

# Diels–Alder cycloadditions by microwave-assisted, continuous flow organic synthesis (MACOS): the role of metal films in the flow tube†

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**Thin Pd films have been deposited on the inside of capillary-sized tubes through which compounds undergoing Diels–Alder reactions have been flowed while being heated with microwave irradiation; dramatic rate accelerations are observed in the presence of the film, which has been shown to play both a heating and catalytic role.**

Microwave-assisted organic synthesis (MAOS) has had a significant impact on organic and medicinal chemistry by shortening reaction times dramatically, even though a definitive rationale for how this rate increase manifests itself has yet to be elucidated.<sup>1</sup> More recently, microwave technology has also been applied to flowed<sup>2</sup> reactions;<sup>3</sup> to gain the full advantage of working in flow, reactions should ideally proceed very rapidly and complete during the time between the starting materials entering and departing the reaction tube. Microwave heating by itself has gone a long way toward driving a wide variety of reactions in a flowed format to high levels of completion during the brief time that the reactants spend in the microwave chamber of the synthesizer.<sup>3</sup>

We have demonstrated recently that thin-metal films on the inner wall of the flow tube exert a further rate acceleration on flowed microwave reactions.<sup>4</sup> In cross-coupling processes, the film itself has been demonstrated to be capable of catalyzing Suzuki–Miyaura and Heck reactions, *i.e.*, Pd thin films promoted these transformations without any additional catalyst being added to the reactant stream(s) that enter the flow tube. Metal films have been shown to be potent absorbers of microwave irradiation leading to very high temperatures.<sup>4</sup> Indeed, we have found that metal films that are too thick (*e.g.*, a Pd film of > 10 μm) can absorb so much irradiation, and convert it to heat *via* current, that the glass tube supporting the film can melt. Without microwave irradiation, the above-described cross-coupling reactions did not proceed, indicating that there is not only a catalytic effect, but also a pivotal heating effect supplied by the film. It has been postulated that irregularities (*e.g.*, angles, steps) in metal films accentuate the absorption of microwave irradiation; this may lead to the creation of significant ‘hot-spots’ in the film and therefore these areas are much hotter than the bulk of the film.<sup>4</sup> In microwave synthesizers, the reaction temperature at the surface of the reaction vessel is measured by an infrared

sensor that can provide information only on the portion of the surface that fills the aperture of the sensor, which means that only bulk measurements can be made. Thus, it could be that the majority of the catalysis is happening in these isolated, hotter regions in the film. This could account for why conversion is far greater for microwaved couplings employing the Pd film at 200 °C when compared with the identical reactions performed using an oil bath set at the same temperature, *i.e.*, without microwave irradiation no such hot spots are possible in the Pd film.

To further understand, and perhaps differentiate the roles of heating from catalysis with metal films under microwave irradiation conditions, we have begun to look at different transformations that are not necessarily metal-catalyzed, as are the cross-coupling experiments (*vide supra*). The Diels–Alder reaction of diene **1** with dienophile **2** is reported to proceed very slowly under batch heating conditions without catalysis (80% yield after 24 h refluxing in toluene).<sup>5</sup> We examined this reaction, and related difficult cycloadditions, in flow using microwave irradiation and the results are shown in Table 1.

Compounds **1** and **2** in DMSO were flowed together through a clear glass capillary (Table 1, entry 1) while being irradiated with sufficient power to match the temperature achieved using the reported batch oil bath results (~110 °C).<sup>5</sup> Given the long reaction time reported in batch, and the short residence time in flow (any one slug of reacting solution spends ~120 s in the irradiation zone of the microwave), it is notable that even 12% conversion was attained; a control experiment with no irradiation led to no detectable conversion (Table 1, entry 9). To probe the role of temperature on its own, the same clear tube was run through an oil bath set at 205 °C (Table 1, entry 6) and a sizable increase in conversion to 50% was observed. To see if the Pd film had a stand-alone heating effect, we covered the *outside* of a thin-walled capillary with a metal coating and performed the reaction with microwave irradiation (Table 1, entry 3); the IR sensor in the irradiation chamber recorded a temperature of 205 °C and the same level of conversion (50%) was attained. With such thin glass walls and small reaction volumes, heat transfer is generally accepted to be immediate and complete, thus the temperature of the reaction in the capillary would also be expected to be 205 °C, although it could not be measured directly.<sup>6</sup>

