process.

Propargylamines are versatile synthetic intermediates in organic synthesis[7] and are also key structural elements in natural products and therapeutic drug molecules.[8] The traditional approach for synthesising propargylamines involves the nucleophilic attack of lithium acetylides or Grignard reagents on imines and their derivatives.[9] This method necessitates the use of strictly moisture-free reaction conditions and prohibits the presence of sensitive functionalities (e.g., alcohols, amines and esters), thus limiting its wider application. Over the last decade there has been increasing interest in the development of transition-metal catalysts to accomplish the synthesis of propargyl amines by using the Mannich-type three-component coupling reaction of aldehydes, secondary amines and terminal alkynes through C–H bond activation. Several late transition-metal salts such as Au, Ag, Ir, Ru–Cu, Ru–In and Fe were reported by Li and others to promote this transformation through C–H activation.[10] Environmentally friendly strategies have also been carried out in water, ionic liquids and even under solvent-free conditions.[10c,d,11] Recently, the Mannich three-component coupling strategy has been shown to be promoted by supported nanoparticles including Ag,[12a] Au[12b,c] and Cu,[12d,e] and by oxides CuO[12f] and Ag_2O.[12g] In all cases the metal–acetylide intermediate has been assumed to play a key role in the reaction sequence.

Multi-component reaction (MCR) protocols have been successfully developed for MACOS in the past.[13] However, those protocols were not metal-catalysed. In an effort to increase the applications of MACOS, we envisioned that the three-component coupling reaction to form propargyl amines described above would be a good system to investigate the catalytic role of transition-metal films in the MACOS system. Further, bridging the gap between homogeneous and heterogeneous catalysis can lead to more efficient methods for chemical synthesis.[14]

Results and Discussion

The investigation of the three-component, MACOS-facilitated synthesis of propargyl amines began with an assessment of the catalytic properties of several metal films. Recent literature reports have demonstrated that metallic Au, Ag and Cu nanoparticles can serve as useful catalysts for this reaction,[12] thus we prepared thin films of these metals inside our flow tubes (capillaries) and analysed their composition. The protocols that we have developed for preparing these films (detailed in the Experimental Section) all involve either thermal reduction of a homogeneous solution of metal salts or reduction with hydrazine. Analysis of the resultant films was done by scanning electron microscopy (SEM) to examine both general morphology and microscopic fine structure, and by energy-dispersive X-ray (EDX) analysis to determine chemical composition.

The SEM analysis of film morphology indicated a very developed microstructure (with the exception of the Ag mirror film) consisting of porous clusters of metal nanoparticles that are closely held together (Figure 1 a–e). The existence of such clusters could increase the catalytic activity of the film under microwave irradiation as previously suggested.[6] Further, irregularities of morphology such as steps or sharp corners on the metal–film surface have been postulated to lead to the formation of hot spots that are much higher than the bulk temperature of the film as recorded by the infrared (IR) sensor in the microwave cavity.[6] This could lead to a large increase in reactivity under MACOS conditions because the flowing reaction mixture contacts these areas in the structure of the film through the formation of microscopic (or larger) pockets of super-heated, vapour-phase reactants. This would be analogous to flash vacuum thermolysis (FVT) in which compounds are warmed into the gas phase under high vacuum and drawn into contact with the walls of a super-heated (e.g., 500–700 °C) quartz reaction tube.

EDX analysis illustrated that the films are primarily metallic in composition (Figure 1 f–h). The films are not produced with the exclusion of oxygen, thus oxygen detected by the method could exist in the form of metal oxides on the surface of the film. The role of these metal oxides, which surely exist in all metal films, has yet to be examined. Further, it has not yet been determined if these oxides are reduced back to the metallic form because at least some of the reactions that have been done with metal films in MACOS, such as cross coupling reactions, are conducted in a potentially reducing environment.[6] Although Pd readily changes oxidation state during the various catalytic cycles in which it is employed, Au resists such changes. Further, CuO and Ag_2O nanoparticles have already been shown to catalyse the reaction under investigation in this report, so it could very well be that it is the oxidised form of the metal that is mediating the transformations in this study.

With the metal-coated capillaries in hand, we embarked on the development of a general MACOS method for the preparation of propargyl amines. With some optimisation by using a Cu-coated capillary, a general protocol by using premixed solutions of **1**, **2** and **3** was developed (Table 1, entry 1). Attempted runs by using either Pd or Ag films (Table 1, entries 2 and 3) failed to provide any conversion whatsoever. However, Au films were shown to be reactive in the transformation, although conversions with the Au films were slightly lower when compared directly with the identical transformation that used Cu.

To improve combinatorial efficiency when collecting a larger number of compounds for biological evaluation, for example, it would be desirable to infuse the starting materials into the mixing chamber separately, rather than as premixed solutions that would require a separate flask for every molecular combination desired. To examine how this would work for the current MACOS setup, compound **4a**

