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Tetrahedron 61 (2005) 9349–9355
Tetrahedron

Automated batch scale-up of microwave-promoted Suzuki and Heck coupling reactions in water using ultra-low metal catalyst concentrations

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Received 3 June 2005; revised 13 July 2005; accepted 15 July 2005

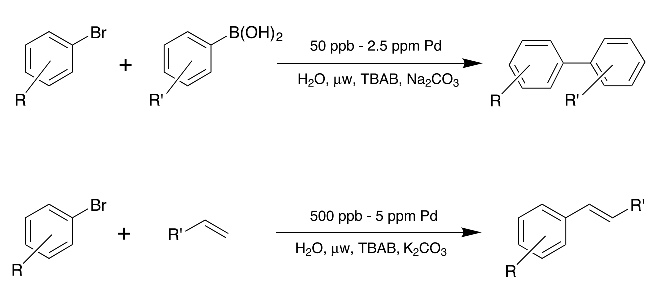
Available online 3 August 2005

Abstract—Representative Suzuki and Heck couplings in water using ultra-low catalyst concentrations have been scaled-up using an automated batch stop-flow microwave apparatus. Our scale-up methodology shows proof of concept and is easy, fast and cheap to run.

1. Introduction

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories. It was not until 1986 that the first reports of microwave-heating in organic synthesis appeared in the literature.[1,2] The work was performed using a domestic microwave. Since these publications, much has changed in terms of the apparatus available for microwave-promoted synthesis and the technique has found a valuable place in the synthetic chemist's toolbox. This is evidenced by the large number of papers and reviews currently appearing in the literature.[3–5] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Also, as the field matures, people are finding that they can perform chemistry using microwave heating that can not be achieved using 'conventional' heating methods, this opening up new avenues for synthesis.

Our research in the area of microwave-promoted chemistry recently led to the discovery that it is possible to perform Suzuki[6] and Heck[7] couplings in water using ultra-low quantities of palladium catalyst (Scheme 1). Water is an excellent solvent for microwave-promoted synthesis. Although it has a dielectric loss factor which puts it into the category of only a medium absorber, even in the absence of any additives it heats up rapidly upon microwave irradiation. Using a sealed vessel it is possible to heat water to well above its boiling point. Water also offers practical advantages over organic solvents.[8] Our reactions were performed using a scientific microwave apparatus, working on a 1 mmol scale in a 10 mL sealed glass vessel. The reactions are run using between 50 ppb and 5 ppm palladium, and are complete in between 5 and 20 min depending on the coupling and the substrate used. This therefore offers an easy, fast and efficient route to biaryl- and alkene-functionalised products. Lengthy metal extraction steps for product purification are not required because such small quantities of metal catalyst are used.[9] Indeed, in many cases the metal could be left in the product. Since both the Suzuki[10] and Heck[11] couplings are used on a regular basis in the chemical industry for the preparation of, for example, pharmaceuticals, natural products and advanced materials, we were keen to address issues of scale-up to prepare gram instead of milligram of product. The results from our laboratory are presented here.



Scheme 1. Suzuki and Heck couplings in water.

Keywords: Microwave; Water; Suzuki.
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doi:10.1016/j.tet.2005.07.063

2. Results and discussion

Scale-up of microwave-promoted reactions has been an issue of considerable interest over the last few years. Although chemists are discovering that microwave chemistry has the advantage of greatly reducing reaction times and improving product yields when run on small scales, translation of methodologies to larger scale apparatus can be problematic. There are two possible scale-up options. The first is to use a continuous flow microwave cell,[12] this technology being used successfully for a number of different reactions.[13–15] Included in this list is a Suzuki coupling.[16] The authors use 20 mol% $PdCl_2(PPh_3)_2$ as the catalyst, ethanol as the solvent and triethylamine as a base. The Suzuki reaction has also been used to demonstrate the applicability of a micro-reactor and a flow-capillary reactor, both developed for use in conjunction with microwave heating.[17,18,19] A circulating fluidized-bed reactor has also been developed for microwave-promoted catalysis and used for the decomposition of trichloroethylene but not for fine-chemicals synthesis.[20] The drawbacks of a continuous flow microwave apparatus are that it can be difficult to process solids, highly viscous liquids or heterogeneous reaction mixtures. Also, adaptation of conditions from simple small scale reactions to the continuous flow cell could end up being time consuming.