To probe catalytic roles of the Pd thin film, several experiments were carried out. A Pd thin film was laid down on the inner surface of the capillary and the MACOS reaction

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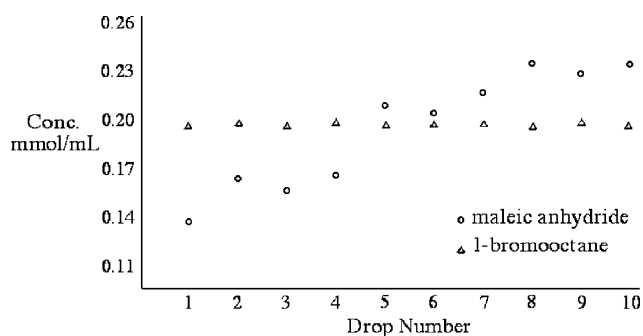
**Table 1** Diels–Alder cycloaddition reactions by MACOS employing Pd-coated and non-Pd-coated capillaries

Entry	Capillary (1200 μm ID)	Diene (1.0 eq.)	Dienophile ( <i>X</i> eq.)	Pressure/atm <sup>a</sup>	Temp./°C	Product (% conversion) <sup>b</sup>
1	Clear <sup>c</sup>	<b>1</b>	<b>2</b> (0.67)	1	115	<b>7</b> (12)
2	Clear <sup>c</sup>	<b>1</b>	<b>2</b> (0.67)	5	110	<b>7</b> (39)
3	Pd-coated outside <sup>d</sup>	<b>1</b>	<b>2</b> (0.67)	1	205	<b>7</b> (50)
4	Pd-coated inside <sup>e</sup>	<b>1</b>	<b>2</b> (0.67)	1	205	<b>7</b> (93) [80] <sup>f</sup>
5	Pd-coated inside <sup>e</sup>	<b>1</b>	<b>2</b> (0.67)	5	180	<b>7</b> (99)
6	Clear <sup>c</sup>	<b>1</b>	<b>2</b> (0.67)	1	205 (oil bath)	<b>7</b> (50)
7	Pd-coated inside <sup>e</sup>	<b>1</b>	<b>2</b> (0.67)	1	205 (oil bath)	<b>7</b> (75)
8	Pd-coated inside <sup>e</sup>	<b>3</b>	<b>4</b> (1.5)	1	23	<b>8</b> (16)
9	Clear <sup>c</sup>	<b>1</b>	<b>2</b> (0.67)	1	23	<b>7</b> (0)
10	Clear <sup>c</sup>	<b>3</b>	<b>4</b> (1.5)	1	115	<b>8</b> (10)
11	Clear <sup>c</sup>	<b>3</b>	<b>4</b> (1.5)	5	110	<b>8</b> (70)
12	Pd-coated outside <sup>d</sup>	<b>3</b>	<b>4</b> (1.5)	1	205	<b>8</b> (58)
13	Pd-coated inside <sup>e</sup>	<b>3</b>	<b>4</b> (1.5)	1	205	<b>8</b> (86) [70] <sup>f</sup>
14	Pd-coated inside <sup>e</sup>	<b>3</b>	<b>4</b> (1.5)	5	180	<b>8</b> (96)
15	Clear <sup>c</sup>	<b>3</b>	<b>4</b> (1.5)	1	205 (oil bath)	<b>8</b> (46)
16	Pd-coated inside <sup>e</sup>	<b>3</b>	<b>4</b> (1.5)	1	205 (oil bath)	<b>8</b> (64)
17	Pd-coated inside <sup>e</sup>	<b>3</b>	<b>4</b> (1.5)	1	23	<b>8</b> (5)
18	Clear <sup>c</sup>	<b>3</b>	<b>4</b> (1.5)	1	23	<b>8</b> (0)
19	Clear <sup>c</sup>	<b>5</b>	<b>6</b> (1.5)	1	115	<b>9</b> (10)
20	Clear <sup>c</sup>	<b>5</b>	<b>6</b> (1.5)	5	110	<b>9</b> (50)
21	Pd-coated outside <sup>d</sup>	<b>5</b>	<b>6</b> (1.5)	1	205	<b>9</b> (47)
22	Pd-coated inside <sup>e</sup>	<b>5</b>	<b>6</b> (1.5)	1	205	<b>9</b> (90) [74] <sup>f</sup>
23	Pd-coated inside <sup>e</sup>	<b>5</b>	<b>6</b> (1.5)	5	180	<b>9</b> (87)
24	Clear <sup>c</sup>	<b>5</b>	<b>6</b> (1.5)	1	205 (oil bath)	<b>9</b> (54)
25	Pd-coated inside <sup>e</sup>	<b>5</b>	<b>6</b> (1.5)	1	205 (oil bath)	<b>9</b> (72)
26	Pd-coated inside <sup>e</sup>	<b>5</b>	<b>6</b> (1.5)	1	23	<b>9</b> (1)
27	Clear <sup>c</sup>	<b>5</b>	<b>6</b> (1.5)	1	23	<b>9</b> (0)