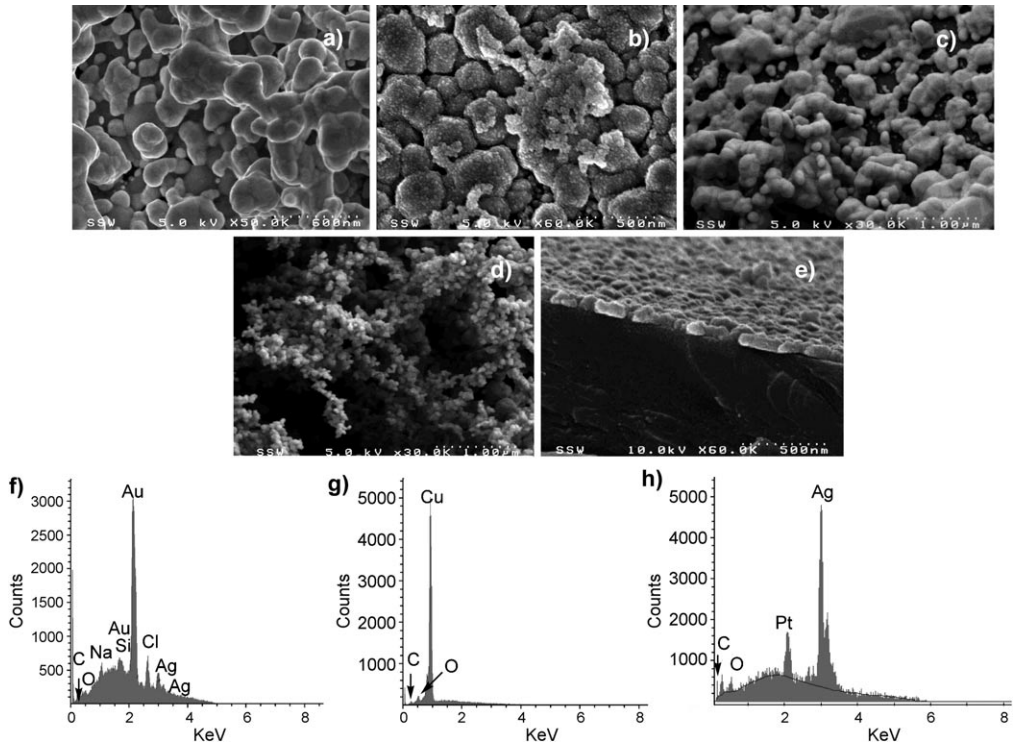


Figure 1. SEM images of all of the 6 μm metal films that were used in this study and their corresponding EDX analysis: a) Au film supported on a very thin Ag lining taken at ×50000 magnification, b) Cu film taken at ×60000 magnification, c) Ag colloidal film taken at ×30000 magnification, d) Pd film taken at ×30000 magnification, e) side view of Ag mirror film attached to the glass wall taken at ×60000 magnification. The EDX spectra of f) the Au film from (a), g) the Cu film from (b), h) the colloidal Ag film from (c).

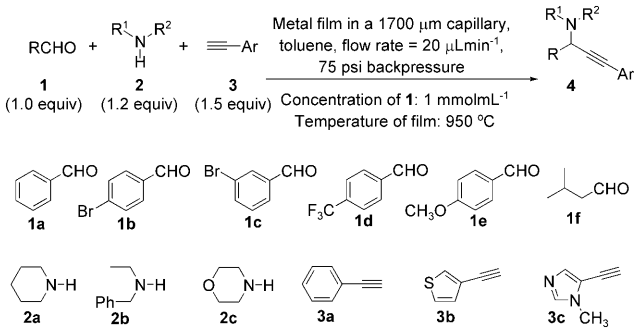
was prepared by flowing **1**, **2** and **3** into the mixing chamber from three separate syringes (Table 1, entry 4). The reaction proceeded equally well as when premixed solutions were used (Table 1, entry1). From this we can conclude that if the flow is laminar when it passes through the irradiation zone of the microwave, it does not effect conversion. Certainly flow through the MACOS reactor in the absence of microwave irradiation is indeed laminar, which we confirmed by using two dye solutions prepared with the same solvent. However, we strongly believe that there is no laminar flow while our reactions are being irradiated (see below).

An issue that has been frequently raised about microreactors is their capacity to prepare compounds on a larger scale, for example, beyond 1–20 mg of final product. To address this we performed the reactions shown in Table 1, entries 10 and 11. The substrates gave good conversion to **4e** when run for 40 min by using the standard conditions in Table 1, entry 10, which after purification yielded 213 mg of **4e**. To improve throughput, we doubled the concentration of the starting materials and also doubled the flow rate (Table 1, entry 11), which lowered conversion, but allowed for the collection of half a gram of product in just 40 min. Running the reaction for a longer period of time and/or through multiple capillaries in parallel (scaling out) will lead to the production of enough material to do most, if not all preclinical work if this was a drug candidate. The rest of the results in Table 1 illustrate that the process works well for a wide variety of chemical structures, both with the Cu or Ag films.

In past MACOS studies from our group, an important reaction parameter that could only be estimated is the temperature of the metal film, therefore, we have not had an accurate measure of the actual temperature at which the conversion is taking place.[6] The problem with the built-in IR sensor in the Biotage Initiator Synthesiser is that it was designed to read the temperature of the vials that were designed for the irradiation chamber. The sensor is comprised of a number of individual pixels and the temperature that is read is the average of all of the pixels. When a standard microwave vial is used, the temperature is very accurate because the sensor is small relative to the diameter of the tube. However, the capillaries only cover approximately 20% of the area of the sensor, which means that most of the pixels are targeting the air surrounding the tube.

To better assess the temperature, we machined a window into the end of the irradiation waveguide of the initiator (Figure 2, left) through which we focused a FLIR Systems Thermovision™ A320 high definition IR camera. The field of view measured by this camera can be focused down to the level of only a few pixels, which is far narrower than the diameter of the capillary, meaning that the temperature of isolated areas within the film can be accurately assessed. The temperature recorded by the built-in sensor for the reactions in Table 1 was 185 °C; the temperature recorded by

Table 1. A three-component MCR procedure for the preparation of propargyl amines by MACOS by using an Au- or Cu-coated capillary flow tube.



Entry (Product)	Aldehyde (**1**)	Amine (**2**)	Alkyne (**3**)	Cu film %conversion[a] (% yield)	Au film % conversion[a]
1 (**4a**)	**1a**	**2a**	**3a**	82 (76)	75
2 (**4a**)[b]	**1a**	**2a**	**3a**	– (0)	–
3 (**4a**)[c]	**1a**	**2a**	**3a**	– (0)	–
4 (**4a**)	**1a**	**2a**	**3a**	80[d]	–
5 (**4a**)[e]	**1a**	**2a**	**3a**	– (29)	8
6 (**4b**)	**1b**	**2a**	**3a**	84 (78)	78
7 (**4c**)	**1c**	**2a**	**3a**	90 (84)	70
8 (**4c**)[e]	**1c**	**2a**	**3a**	– (34)	11
9 (**4d**)	**1d**	**2a**	**3a**	85 (74)	68
10 (**4e**)	**1e**	**2a**	**3a**	82 (76)	90
11 (**4e**)	**1e**	**2a**	**3a**	60 (55)[f]	–
12 (**4f**)	**1f**	**2a**	**3a**	90 (82)	–
13 (**4g**)	**1f**	**2b**	**3a**	81 (75)	–
14 (**4h**)	**1f**	**2c**	**3a**	80 (75)	–
15 (**4i**)	**1b**	**2b**	**3a**	83 (74)	73
16 (**4j**)	**1a**	**2c**	**3a**	90 (82)	70
17 (**4k**)	**1b**	**2c**	**3a**	78 (70)	–
18 (**4l**)	**1a**	**2a**	**3b**	75 (67)	65
19 (**4m**)	**1e**	**2b**	**3b**	68 (60)	–
20 (**4n**)	**1b**	**2c**	**3b**	74 (68)	–
21 (**4o**)	**1a**	**2a**	**3c**	72 (65)	–
22 (**4p**)	**1b**	**2c**	**3c**	72 (67)	–