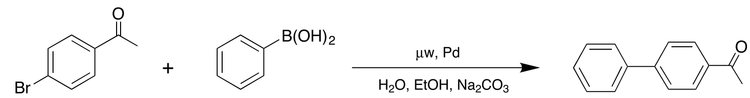
The other option is to use a batch-type process. This could either involve using one large vessel or parallel batch reactors. For a microwave operating at the typical frequency of 2.45 GHz, microwave penetration is generally in the order of cm, depending on the dielectric properties of the reaction medium. This therefore limits the size of a large batch reactor. Success has been found using one large batch reactor,[21–23] and also using the parallel approach. The latter has recently been applied successfully by Kappe and co-workers to the scale-up of reactions such as the Biginelli dihydropyrimidine synthesis, the Diels–Alder cycloaddition as well as a Heck coupling.[24] and by Alcázar and co-workers to alkylation reactions.[25] In both reports, translation of reaction conditions developed on commercially available single-mode to a multimode reactor for the scale-up proved not to be a problem. The disadvantage, however, of these batch reactors are that the individual reaction vessels need to be filled with reagents and loaded into the microwave cavity manually.

We decided to focus our attention on the CEM Voyager microwave system. This combines the advantages of a batch reactor with those of a continuous flow reactor. It is a single-mode apparatus with one, 80 mL vessel in the microwave cavity. The reaction mixture is pumped into and out of the vessel by a peristaltic pump, these functions, as well as running the reaction, being controlled using a computer. This gives a high degree of automation to the process. The reaction mixture can be introduced into the microwave vessel from two separate feed lines. After the reaction is complete, the reaction vessel can be vented to remove an overpressure and then the contents of the reactor pumped into a collection vessel. Since only one reaction vessel is used, the time taken to cool the reaction mixture down to room temperature at the end of the run are significantly shorter than those reported for the parallel batch reactors using multimode apparatus (20–30 min). If necessary, the reactor can then be cleaned with solvent before the next run.

Our first objective was to test the scalability of our coupling protocols in moving to the larger 80 mL reaction vessel from the smaller 10 mL reaction vessels in which we had performed all our original work. This work was performed with the same microwave apparatus as that used for the smaller scale experiments, the only difference being the size of vessel used and the temperature measurement device (fiber-optic probe directly placed into the reaction mixture by way of an immersion well as opposed to an external IR sensor located outside the reaction vessel). Starting with the Suzuki reaction we focused on the coupling of 4-bromoacetophenone with phenylboronic acid. Optimisation data are shown in Table 1. Our coupling protocols developed earlier involved either the use of tetrabutylammonium bromide (TBAB) as a phase-transfer agent in conjunction with water as the only solvent or else a 1:1 water/ethanol mixture as the reaction medium (no TBAB). The mixture is stirred throughout the reaction. For scale-up purposes we felt that the water/ethanol solvent system would be more useful so we focused on this. On the 1 mmol scale in the 10 mL reaction vessels, our optimum reaction conditions were 1.3 equiv boronic acid, 1 equiv aryl halide, 3.7 equiv Na_2CO_3, 250 ppb palladium[†] and 1 mL each of water and ethanol. The reaction mixture was heated to 150 °C and held at this temperature for 5 min before cooling back to room temperature. With 4-bromoacetophenone we obtained a 99% product yield (Table 1, entry 1). Repeating this reaction on a 10 mmol scale keeping the ratios of reagents and reaction conditions the same, but using 10 mL each of water and ethanol gave a 96% yield of the desired product (Table 1, entry 2). This shows the direct scalability of the chemistry from the small to the large reaction vessels. Our attention turned to how we would be able to pump the reaction mixture into the vessel in the stop-flow apparatus. The best method was to introduce the aryl halide, boronic acid and palladium dissolved in ethanol and the base dissolved in water. Both of these mixtures were homogeneous and we envisioned could easily be pumped. We could have moved directly to the Voyager stop-flow apparatus with these conditions. However, we decided to study the effects on product yield of reducing the palladium concentration, the quantity of base in the reaction and the stoichiometric ratio of the boronic acid and aryl halide to 1:1. Reducing the quantity of base used from 3.7 to 1 equiv has little effect on product yield (Table 1, entries 3 and 4). Reduction of the palladium concentration from 250 to 50 ppb also has negligible effect on the product yield (Table 1, entries 5 and 6). A stoichiometric ratio of boronic acid and aryl halide of 1:1 gives a comparable yield to the original ratio of 1.3:1 (Table 1, entry 7). We also investigated the effects of adding a small volume of organic solvent to the reaction mixture, this being necessary when using the Voyager in order to clean the lines between the peristaltic pump and the reaction vessel thus avoiding contamination. Addition of 4 mL ethyl acetate to the reaction mixture has little effect on product yield (Table 1,

