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# Heck Reactions in Aqueous Miniemulsions

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Carrying out organic reactions in water-based nanoreactors represents a 'green' method for the preparation of organic compounds. This process eliminates the need for solvents, thus reducing the effect of high volumes of solvent on the environment. In this work, we demonstrate a successful Heck cross-coupling reaction, one of the most used approaches to form C–C bonds using a palladium catalyst, in a miniemulsion. The miniemulsion droplet sizes were small (25 to 42 nm), and the reactions resulted in high conversions of three different products with high *trans* stereoisomers.

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## Introduction

It is well established that carrying out organic reactions in water-based nanoreactors can have advantages over that in solution or bulk.[1] Nanoreactors can concentrate reactants through compartmentalization,[2] resulting in a considerable increase in the rate of product formation. Furthermore, water provides an environmentally friendly medium,[3] with the potential to significantly reduce the amount of organic solvents in the synthesis of pharmaceuticals and fine chemicals. Eliminating organic solvents, especially volatile organic solvents (VOCs), would also significantly reduce the cost of production as the solvents usually constitute over 80 % of the total reaction mass.

The Heck reaction,[4] catalysed by palladium (Pd), represents one of the most important synthetic methods for the formation of C–C bonds in both the pharmaceutical and fine chemical industries.[5,6] This reaction has found utility, ranging from the synthesis of highly complex small molecules[7] to conjugated polymers.[8] There are now many reports on the use of surfactant and polymer micelles in water to carry out Heck reactions.[9–14] In some cases, the Pd catalyst is captured into nanoparticles stabilised by surfactant,[9–12] and in other cases the Pd catalyst is bound to the micelle-forming polymer through covalently linked ligands on the side chains.[13,14] All these methods have been used with great success. However, there are only a few reports of the Heck reaction being carried out in microemulsions[15–18] using commercially available Pd/ligand catalysts, and there are no reports to our knowledge of Heck reactions in miniemulsions. The advantage of micro- and miniemulsions is the co-location of reagents and catalyst complexes in surfactant stabilised droplets ranging in size from ~20 to 500 nm, resulting in the potential for faster and better controlled reactions owing to compartmentalization but also to the excellent heat transfer through the water phase. The latter becomes important in organic and polymer reactions that have the potential to explode from highly exothermic reactions.

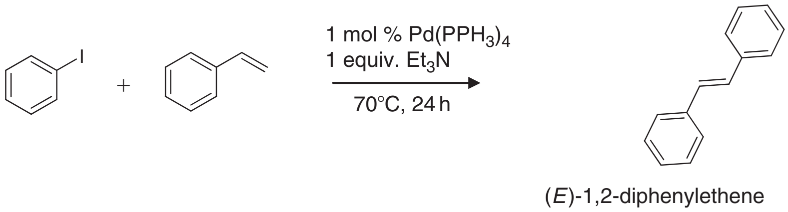
Miniemulsions are formed by the high shear mixing of surfactant, reactants, water and costabilizer that form stable organic droplets in a continuous water phase. The costabilizer (e.g. hexadecane) is an important ingredient that acts as a swelling agent, and thus limits the diffusion of reagents from the smaller droplets to the larger ones (i.e. inhibits Ostwald ripening).[19,20] Without costabilizer, diffusion of reagents via the action of Ostwald ripening from small to larger droplets results in the growth of the larger droplets until they reach a critical size of usually greater than 500 nm, become buoyant and then rise to form a single organic phase at the top of the reaction vessel. Miniemulsions are typically formed through high shear, by subjecting the system to ultrasonication, homogenizer or microfluidizer,[19,20] and have been extensively used to produce hydrophobic polymers without the need of an organic solvent.[19,20] The resulting nanoparticles are easy to process due to the low viscosity medium.