[a] Unless noted otherwise, all reaction mixtures were premixed, taken up into a single syringe and infused through the MACOS capillary reactor. [b] Performed with Pd-coated capillary. [c] Performed with Ag-coated capillary. [d] All three reaction components were dissolved separately, taken up into three separate syringes and infused into a MACOS reactor head equipped with three inlet ports. The streams mixed at the point of contact and then flowed down the attached capillary through the microwave chamber. The concentrations of the aldehyde, amine and alkyne were 3.0, 3.6 and 4.5 mmol mL^{-1}, respectively. The flow rate of each syringe was set at 7 μL min^{-1} and the transformation was run long enough to collect 800 μL of effluent. [e] Performed with oil bath at 185 °C. [f] A larger-scale run was performed by infusing the aldehyde (2.0 mmol mL^{-1}), amine (2.4 mmol mL^{-1}) and alkyne (3.0 mmol mL^{-1}) into the reactor at a rate of 40 μL min^{-1} for 40 min leading to the isolation of **4e** (495 mg).

the external IR camera was 950 °C! To assess whether this was a localised or bulk heating effect, the reactions in Table 1, entries 1 and 7 were repeated (Table 1, entries 5 and 8, respectively) by using an oil bath. Metal-film-coated capillaries were allowed to sit in an oil bath set to 185 °C for 20 min to come to temperature, after which time the reaction mixtures were flowed through them in the usual way and the product was collected. With both Au and Cu, dramatic reductions in conversion were observed, which supports the notion that the bulk of the film is well above the 185 °C recorded by the internal temperature sensor. Further, when the field of view of the external camera was widened (Figure 2, right), it became clear that the temperature in the middle of the capillary exceeds 900 °C, and although the temperature steadily decreases when moving away from the middle of the waveguide, it is never less than 700 °C.

We have speculated in the past that these reactions may be, at least in part, gas-phase reactions. With these new temperature findings in hand, it does seem unlikely that reaction streams are a continuous column of homogeneous liquid. There is visual evidence for this because the stream of liquid entering the mixing chamber contained newly created, small gas bubbles that were observed to move up and down slightly, despite the constant force of the syringe pumps pushing the material forward into the mixing chamber. Movement of the solvent, and perhaps some of the reagents, to the gas phase would create higher local pressure areas than that supplied by the pumps, which would account for why the gas bubbles would be moving upstream against the direction of flow. Indeed, the effluent exiting the microwave chamber is not a continuous liquid stream, but rather gives the appearance of liquid plugs in the tubing. So, what is happening at the molecular level? We speculate that the reactions are similar to flash vacuum thermolysis (FVT) in which reactants are brought into the gas phase under typically very high vacuum and flowed through super-heated (usually quartz) reaction tubes. Contact with the tube walls provides the energy necessary for reactions with high transition-state barriers such as retro Diels–Alder reactions. If this is true in the case of MACOS using metal films, several major advantages can be realised. The system that we have developed does not require high vacuum, in fact, no vacuum is required at all. The metal film can supply extremely high temperatures to address high-transition-state-barrier transformations; it can also provide a catalytically active metal surface to catalyse a vast array of transformations. In terms of sustainability, microwave reactors have been argued both positively and negatively in terms of how much energy they consume. What we can say in the MACOS set up is that the temperatures attained are reached with the lowest possible power setting currently available on the Biotage Initiator Synthesiser. In the batch reaction mode, it typically requires full power (300–400 Watts) to attain sustained temperatures of 200–250 °C in solvents such as DMF or DMSO; with the MACOS set up the average power setting is 30 Watts, which is still far too much power and this leads to capillary failure if reactions are not monitored. To address this we are designing and constructing our own microwave applicator to control power down to the level of one single Watt.

Conclusion

In summary, we have demonstrated for the fist time that temperatures can exceed 900 °C when a strongly microwave-

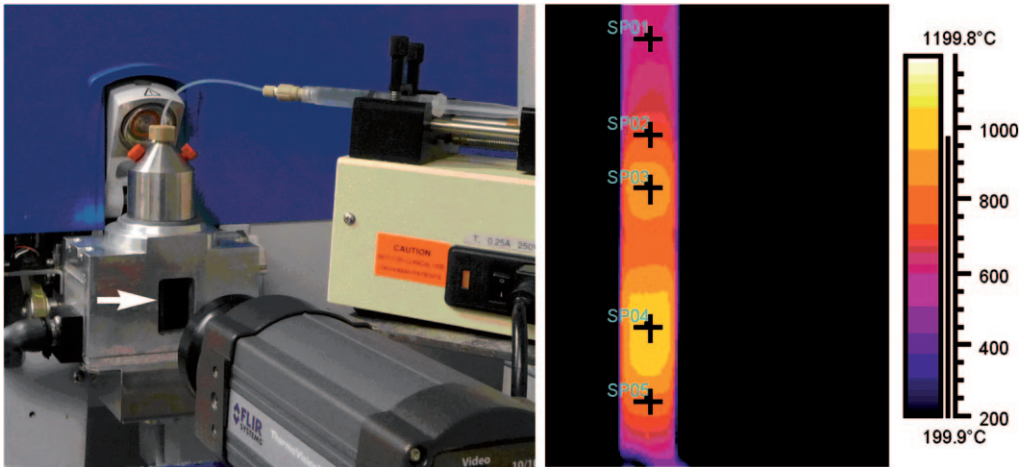


Figure 2. Thermal IR imaging of Cu-coated capillary while the flowed reaction is irradiated with microwaves. The left picture shows a small portal (white arrow) that has been machined into the end of the Biotage Initiator Synthesiser waveguide through which the FLIR Systems Thermovision™ A320 camera is focused on the metal-coated capillary can be seen. No microwave irradiation escapes the irradiation zone, which is constantly monitored with a microwave sensor. The right picture shows the thermal image of the Cu-coated capillary The central point of the capillary in the irradiation zone (SP04) shows a temperature of approximately 950 °C.

conducting thin-metal film is irradiated. Au and Cu films have been shown to be very proficient at catalysing the three-component coupling of terminal alkynes, amines and aldehydes to produce propargyl amines. The process can be conducted by using three separate streams of reactants, or by premixing the reaction components and infusing the reaction through one single syringe, and larger quantities of product can be attained readily by scaling out the process.