[†] When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is however, avoided by using an acid stabilized stock solution. We therefore used a commercially available 1000 ppm palladium solution stabilized with 20% HCl as our catalyst source. This was diluted accordingly to give solutions of the desired concentrations. For low concentrations, a couple of drops of HCl were added to avoid precipitation of the palladium from solution. In addition, the solutions were prepared freshly each day from the 1000 ppm stock.

Table 1. Optimisation of conditions for the scale-up of microwave-promoted Suzuki coupling reactions in water[a]

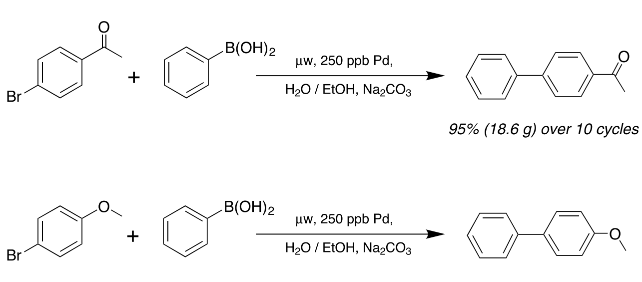


Entry	Aryl halide/mmol	Boronic acid/mmol	Na_2CO_3/mmol	H_2O/mL	EtOH/mL	Pd/ppb	Biaryl yield/%
1	1	1.3	3.7	1	1	250	99
2	10	13	37	10	10	250	96
3	10	13	20	10	10	250	98
4	10	13	10	10	10	250	99
5	10	13	10	10	10	100	99
6	10	13	10	10	10	50	99
7	10	10	10	10	10	50	96
8[b]	10	10	10	10	10	250	91
9[c]	10	10	10	10	10	50	75
10[c]	10	10	10	10	10	250	99
11[d]	10	10	10	10	10	50	45
12[d]	10	10	10	10	10	250	91

[a] Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 150 °C where it was then held for 5 min.
[b] Run using an additional 4 mL ethyl acetate as solvent.
[c] Using 4-bromotoluene as the aryl halide substrate.
[d] Using 4-bromoanisole as the aryl halide substrate.

entry 8). We next screened 4-bromotoluene (Table 1, entries 9 and 10) and 4-bromoanisole (Table 1, entries 11 and 12) as substrates in the reaction using the 80 mL reaction vessel. We found that the optimum catalyst concentration was 250 ppb, this reflecting our previously published observations using the 10 mL vessel.

In moving to the Voyager, we set the apparatus firstly to run one cycle of a 10 mmol reaction using 1 equiv aryl halide, 1 equiv boronic acid, 1 equiv Na_2CO_3 and a 250 ppb palladium concentration. Using 4-bromoacetophenone and phenylboronic acid as test substrates, we found that the pumping of the reagents into the reaction vessel was easy, the reaction was run and was successful but pumping the product out of the vessel at the end was initially problematic. This was because the biaryl product solidifies below 90 °C and blocks the exit tube. This problem was easily overcome by programming an additional step into the protocol. After the reaction mixture has cooled to 110 °C, the excess pressure in the reaction vessel is vented and 15 mL ethyl acetate added to dissolve the biaryl product. The entire mixture is then pumped into the collection vessel. This makes for easy removal of the product and also removes the need for an additional cleaning step at the end of the protocol. We then ran 10 cycles of a 10 mmol reaction using 4-bromoacetophenone and 4-bromoanisole as aryl halide substrates (Scheme 2). Monitoring the product yield of the first four reaction mixtures showed that batch-to-batch consistency was excellent, variations of 2% being observed. The overall reaction yield from the combination of all ten product mixtures was 95% (18.6 g) with 4-bromoacetophenone and 93% (17.1 g) with 4-bromoanisole. Each cycle took approximately 15 min; 2 min to load the reaction vessel, 11 min for the reaction (3 min to reach temperature, 5 min to run reaction at 150 °C, 3 min for cool-down to 110 °C) and 2 min to pump the product out. Since the reaction is run in aqueous medium and only 250 ppb palladium is used, product isolation is easy and there is no need for a dedicated palladium removal step.