<sup>a</sup> For 1 atm reactions, the only pressure in the system originated from the pressure of the syringe pump that pushed the solution into and through the capillary, otherwise it was an open system. For 5 atm reactions, the outlet end of the capillary was pushed through a septum into a sealed vial that was charged with ~75 psi of air pressure. <sup>b</sup> Percent conversion was determined by taking samples of the effluent from the capillary and analyzing it directly by <sup>1</sup>H NMR spectroscopy. <sup>c</sup> All capillaries used for this study were 12 cm long (1180 μm ID); approximately 2.5 cm of the tube resides in the actual irradiation zone of the microwave. <sup>d</sup> Pd colloids were deposited on the *outer* surface of the capillary; the inner surface of the capillary had no metal coating on it and the reaction mixture was flowed through it. <sup>e</sup> Pd colloids were deposited on the *inner* surface of the capillary; the reaction mixture was flowed through the capillary where it was in direct contact with the metal film. <sup>f</sup> % Yield following silica gel chromatography.

repeated (Table 1, entry 4). Remarkably, conversion was now essentially quantitative, which meant that a reaction that once proceeded to only 80% conversion under 24 h of constant reflux in toluene solvent under batch conditions could now reach completion in less than 2 minutes with MACOS. In order to dissect out the role of the microwave irradiation, the reaction was performed at the same temperature (*i.e.*, 205 °C), but in an oil bath (Table 1, entry 7). Conversion dropped sharply to 75%, suggesting that microwave irradiation is necessary and simple bulk heating of the film, as one would achieve in the oil bath, does not entirely suffice to promote the highest possible conversion. Interestingly, when the same transformation was simply flowed with no microwave irradiation through the same Pd-coated capillary, 16% conversion was achieved (Table 1, entry 8); with no film the conversion was 0% (entry 9). It would appear as though the metal film is playing a catalytic role in addition to its involvement in heating.

The pressure within the flow system was also investigated. With no imposed backpressure at the end of the flow system, the only pressure generated during the MACOS process comes from the heat of the reacting solution, the syringe pumps, and the walls of the tubing, thus essentially it is functioning under standard atmospheric pressure (*i.e.*, 1 atm or 15 psi). Under these conditions, the solvent cannot exceed its boiling point, thus no overpressure is possible; when this temperature is reached, the solvent changes state rapidly to a gas and the plug of reactant in the irradiation zone is promptly expelled from the capillary. With 5 atm (75 psi) of induced backpressure in the MACOS set-up, no cavitation of the liquid occurs and the reaction flows as a continuous stream. In all cases where backpressure is imparted on the system (*e.g.*, Table 1, entries 2 *vs.* 1 and 5 *vs.* 4), superior conversion was obtained. All results obtained employing reactant pairs **3** with **4** and **5** with **6** were essentially identical to those obtained with **1** and **2** when similar experiments to those described above were repeated.