Experimental Section

Microwave irradiation experiments: All MACOS experiments were performed in borosilicate glass tubes (1700 μm internal diameter, ID), by using a single-mode Biotage Smith Creator Synthesiser, operating at a frequency of 2.45 GHz with irradiation power from 0 to 300 W. The glass reactor was fed reactants from Hamilton gastight syringes attached to a Harvard 22 syringe pump pre-set to the desired flow rate. The system was connected to a sealed collection vial, where a pressurised airline was attached to create backpressure (pressure inside the system reached 75 psi). The temperature read on the surface of the capillary by the built-in IR sensor of the microwave was used to control the operation of the magnetron. All reagents and solvents were purchased from commercial sources and were used without additional purification. Column chromatography purifications were carried out by using the flash techniques on silica gel 60 (200–400 mesh). NMR spectroscopy was run by using a Bruker Advance 400 MHz instrument. Proton NMR spectra were calibrated to 7.26 ppm for the signal from the residual proton of the deuterated chloroform solvent, whereas carbon NMR spectra were calibrated to 77.00 ppm for the signal from the central peak in the triplet for deuterated chloroform.

General procedure for creating the Pd and Ag film coating inside of the capillaries (1700 micron ID)

Pd film coating: The glass capillaries (1700 μm ID) were filled with a solution of palladium acetate in DMF (0.1 mmol mL^{-1}), capped at both ends with Teflon tape and placed inside a muffle furnace. The temperature was increased to 120 °C. After 10–30 min metallic Pd began to be released from the solution was and deposited on the inner side of the glass. The reactors were rinsed with acetone and then calcinated in the same furnace at 400 °C (3×1 min) before use in MACOS.

Ag film coating (the "silver mirror" layer): Tollens' reagent was prepared by adding NaOH solution (2.0 mL of 4 M) drop-wise into $AgNO_3$ solution (20 mL of a 3% solution), forming a grey precipitate that was titrated with a solution of NH_4OH (4 M) until the solution became clear. Tollens' reagent (0.5 mL) was added to a 2 mL vial containing D-glucose solution (0.5 mL of a 5% solution). The glass reactors (1700 μm ID) were filled with this mixture, capped at both ends with Teflon tape and left to develop at RT. After the Ag coating was fully developed (5–10 min), the capillaries were rinsed with acetone and placed inside a muffle furnace for calcination at 400 °C before use.

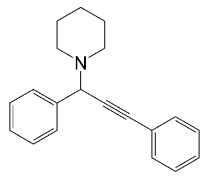
Ag film coating (the "colloidal silver" layer): The glass capillaries (1700 μm ID) were filled with a colloidal solution of silver oxide in ethylene glycol (0.5 mmol mL^{-1}) and then capped at both ends with Teflon tape. They were then placed inside a muffle furnace and the temperature was gradually increased to 140 °C. After the Ag coating was fully developed (30 min), the capillaries were rinsed with acetone and placed inside a muffle furnace for calcination at 400 °C before use.

General procedure for creating the Cu film coating inside of the glass capillaries (1700 micron ID): Borosilicate glass capillaries (1700 μm ID) were filled with a solution of $[Cu(OAc)_2]$ in hydrazine (0.5 mmol mL^{-1}), capped at both ends and placed inside a muffle furnace (120 °C). After 10 min, metallic Cu was gradually released from the solution and deposited on the inner side of capillary wall. After rinsing with acetone, the capillaries were placed inside a muffle furnace for calcination at 400 °C (3× 1 min) before use in MACOS.

General procedure for creating the gold-on-silver film coating inside of the glass capillaries (1700 micron ID): Tollens' reagent (0.5 mL) was added to a 2 mL vial containing D-glucose solution (0.5 mL of a 5% solution). The glass capillaries (1700 μm ID) were filled with this mixture, capped at both ends, and left to develop at RT. After the Ag coating was fully developed (15 min), the capillaries were rinsed with acetone and placed inside a muffle furnace for calcination at 500 °C (3×1 min). The gold coating solution was prepared by mixing an aqueous solution of $AuCl_3$ (0.5 mL, 0.4 mmol mL^{-1}) with aqueous $Na_3C_6H_5O_7{\cdot}2H_2O$ (0.5 mL of a 2% solution). The Ag-lined capillaries were filled with the mixture, capped at both ends, and left to develop at RT for 30 min. After emptying the reactors and rinsing them with acetone, they were calcinated at 500 °C (3×1 min) before use in MACOS.

General procedure for the synthesis of propargyl amines: A stock solution containing the substituted benzaldehyde **1** (1.0 mmol mL^{-1},

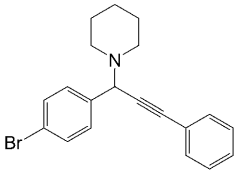
1.0 equiv), secondary amine **2** (1.2 mmol mL^{-1}, 1.2 equiv) and alkyne **3** (1.5 mmol mL^{-1}, 1.5 equiv) in toluene was prepared. The continuous-flow microwave system was primed with toluene and an aliquot from the homogenous stock solution (1–3 mL) was taken up in a Hamilton gastight syringe that was connected to the reactor system with the aid of Microtight™ fittings. The syringe was placed in a Harvard 22 syringe pump that was set to deliver 20 μL min^{-1} and the single-mode microwave was programmed so as to keep the temperature constant at a specified level. The output from the reactor was fed into a sealed vial under backpressure (75 psi). The percentage conversion was determined by ^{1}H NMR spectroscopy on an aliquot taken directly from this vial. Typically 0.8–0.9 mL of the crude reaction mixture was collected and the product was purified by silica gel column chromatography and the percent yield determined.