The aim of this work is to carry out Heck reactions catalyzed by a commercially available Pd complex in a miniemulsion using the same ingredients as that for the polymerizations. We found process conditions to produce stabilised droplets ranging from 25 to 42 nm in diameter ($D_H$) following the procedure by Landfester and coworkers.[21] Three different sets of reagents were used in miniemulsions, giving quite high conversion of reactants to product and high *trans* stereoisomer formation. Thus, in the continuing quest for green technology in chemical processes, the miniemulsion concept is an exciting alternative to effect inorganic[22] and organic reactions[23,24] in aqueous media, particularly the palladium-catalyzed cross-coupling reaction.[25]

## Results and Discussion

The first cross-coupling reaction, considered the gold standard of Heck coupling, involves the coupling of styrene and

**Table 1. Comparison of palladium-catalyzed Heck cross-coupling reaction in miniemulsion and organic solvents at 70°C for 24 h**



| Entry[A] | Solvent | Catalyst loading [mol %] | Conversion of iodobenzene [%][B] *(E %)*[C] |
|---|---|---|---|
| 1[D] | DMF | 1 | 51 *(83)* |
| 2[E] | Toluene | 1 | 0 *(N/A)* |
| 3[F] | Miniemulsion | 1 | 99 *(82)* |

[A] Reactions are carried out using styrene (0.0024 mol), iodobenzene (0.0024 mol), triethylamine (0.0024 mol) and $Pd(PPh_3)_4$ (1 mol %) at 70°C for 24 h.
[B] Determined by $^1H$ NMR spectroscopy.
[C] Determined by GC-MS.
[D] Reactions carried out in 2.00 g of DMF.
[E] Reactions carried out in 2.00 g of toluene.
[F] Reactions carried out in 0.0450 g SDS in 2.00 g of water with 0.0600 g hexadecane as co-surfactant/hydrophobe and reaction was run for 25 h.

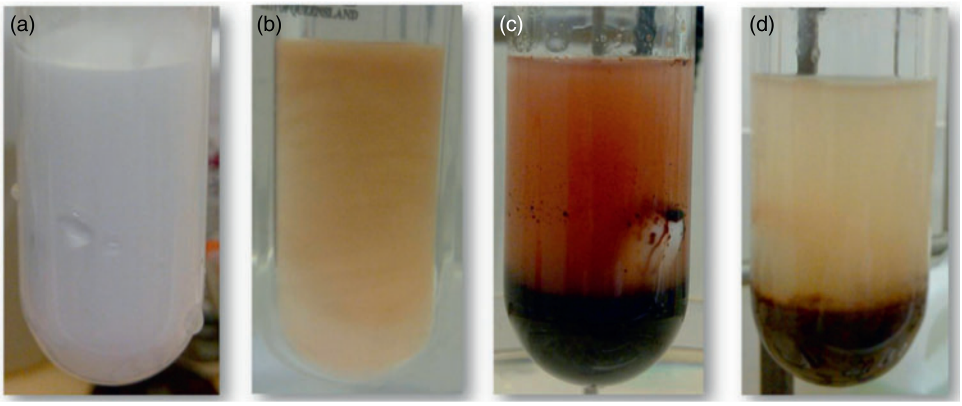


**Fig. 1.** The Heck reaction in a miniemulsion. (a) After ultrasonication; (b) during the reaction; (c) immediately after the reaction (24 h); and (d) left to stand for a further 1 h.

iodobenzene to produce stilbene ((*E*)-1,2-diphenylethene, Table 1). In both DMF and toluene using $Pd(PPh_3)_4$ (1 mol % to reactants), the product conversion was 51 and 0 %, respectively, after 24 h at 70°C (Table 1). In the miniemulsion approach, a white milky solution as shown in Fig. 1a was formed using sodium dodecylsulfate (SDS), hexadecane (costabilizer) and water. An initial droplet diameter ($D_H$) of 29 nm after ultrasonication at room temperature gave a stable miniemulsion for over 24 h. The product precipitated out during the reaction (Fig. 1b). At the end of the reaction and as soon as the stirring was stopped, the product settled to the bottom of the reaction mixture (Fig. 1c). Leaving the mixture to stand for another hour gave a phase separation of the product from the aqueous phase (Fig. 1d). This allowed the product to be isolated by simply decanting the aqueous phase, and further purified by solvent extraction and column chromatography. The conversion of iodobenzene to product was close to 100 % (Table 1) as monitored by $^1H$ NMR spectrometry over 25 h (Fig. 2a). The loss of styrene (6.7 ppm) and iodobenzene (7.7 ppm) and the formation of a single peak from that of *trans*-stilbene (or (*E*)-1,2-diphenylethene, 7.1 ppm) after 25 h, suggest that the catalyst allows the reaction to reach near quantitative conversion and with high yields of the *E* stereoisomer (Table 1).