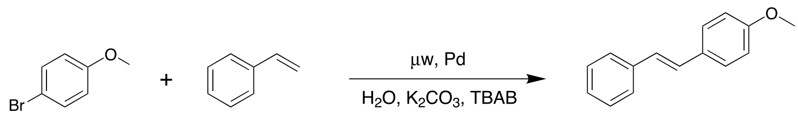


Scheme 2.

We next, turned our attention to the Heck reaction. For optimisation of reaction conditions, we focused on the coupling of 4-bromoanisole with styrene. Optimisation data are shown in Table 2. On the 1 mmol scale in the 10 mL reaction vessels, our optimum reaction conditions were 1 equiv aryl halide, 2 equiv styrene, 3.7 equiv K_2CO_3, 1 equiv TBAB, 1–5 ppm palladium and 2 mL water. The reaction mixture was heated to 170 °C and held at this temperature for 10 min before cooling back to room temperature. We found that increasing the quantity of palladium added does not improve product yields significantly once above a level of 2 ppm (Table 2, entries 1–3). Important to note is that the reaction mixture is NOT stirred since this gives higher product yields.[‡] Repeating this reaction on a 10 mmol scale keeping the ratios of reagents and reaction conditions the same, but using 5 ppm Pd and 20 mL water gave a 76% yield of the desired product (Table 2, entry 4). This is only slightly lower

[‡] As discussed in our initial report, we attribute the effects of stirring to problems associated with competitive decomposition of the starting aryl halide and styrene during the course of the reaction. In the absence of stirring, the reaction mixture forms two distinct phases; a lower aqueous layer containing the base and an upper organic layer containing the organic substrates. We believe that one of the key roles of the water is simply to dissolve the base and that the coupling reaction takes place either at the aqueous/organic interface or else the palladium migrates to the organic phase where it could feasibly be stabilized as a cluster or lower order species by the TBAB. When the reaction mixture is stirred the aryl halide is more exposed to the basic aqueous medium and this could accelerate the competitive decomposition process.

Table 2. Optimisation of conditions for the scale-up of microwave-promoted Heck coupling reaction in water[a]



Entry	Aryl halide/mmol	Styrene/mmol	K_2CO_3/mmol	TBAB/mmol	H_2O/mL	Co-solvent	Pd/ppm	Stilbene yield/%
1	1	2	3.7	1	2	None	10	90
2	1	2	3.7	1	2	None	2.5	83
3	1	2	3.7	1	2	None	1	59
4	10	20	37	10	20	None	5	76
5	10	20	37	2.5	20	None	5	32
6	10	12	37	10	20	None	5	64
7	10	20	20	10	20	None	5	53
8	10	20	37	10	17.5	Ethanol, 2.5 mL	5	65
9	10	20	37	10	17.5	nmp, 2.5 mL	5	27
10	10	20	37	10	17.5	dmf, 2.5 mL	5	66
11[b]	10	20	37	10	17.5	dmf, 2.5 mL	5	91
12[b]	10	20	37	10	15	dmf, 5 mL	5	80
13[b]	10	20	37	10	17.5	dmf, 3.5 mL	5	74
14[b,c]	10	20	37	10	17.5	dmf, 2.5 mL	5	74
15[c,d]	10	20	37	10	17.5	dmf, 2.5 mL	5	67
16[b,e]	10	20	37	10	17.5	dmf, 2.5 mL	5	79
17[d,e]	10	20	37	10	17.5	dmf, 2.5 mL	5	92

[a] Initial microwave irradiation of 120 W was used, the temperature being ramped from rt to 170 °C where it was then held for 10 min.
[b] Ramped from rt to 170 °C where it was then held for 20 min.
[c] Using 4-bromotoluene as the aryl halide substrate.
[d] Ramped from rt to 170 °C where it was then held for 15 min.
[e] Using 4-bromoacetophenone as the aryl halide substrate.

than in the case of the 1 mmol reaction but, rather than increase the palladium concentration, we decided to stay at this level.