4a

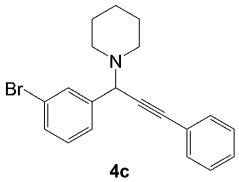
*(1,3-Diphenyl-2-propynyl)piperidine (**4a**)*: Following the general procedure, benzaldehyde, piperidine and phenylacetylene were reacted and 0.95 mL of the crude reaction mixture was collected. Purification by flash chromatography (14% ethyl acetate in hexane) afforded **4a** (201 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.68 (m, 2H), 7.59–7.54 (m, 2H), 7.48–7.31 (m, 6H), 4.86 (s, 1H), 2.65–2.58 (m, 4H), 1.69–1.61 (m, 4H), 1.52–1.44 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 132.1, 128.9, 128.6, 128.3 (two signals overlap), 127.8, 123.4, 87.9, 86.1, 62.4, 50.7, 26.2, 24.4 ppm (the spectra matched that found in the literature).[10b]

*(1-(4-Bromophenyl)-3-phenyl-2-propynyl)piperidine (**4b**)*: Following the general procedure, 4-bromobenzaldehyde, piperidine and phenylacetylene were reacted and 0.90 mL of the crude reaction mixture was collected. Purification by flash chromatography (18% ethyl acetate in hexane) afforded **4b** (247 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 4H), 7.54–7.50 (m, 2H), 7.41–7.34 (m, 3H), 4.78 (s, 1H), 2.62–2.54 (m, 4H), 1.66–1.58 (m, 4H), 1.53–1.47 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 131.8, 131.1, 130.2, 128.3, 128.1, 123.1, 121.4, 88.2, 85.3, 61.8, 50.7, 26.2, 24.4 ppm (the spectra matched that found in the literature).[10b]



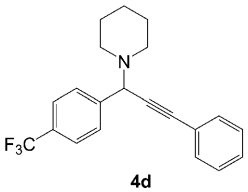
4b

*[1-(3-Bromophenyl)-3-phenyl-2-propynyl]piperidine (**4c**)*: Following the general procedure, 3-bromobenzaldehyde, piperidine and phenylacetylene were reacted and 0.79 mL of the crude reaction mixture was collected. Purification by flash chromatography (14% ethyl acetate in hexane) afforded **4c** (237 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.65–7.62 (m, 1H), 7.60–7.56 (m, 2H), 7.47–7.43 (m, 1H), 7.40–7.35 (m, 3H), 7.28–7.24 (m, 1H), 4.81 (s, 1H), 2.64–2.54 (m, 4H), 1.69–1.57 (m, 4H), 1.55–1.48 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 131.9, 131.4, 130.9, 129.9, 128.4, 128.2, 127.1, 123.1, 122.4, 88.4, 85.1, 61.9, 50.7, 26.2, 24.7 ppm (the spectra matched that found in the literature).[10b]



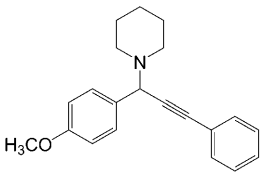
4c

*[1-(4-Trifluoromethylphenyl)-3-phenyl-2-propynyl]piperidine (**4d**)*: Following the general procedure, 4-(trifluoromethyl)benzaldehyde, piperidine and phenylacetylene were reacted and 0.80 mL of the crude reaction mixture was collected. Purification by flash chromatography (16% ethyl acetate in hexane) afforded **4d** (203 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1, 2H), 7.58–7.54 (m, 2H), 7.39–7.34 (m, 3H), 4.86 (s, 1H), 2.62–2.55 (m, 4H), 1.70–1.57 (m, 4H), 1.53–1.45 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 131.8, 129.7 (q, $^2J(^{13}C,^{19}F)$ = 32.2 Hz), 128.7, 128.4, 128.3, 125.1, 124.3 (q, $^1J(^{13}C,^{19}F)$ = 271.9 Hz), 123.0, 88.6, 84.9, 62.0, 50.8, 26.2, 24.4 ppm (the spectra matched that found in the literature).[10b]



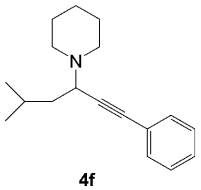
4d

*[1-(4-Methoxyphenyl)-3-phenyl-2-propynyl]piperidine (**4e**)*: Following the general procedure, 4-methoxybenzaldehyde, piperidine and phenylacetylene were reacted and 0.92 mL of the crude reaction mixture was collected. Purification by flash chromatography (20% ethyl acetate in hexane) afforded **4e** (213 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.54 (m, 4H), 7.38–7.33 (m, 3H), 6.96–6.91 (m, 2H), 4.78 (s, 1H), 3.85 (s, 3H), 2.63–2.53 (m, 4H), 1.69–1.55 (m, 4H), 1.54–1.46 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 131.8, 130.7, 129.6, 128.3, 128.0, 123.4, 113.4, 87.6, 86.5, 61.8, 55.3, 50.6, 26.2, 24.5 ppm (the spectra matched that found in the literature).[10b]



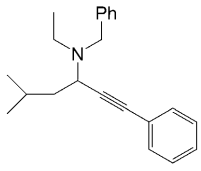
4e

*1-(1-Isobutyl-3-phenyl-prop-2-ynyl)piperidine (**4f**)*: Following the general procedure, isovaleraldehyde, piperidine and phenylacetylene were reacted and 0.72 mL of the crude reaction mixture was collected. Purification by flash chromatography (14% ethyl acetate in hexane) afforded **4f** (148 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.44 (m, 2H), 7.35–7.28 (m, 3H), 3.63–3.57 (m, 1H), 2.76–2.68 (m, 2H), 2.56–2.47 (m, 2H), 1.92 (septet, J = 7.1 Hz, 1H), 1.75–1.54 (m, 6H), 1.52–1.44 (m, 2H), 1.03–0.96 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 128.2, 127.7, 123.6, 88.1, 85.6, 56.7, 50.6, 42.3, 26.2, 25.4, 24.6, 23.2, 22.1 ppm (the spectra matched that found in the literature).[15]



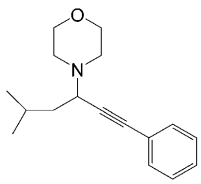
4f

*N-Benzyl-N-ethyl-5-methyl-1-phenylhex-1-yn-3-amine (**4g**)*: Following the general procedure, isovaleraldehyde, *N*-ethylbenzylamine and phenylacetylene were reacted and 0.75 mL of the crude reaction mixture was collected. Purification by flash chromatography (6% ethyl acetate in pentane) afforded **4g** as a colourless oil (172 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.50 (m, 2H), 7.48–7.44 (m, 2H), 7.42–7.34 (m, 5H), 7.32–7.28 (m, 1H), 3.97 (d, J = 14.2 Hz, 1H), 3.82 (t, J = 8.2 Hz, 1H), 3.53 (d, J = 14.2 Hz, 1H), 2.79–2.68 (m, 1H), 2.63–2.54 (m, 1H), 1.98 (septet, J = 7.1 Hz, 1H), 1.78–1.69 (m, 1H), 1.67–1.59 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 0.98–0.91 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5, 131.8, 128.8, 128.3, 128.1, 127.8, 126.7, 123.7, 88.9, 84.7, 55.1, 50.9, 45.0, 43.1, 24.8, 22.8, 22.3, 13.7 ppm; elemental analysis calcd for $C_{22}H_{27}N$: C 86.51, H 8.91, N 4.59; found: C 86.61, H 9.13, N 4.72.