**Fig. 1** Changes in the concentration of 1-bromooctane and maleic anhydride in a solution that was flowed through a capillary lined with a Pd thin film.‡

Based on the above experimentation, it is clear that the Pd film has both a heating and a catalytic role in these Diels–Alder cycloadditions; just how the film catalyzes the transformation is not clear. EDX analysis of the Pd film indicates that it is 94% Pd, 5.5% C, and 0.3% O by weight, therefore it is presumed that the vast majority of the film is Pd(0). To probe this, we flowed hydrogen gas down the inside of a Pd-coated capillary; significant sparking ensued, confirming that a significant portion of the film’s surface is indeed metallic Pd. At first glance, it would seem reasonable to try and invoke a Lewis acid-type role for the film that would be analogous to the well-established role of conventional electron-deficient metals in homogeneous catalysis, such as complexes of boron or aluminium. However, given the electron-rich nature of a metallic film, such as Pd(0) in this case, it might seem counter-intuitive to invoke such a role for the film. That said, reduced metals are definitely known to coordinate suitable substrates, such as is the case with olefins and Pd/C under catalytic hydrogenation conditions. To probe such a coordinative role of the Pd(0) film in these MACOS reactions we prepared a solution comprised of an equimolar amount of maleic anhydride and 1-bromooctane (0.2 M in each) and simply flowed this solution through a metal-coated capillary at rt (with no microwave irradiation) and collected the effluent one drop at a time and analyzed each drop for its composition (Fig. 1). Whereas the control 1-bromooctane, which presumably could not coordinate to the film, came straight through the capillary, the maleic anhydride displayed affinity behavior. In other words, the film sequestered maleic anhydride out of the solution that was being constantly infused at a fixed concentration. This is seen when one looks at the amount of maleic anhydride in drops 1 through 5. When the available sites on the film become saturated, 2 came straight through and the slight over-concentration seen in drops 5–10 is caused by the

retained/coordinated material being returned to the infusing stream. After flowing for long enough, the concentration of maleic anhydride equalled the infusing concentration, *i.e.*, 0.2 mmol mL<sup>-1</sup>. Thus, it would be reasonable to invoke a catalytic role for the Pd(0) film that involves coordination of the dienophile to the metal surface.

In summary, we have demonstrated that very long reaction times for batch reactions using conventional heating can be reduced to much shorter time frames using MACOS. Further, reactions that transform so quickly are typically cleaner as the completed product does not sit in a high temperature environment for prolonged periods while the rest of the starting materials react. A Pd thin film on the flow tube walls dramatically shortens the reaction time; this film has been shown to play a significant role both in effective heating and in catalyzing these transformations.

## Notes and references

‡ A stock solution containing equal molar portions of 1-bromooctane and maleic anhydride (0.2 mmol mL<sup>-1</sup> each) in DMSO was flowed through a Pd-coated capillary and each droplet of effluent separately collected. The relative concentration of the two solutes was determined by proton NMR spectroscopy.

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- We recognize that the IR sensor measurement given by the Biotage Initiator Synthesizer™ is not likely to deliver an accurate measure of the temperature inside the capillary. However, we have not yet been successful in obtaining more accurate measurements, for example employing a miniature thermocouple, because such devices also couple with microwave irradiation leading to current and heating itself; this would lead to erroneous results. What we can say is that the temperature in or at the surface of the metal film is likely higher than 200 °C, as read by the IR sensor, but less than 600 °C, which is the melting temperature of borosilicate glass.