Again we could have moved directly to the Voyager stop-flow apparatus with these conditions without further optimisation but we wanted to investigate the effects of reducing the quantity of TBAB, styrene or base used in the reaction. We found that product yields dropped as a result in all cases (Table 2, entries 5–7). We also needed to develop a methodology that would allow us to pump the reaction mixture into the vessel in the stop-flow apparatus. We wanted to dissolve the organic substrates into a suitable solvent for pumping and screened ethanol, nmp and dmf as possible candidates for this role. We prepared different stock solutions and, pouring these into the 80 mL vessel, ran the reaction (Table 2, entries 8–10). The use of any of the three solvents resulted in lower product yields than using neat water but dmf was the least deleterious. Building in this, we found that simply extending the reaction time to 20 min using water/dmf as the reaction mixture led to a 91% product yield (Table 2, entry 11). The relative ratio of water to dmf was found to be important (Table 2, entry 12). The optimum ratio was found to be 7:1 water to dmf. We also ran the reaction using an additional 1 mL of dmf, this being necessary when using the Voyager for purposes of flushing the lines (Table 2, entry 13). This has a slightly deleterious effect on the product yield.[§] Whilst it is clear that using less dmf overall would be ideal, we found that the solubility of solid substrates in smaller volumes than 4 mmol/mL begins to cause a problem when pumping reagents into the stop-flow vessel thus we decided to take forward our conditions of 2.5 mL dmf for introduction of the reagents followed by 1 mL dmf for cleaning. We screened 4-bromotoluene (Table 2, entries 14 and 15) and 4-bromoacetophenone (Table 1, entries 16 and 17) as substrates in the reaction using the 80 mL reaction vessel. We found that shorter reaction times can be employed when using these substrates. Indeed, with 4-bromoacetophenone, a reaction time of 20 min gives a lower yield than a reaction time of 10 min. We attribute this to competitive decomposition of the stilbene product in the hot basic aqueous medium.

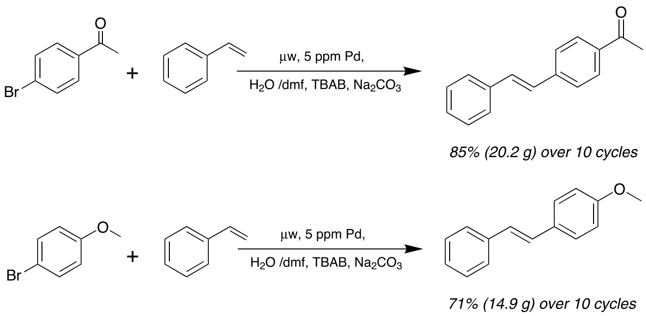
Moving to the Voyager, again we set the apparatus firstly to run one cycle of a 10 mmol reaction using 4-bromoanisole and styrene as test substrates. Pumping of the reagents into the reaction vessel was easy, the reaction was run and, after the reaction mixture had cooled to 110 °C, the excess pressure in the reaction vessel was vented and 15 mL dmf added to dissolve the product. The entire mixture was then pumped into the collection vessel and the product isolated. An 73% yield was obtained. We then ran ten cycles of a 10 mmol reaction. The overall reaction yield from the combination of all ten product mixtures was 71% (14.9 g). Each cycle took approximately 26 min (3 min to reach temperature, 20 min to run reaction at 150 °C, 3 min for cool-down to 110 °C). We then repeated the procedure using 4-bromoacetophenone. Since our previous optimisation experiments with this substrate showed that a reaction time of only 15 min rather than 20 min was needed so this was applied when using the Voyager. From the ten cycles of 10 mmol, we obtained a 85% (20.2 g) yield.