4g

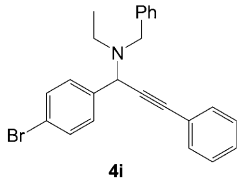
*4-(5-Methyl-1-phenylhex-1-yn-3-yl)morpholine (**4h**)*: Following the general procedure, isovaleraldehyde, morpholine and phenylacetylene were reacted and 0.75 mL of the crude reaction mixture was collected. Purification by flash chromatography (20% ethyl acetate in pentane) afforded **4h** as a pale-yellow oil (144 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.41 (m, 2H), 7.34–7.27 (m, 3H), 3.84–3.70 (m, 4H), 3.64–3.57 (m, 1H), 2.82–2.72 (m, 2H), 2.64–2.54 (m, 2H), 1.93 (septet, J = 6.8 Hz, 1H), 1.72–1.52 (m, 2H), 1.03–0.94 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 128.2, 127.9, 123.2, 87.1, 86.2, 67.2, 56.2, 49.7, 41.8, 25.2, 23.0,



4h

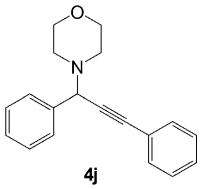
22.2 ppm; HRMS calcd for $C_{17}H_{23}NO$: 258.1858; found: 258.1851; elemental analysis calcd for $C_{17}H_{23}NO$: C 79.33, H 9.01, N 5.44; found: C 79.53, H 8.82, N 5.48.

N-Benzyl-1-(4-bromophenyl)-N-ethyl-3-phenylprop-2-yn-1-amine (***4i***): Following the general procedure, 4-bromoaldehyde, *N*-ethylbenzylamine and phenylacetylene were reacted and 0.70 mL of the crude reaction mixture was collected. Purification by flash chromatography (10% ethyl acetate in pentane) afforded **4i** as a pale-brown oil (199 mg, 74% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.70–7.60 (m, 4H), 7.58–7.52 (m, 2H), 7.49–7.41 (m, 5H), 7.40–7.34 (m, 2H), 7.32–7.27 (m, 1H), 4.99 (s, 1H), 3.88 (d, J = 14.2 Hz, 1H), 3.56 (d, J = 14.2 Hz, 1H), 2.68–2.57 (m, 2H), 1.16 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 139.9, 139.0, 131.8, 131.1, 130.1, 128.8, 128.4, 128.3, 128.2, 126.9, 123.0, 121.1, 88.3, 84.7, 56.1, 54.9, 44.5, 13.4 ppm; HRMS calcd for $C_{24}H_{22}BrN$: 403.0936; found: 403.0908.



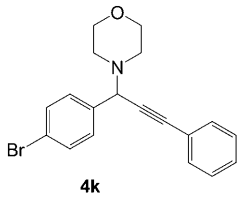
4i

4-(1,3-Diphenylprop-2-ynyl)morpholine (***4j***): Following the general procedure, benzaldehyde, morpholine and phenylacetylene were reacted and 0.75 mL of the crude reaction mixture was collected. Purification by flash chromatography (15% ethyl acetate in pentane) afforded **4j** (170 mg, 82% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.72–7.67 (m, 2H), 7.61–7.56 (m, 2H), 7.46–7.33 (m, 6H), 4.86 (s, 1H), 3.79–3.69 (m, 4H), 2.70–2.64 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 138.0, 131.7, 128.6, 128.4, 128.3, 128.2, 127.7, 123.0, 88.3, 85.2, 67.0, 61.9, 49.9 ppm (the spectra matched that found in the literature).[11c]



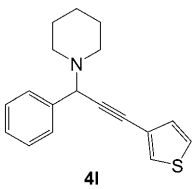
4j

4-[1-(4-Bromophenyl)-3-phenylprop-2-ynyl]morpholine (***4k***): Following the general procedure, 4-bromoaldehyde, morpholine and phenylacetylene were reacted and 0.82 mL of the crude reaction mixture was collected. Purification by flash chromatography (15% ethyl acetate in pentane) afforded **4k** (202 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ07.61–7.47 (m, 6H), 7.40–7.32 (m, 3H), 4.77 (s, 1H), 3.81–3.69 (m, 4H), 2.68–2.59 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 131.8, 131.3, 130.3, 128.5, 128.4, 122.7, 121.8, 88.9, 84.3, 67.1, 61.4, 49.8 ppm (the spectra matched that found in the literature).[11c]



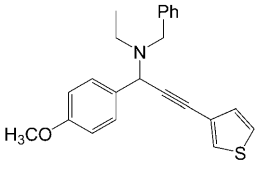
4k

1-(1-Phenyl-3-(thiophen-3-yl)prop-2-ynyl)piperidine (***4l***): Following the general procedure, benzaldehyde, piperidine and 3-ethynylthiophene were reacted and 0.82 mL of the crude reaction mixture was collected. Purification by flash chromatography (20% dichloromethane in pentane) afforded **4l** as a yellow oil (154 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 2H), 7.52 (d, J = 3.1 Hz, 1H), 7.43–7.36 (m, 2H), 7.35–7.29 (m, 2H), 7.23–7.20 (m, 1H), 4.81 (s, 1H), 2.64–2.52 (m, 4H), 1.69–1.56 (m, 4H), 1.53–1.44 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 130.2, 128.5, 128.4, 128.0, 127.4, 125.2, 122.3, 85.7, 82.7, 62.5, 50.7, 26.2, 24.4 ppm; HRMS calcd for $C_{18}H_{19}NS$: 281.1238; found: 281.1211; elemental analysis calad for $C_{18}H_{19}NS$: C 76.82, H 6.81, N 4.98; found: C 76.90, H 6.82, N 5.04.