3. Conclusion

We have shown that Suzuki and Heck couplings in water

[§] Using ethyl acetate in the wash step as in the Suzuki reaction was not possible in the case of the Heck couplings because, if this is added, very high pressures are developed during the course of the reaction. Thus, for safety, dmf was used and the resultant drop in product yield accepted.

using ultra-low catalyst loadings and microwave heating can be easily scaled up from the 1 to 10 mmol scale and adapted to the automated stop-flow Voyager apparatus. It would be possible to take conditions directly from small scale experiments and transfer them to the Voyager with few, if any, modifications, particularly in the case of the Suzuki coupling. Since microwave reactions can be performed so rapidly, we decided to take some time to re-optimise the reaction conditions so as to minimise the quantities of additives, reduce the stoichiometric excesses of reagents where possible and also improve product yields. The additional optimisation experiments for both couplings took us very little time to complete. Our results from the Voyager compare favourably with Suzuki[26] and Heck[27] coupling protocols that have been scaled up using conventional heating and reported in the literature. Although not at this stage at a kg level, our methodology shows proof of concept and is easy, fast and cheap to run. The capital cost of one or more Voyager systems is less than that of a large batch reactor and the associated reagent/product transport and heating apparatus for use with conventional heating. Also, and very importantly, due to the relatively small volumes of each reaction cycle and the protection measures built in to the microwave apparatus, the reaction is very safe to run. Work is currently underway to increase the scale of the reaction as well as investigate the scope for scale-up of other microwave-promoted methodologies developed in our laboratory (Scheme 3).



Scheme 3.

4. Experimental

4.1. General methods

All materials were obtained from commercial suppliers and used without further purification. The palladium stock solution used was elemental Pd in 20% HCl. Concentration 1000 mg/mL. Baker cat. no. 5772-04. Ultra-pure water, purified to a specific resistance of >16 mΩ cm was used for the optimisation experiments. Standard distilled water was used for the automated stop-flow batch reactions. All reactions were carried out in air. ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a 300 MHz spectrometer.

4.2. Description of the microwave apparatus

Microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Optimisation reactions were performed in a thick-walled glass vessel (capacity 80 mL, maximum working volume 50 mL) sealed with a septum with ports for pressure and temperature measurement devices. The pressure is controlled by a load cell connected directly to the vessel. The pressure limit was set to 300 psi for all reactions, beyond, which the apparatus shuts down. This upper limit was never reached in any of the runs but is set as a safety measure. The temperature of the contents of the vessel was monitored using a calibrated fiber-optic probe inserted into the reaction vessel by means of a sapphire immersion well. The contents of the vessel are stirred, when required, by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were monitored using commercially available software provided by the microwave manufacturer. For the automated stop-flow batch reactions, the CEM Voyager apparatus was used. The basic running of the microwave steps remains the same as with the Discover; the reactions being performed in the same thick-walled glass vessel, the pressure being controlled by a load cell connected directly to the vessel and the temperature monitored using a fiber-optic probe. Two additional ports allow for introduction of the reagents into the reaction vessel via a PFA tube of 1.6 mm ID and venting of the vessel at the end of the reaction via another PFA tube. At the end of the reaction, the product is pumped out using the same PFA tube as that used for introduction of the reagents. Movement of material in and out of the vessel is by way of a peristaltic pump and an automated valve mechanism.

4.3. Representative example of a Suzuki coupling using the 80 mL vessel for optimisation: reaction between 4-bromoacetophenone and phenylboronic acid

In an 80 mL glass vessel was placed 4-bromoacetophenone (1.99 g, 10.0 mmol), phenylboronic acid (1.22 g, 10.0 mmol), Na_2CO_3 (1.06 g, 10 mmol), palladium stock solution and ethanol (10 mL). Water was added to give a total solvent volume of 20 mL. The vessel was sealed and placed into the microwave cavity. Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to the desired temperature of 150 °C. Once this was reached, taking around 3 min, the reaction mixture was held at this temperature for a further 5 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (100 mL) and ethyl acetate (100 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuuo leaving the crude product, which was characterised by comparison of NMR data with that in the literature.