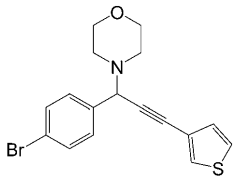
4l

N-Benzyl-N-ethyl-1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-amine (***4m***): Following the general procedure, 4-methoxybenzaldehyde, *N*-ethylbenzylamine and 3-ethynylthiophene were reacted and 0.62 mL of the crude reaction mixture was collected. Purification by flash chromatography (30% dichloromethane in pentane) afforded **4m** as a yellow oil (132 mg, 60% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.68–7.62 (m, 2H), 7.60 (d, J = 3.0 Hz, 1H), 7.47–7.41 (m, 2H), 7.40–7.33 (m, 3H), 7.30–7.26 (m, 2H), 6.97–6.91 (m, 2H), 4.98 (s, 1H), 3.87 (d, J = 14.1 Hz, 1H), 3.84 (s, 3H), 3.53 (d, J = 14.1 Hz, 1H), 2.61 (q, J = 7.1 Hz, 2H), 1.14 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.9, 140.3, 131.6, 130.1, 129.3, 128.7, 128.5, 128.1, 126.7, 125.4, 122.3, 113.3, 85.2, 82.6, 55.9, 55.2, 54.6, 44.3, 13.3 ppm. HRMS calcd for $C_{23}H_{23}NOS$: 361.1500; found: 361.1508; elemental analysis calcd for $C_{23}H_{23}NOS$: C 76.42, H 6.41, N 3.87; found: C 76.12, H 6.65, N 4.02.



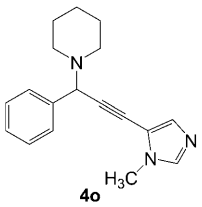
4m

4-[1-(4-Bromophenyl)-3-(thiophen-3-yl)prop-2-ynyl]morpholine (***4n***): Following the general procedure, 4-bromobenzaldehyde, morpholine and 3-ethynylthiophene were reacted and 0.86 mL of the crude reaction mixture was collected. Purification by flash chromatography (18% ethyl acetate in pentane) afforded **4n** as a yellow oil (212 mg, 68% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.60–7.52 (m, 5H), 7.39–7.35 (m, 1H), 7.24–7.21 (m, 1H), 4.78 (s, 1H), 3.76–3.66 (m, 4H), 2.64–2.56 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 137.3, 131.2, 130.3, 129.9, 128.9, 125.5, 121.7, 121.5, 84.0, 83.7, 67.0, 61.4, 49.8 ppm; HRMS calcd for $C_{17}H_{16}BrNOS$: 361.0136; found: 361.0131; elemental analysis calcd for $C_{17}H_{16}BrNOS$: C 56.36, H 4.45, N 3.87; found: C 56.22, H 4.46, N 3.66.



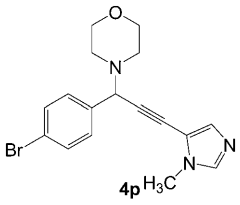
4n

1-[3-(1-Methyl-1 H-imidazol-5-yl)-1-phenylprop-2-ynyl]piperidine (***4o***): Following the general procedure, benzaldehyde, piperidine and 5-ethynyl-1-methyl-1 *H*-imidazole were reacted and 0.80 mL of the crude reaction mixture was collected. Purification by flash chromatography (10% methanol in acetonitrile) afforded **4o** as a colourless oil (145 mg, 65% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.67–7.62 (m, 2H), 7.47 (s, 1H), 7.44–7.38 (m, 2H), 7.36–7.31 (m, 1H), 7.28 (s, 1H), 4.91 (s, 1H), 3.74 (s, 3H), 2.60–2.54 (m, 4H), 1.69–1.55 (m, 4H), 1.52–1.46 ppm (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 138.4, 138.2, 133.8, 128.3, 128.1, 127.6, 116.2, 93.0, 75.9, 62.5, 50.7, 32.1, 26.2, 24.4 ppm; HRMS calcd for $C_{18}H_{21}N_3$: 279.1735; found: 279.1731; elemental analysis calcd for $C_{18}H_{21}N_3$: C 77.38, H 7.58, N 15.04; found: C 77.45, H 7.72, N 14.89.



4o

4-[1-(4-Bromophenyl)-3-(1-methyl-1 H-imidazol-5-yl)prop-2-ynyl]morpholine (***4p***): Following the general procedure, 4-bromobenzaldehyde, morpholine and 5-ethynyl-1-methyl-1 *H*-imidazole were reacted and 0.88 mL of the crude reaction mixture was collected. Purification by flash chromatography (10% methanol in dichloromethane) afforded **4p** as a colourless oil (213 mg, 67% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.58–7.51 (m, 4H), 7.48 (s, 1H), 7.30 (s, 1H), 4.86 (s, 1H), 3.76–3.66 (m, 7H), 2.64–2.55 ppm (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 138.4, 136.9, 134.3, 131.3, 130.2, 121.7, 115.6, 91.6, 76.8, 66.9, 61.5, 49.8, 32.2 ppm; HRMS calcd for $C_{17}H_{18}BrN_3O$: 359.0633; found: 359.0630; elemental analysis calcd for $C_{17}H_{18}BrN_3O$: C 56.68, H 5.04, N 11.66; found: C 56.50, H 5.05, N 11.22.



4p

[1] a) P. J. Tierney, P. Lidstrom, *Microwave Assisted Organic Synthesis* Blackwell Publishing, Oxford, **2005**; b) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

[2] For reviews on miniaturized flow reactors, see: a) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410; *Angew. Chem. Int. Ed.* **2004**, *43*, 406; b) H. Pennemann, P. Watts, S. J. Haswell, V. Hessel, H. Löwe, *Org. Process Res. Dev.* **2004**, *8*, 422.

[3] a) O. Benali, M. Deal, E. Farrant, D. Tapolczay, R. Wheeler, *Org. Process Res. Dev.* **2008**, *12*, 1007; b) J. Hernando, P. Leton, M. P. Matia, J. L. Novella, J. Alvarez-Builla, *Fuel* **2007**, *86*, 1641; c) R. M. Paulus, T. Erdmenger, C. R. Becer, R. Hoogenboom, U. S. Schubert, *Macromol. Rapid Commun.* **2007**, *28*, 484; d) T. N. Glasnov, C. O. Kappe, *Macromol. Rapid Commun.* **2007**, *28*, 395; e) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407; f) T. N. Glasnov, D. J. Vugts, M. M. Koningstein, B. Desai, W. M. F. Fabian, R. V. A. Orru, C. O. Kappe, *QSAR Comb. Sci.* **2006**, *25*, 509; g) R. J. J. Jachuck, D. K. Selvaraj, R. S. Varma, *Green Chem.* **2006**, *8*, 29; h) M. C. Bagley, R. L. Jenkins, M. C. Lubinu, C. Mason, R. J. Wood, *Org. Chem.* **2005**, *70*, 7003; i) S. Saaby, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 3365; j) P. He, S. J. Haswell, P. D. I. Fletcher, *Appl. Catal. A* **2004**, *274*, 111; k) N. S. Wilson, S. R. Sarko, G. Roth, *Org. Process Res. Dev.* **2004**, *8*, 535; l) K. A. Savin, M. Robertson, D. Gernert, S. Green, E. J. Hembre, J. Bishop, *Mol. Diversity* **2003**, *7*, 171; m) U. R. Pillai, E. Sahle-Demessie, R. S. Varma, *Green Chem.* **2004**, *6*, 295; n) T. Cablewski, A. F. Faux, C. R. Strauss, *J. Org. Chem.* **1994**, *59*, 3408.

[4] a) T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, *74*, 1321; b) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, *10*, 1655; c) R. V. Jones, C. Csajagi, Z. Szekelyhidi, I. Kovacs, B. Borcsek, L. Urge, F. Darvas, *Chim. Oggi* **2008**, *26*, 10; d) R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald, B. H. Warrington, *Org. Process Res. Dev.* **2007**, *11*, 704; e) I. R. Baxendale, J. J. Hayward, S. V. Ley, *Comb. Chem. High Throughput Screening* **2007**, *10*, 802; f) M. Brivio, W. Verboom, D. N. Reinhoudt, *Lab Chip* **2006**, *6*, 329; g) G. P. Wild, C. Wiles, P. Watts, *Lett. Org. Chem.* **2006**, *3*, 419; h) Y. Kikutani, T. Kitamori, *Macromol. Rapid Commun.* **2004**, *25*, 158; i) P. Watts, S. J. Haswell, *Drug Discovery Today* **2003**, *8*, 586; j) P. Stonestreet, A. P. Harvey, *Chem. Eng. News* **2002**, *80*, 31; k) D. Vasudevan, C. A. Basha, *Bulletin of Electrochemistry* **2000**, *16*, 341.

[5] a) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8160; b) M. G. Organ, E. Comer, *Chem. Eur. J.* **2005**, *11*, 7223.

[6] a) G. Shore, S. Morin, M. G. Organ, *Angew. Chem.* **2006**, *118*, 2827; *Angew. Chem. Int. Ed.* **2006**, *45*, 2761; b) G. Shore, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 9641; c) G. Shore, M. Tsimmerman, M. G. Organ, *Beilstein J. Org. Chem.* **2009**, *5*, 35; d) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351–1356.

[7] a) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472; b) G. Gao, F. Sanda, T. Masuda, *Macromolecules* **2003**, *36*, 3932; c) K. Hattori, M. Miyata, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 1151; d) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638.

[8] a) L. W. Bieber, M. F. da Silva, *Tetrahedron Lett.* **2004**, *45*, 8281; b) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808; c) I. Naota, H. Takaya, S. I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599.

[9] a) T. Murai, Y. Mutoh, Y. Ohta, M. Murakami, *J. Am. Chem. Soc.* **2004**, *126*, 5968; b) M. E. Jung, A. Huang, *Org. Lett.* **2000**, *2*, 2659.

[10] a) L. Zhang, C. Wei, R. S. Varma, C.-J. Li, *Tetrahedron Lett.* **2004**, *45*, 2443; b) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584; c) C. M. Wei, Z. G. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473; d) C.-J. Li, C. M. Wei, *Chem. Commun.* **2002**, 268; e) C. M. Wei, C.-J. Li, *Green Chem.* **2002**, *4*, 39; f) W-W. Chen, R. V. Nguyen, C.-J. Li, *Tetrahedron Lett.* **2009**, *50*, 2895; g) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; h) N. Gommermann, P. Knochel, *Chem. Commun.* **2003**, 2324; i) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797; j) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; k) P. H. Li, Y. C. Zhang, L. Wang, *Chem. Eur. J.* **2009**, *15*, 2045.

[11] a) V. K. Y. Lo, Y. Liu, M. K. Wong, C. M. Che, *Org. Lett.* **2006**, *8*, 1529; b) S. B. Park, H. Alper, *Chem. Commun.* **2005**, 1315; c) L. Shi, Y. Q. Tu, M. Wang, F. M. Zhang, C. A. Fan, *Org. Lett.* **2004**, *6*, 1001; d) For an approach by using batch microwave radiation, see: N. E. Leadbeater, H. M. Torenius, H. Tye, *Mol. Diversity* **2003**, *7*, 135.

[12] a) S. Wang, L. Song, X. He, Z. Wang, *Synlett* **2009**, *12*, 447; b) X. Zhang, A. Corma, *Angew. Chem.* **2008**, *120*, 4430; *Angew. Chem. Int. Ed.* **2008**, *47*, 4358; c) M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.* **2007**, *9*, 742; d) V. Bansal, N. K. Mishra, A. Kumar, S. Mozumdar, *Synlett* **2007**, *10*, 1581; e) M. L. Kantam, S. Laha, J. Yadav, S. Bhargava, *Tetrahedron Lett.* **2008**, *49*, 3083; f) P. Li, L. Wang, *Tetrahedron* **2007**, *63*, 5455; g) Y. Zhou, T. He, Z. Wang, *Arkivoc* **2008**, 80.

[13] S. Bremner, M. G. Organ, *J. Comb. Chem.* **2007**, *9*, 14.

[14] a) A. Corma, A. Abad, H. Garcia, *Top. Catal.* **2007**, *44*, 237; b) T. Ishida, M. Haruta, *Angew. Chem.* **2007**, *119*, 7288; *Angew. Chem. Int. Ed.* **2007**, *46*, 7154.

[15] B. Sreedhar, P. Surendra Reddy, C. S. Vamsi Krishna, P. Vijaya Babu, *Tetrahedron Lett.* **2007**, *48*, 7882.

Received: August 31, 2009
Published online: November 30, 2009