4.4. Representative example of a Heck coupling using the 80 mL vessel for optimisation: reaction between 4-bromoanisole and styrene

In an 80 mL glass vessel was placed 4-bromoanisole (1.87 g, 1.25 mL, 10.0 mmol), styrene (2.08 g, 2.30 mL, 20.0 mmol), K_2CO_3 (5.11 g, 37 mmol), tetrabutylammonium bromide

(3.22 g, 10.0 mmol), palladium stock solution and organic solvent (if used). Water was added to give a total solvent volume of 20 mL. The vessel was sealed and placed into the microwave cavity. Initial microwave irradiation of 120 W was used, the temperature being ramped from rt to the desired temperature of 170 °C. Once this was reached, taking around 5 min, the reaction mixture was held at this temperature for 20 min. After allowing the mixture to cool to room temperature, the product was isolated and purified using the same procedure as in the Suzuki reaction and was characterised by comparison of NMR data with that in the literature.

4.5. Representative example of a Suzuki coupling using the automated stop-flow apparatus: reaction between 4-bromoacetophenone and phenylboronic acid

Two stock solutions were prepared, one containing sodium carbonate (10.6 g, 100 mmol) in 100 mL water, the other containing 4-bromoacetophenone (19.9 g, 100 mmol), phenylboronic acid (12.2 g, 100 mmol) and palladium stock solution in ethanol (total volume 100 mL). The apparatus was programmed to run a series of operations sequentially. Firstly, 10 mL of each of the stock solutions was introduced into the reaction vessel, washing the transfer tubes with 2 mL ethyl acetate between addition of the first and second solutions and again after introduction of the second. Next in a heating step, an initial microwave irradiation of 300 W was used, the temperature being ramped from rt to the desired temperature of 150 °C. Once this was reached (around 3 min), the reaction mixture was held at this temperature for 5 min. Thirdly, in a cooling step, the reaction mixture was cooled to 110 °C using forced air passing around the glass reaction vessel and then any remaining overpressure vented. Next, 30 mL ethyl acetate was added via the reagent inlet tube and then the whole contents of the vessel pumped out into a collection container. A further 10 mL ethyl acetate was pumped into the vessel to dissolve any remaining organic material and then this pumped into the collection container. This was the end of the procedure. The whole add, heat, remove process was then repeated a further nine times to give a total of 10 cycles of 10 mmol reactions. Each product mixture could be collected individually and the product conversion monitored or all pooled into one collection container. The product was isolated and purified using the same procedure as in case of the 10 mmol optimisation reactions.

4.6. Representative example of a Heck coupling using the automated stop-flow apparatus: reaction between 4-bromoanisole and styrene

Two stock solutions were prepared, one containing sodium carbonate (51.1 g, 370 mmol) and tetrabutylammonium bromide (32.2 g, 100 mmol) in 175 mL water, the other containing 4-bromoanisole (18.7 g, 12.5 mL, 100 mmol), styrene (20.8 g, 23.0 mL, 200 mmol) and palladium stock solution in dmf (total volume 25 mL). The apparatus was again programmed to run a series of operations sequentially. Aliquots of the stock solutions were added; 17.5 mL of the water stock solution and 2.5 mL of the dmf stock solution with washing of the transfer tubes with 0.5 mL dmf between addition of the first and second solutions and again after introduction of the second. The addition steps were performed with the stir module turned on. Next in a heating step in which the stirring was turned OFF, an initial microwave irradiation of 120 W was used to ramp the temperature from rt to the desired temperature of 170 °C. Once this was reached (around 5 min), the reaction mixture was held at this temperature for 20 min. As with the Suzuki reaction, the mixture was cooled to 110 °C, solvent added (in this case dmf), the stirring turned ON, the product mixture stirred and then pumped into the collection container, further solvent pumped into the reaction vessel and then this also transferred to the collection vessel. The whole add, heat, remove process was then repeated a further nine times to give a total of ten cycles of 10 mmol reactions, the product being isolated and purified using the same procedure as in case of the 10 mmol optimisation reactions.

Acknowledgements

The University of Connecticut (RKA) is thanked for financial support. Michael Collins, Sr. and Michael Barnard are thanked for help with the planning and running of the Voyager experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.063

Spectral data for the coupling products and schematics of and information on the CEM Voyager system.

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