The absence of any reaction in toluene was due to the poor solubility of the catalyst in this solvent. Increasing the polarity of the solvent to DMF increased the solubility of the catalyst and so to the yield of product. In the miniemulsion, the catalyst was fully soluble in the mixture of reactants, forming stable droplets upon sonication. The complete solubilization of the commercial catalyst allowed the miniemulsions to produce product in very high yields. These high conversions prompted us to utilize the same conditions for other substrates.

A reaction of 4-methoxyiodobenzene (1 equiv) and *tert*-butylacrylate (1 equiv) was first attempted at a lower temperature of 50°C for 24 h using 1 mol % loading of $Pd(PPh_3)_4$ (Table 2). At this milder temperature, a conversion of 63 %

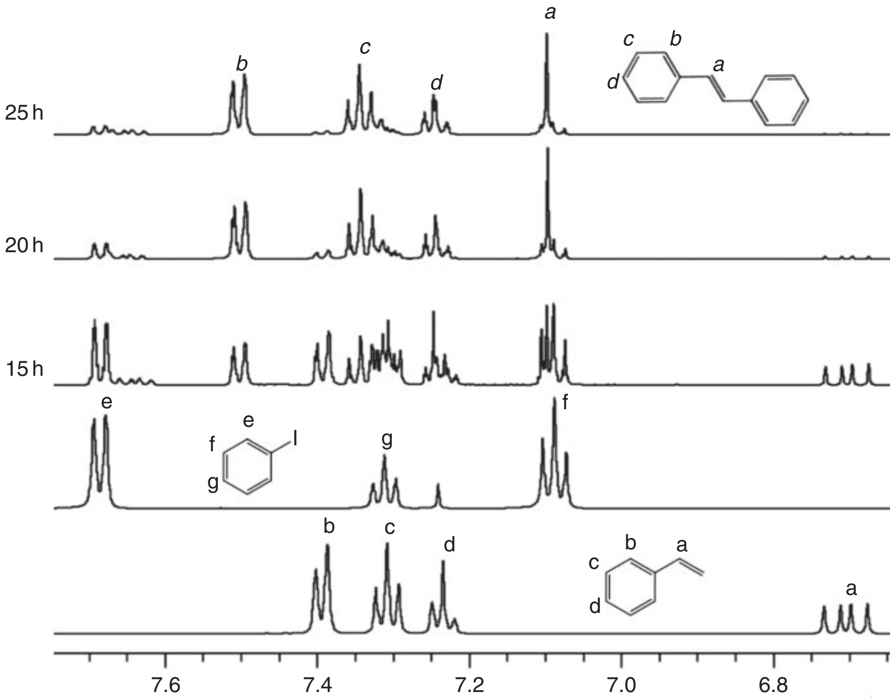
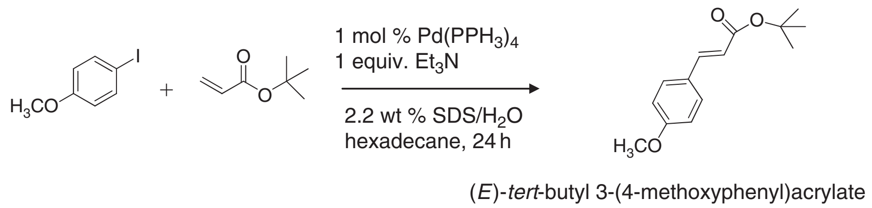


**Fig. 2.** $^1$H NMR spectra of the Heck reaction of iodobenzene and styrene in miniemulsion at time 15, 20 and 25 h.

**Table 2. Heck cross-coupling reaction of 4-methoxyiodobenzene and *tert*-butylacrylate in miniemulsion at different temperatures for 24 h**



| Entry[A] | $D_H$ [nm][B] *(PDI)*[C] | Reaction temperature [°C] | Catalyst loading [mol %] | Conversion of 4-methoxyiodobenzene [%][D] *(E %)*[E] |
|---|---|---|---|---|
| 1 | 93 *(0.089)* | 50 | 1 | 63 *(96)* |
| 2 | 42 *(0.212)* | 50 | 2 | 81 *(96)* |
| 3 | 34 *(0.221)* | 40 | 2 | 1 *(94)* |
| 4 | 35 *(0.311)* | RT | 2 | 0 *(NA)* |

[A] Reactions are carried out using styrene (0.0024 mol), iodobenzene (0.0024 mol), triethylamine (0.0024 mol) and $Pd(PPh_3)_4$ (1 or 2 mol %) in 0.0450 g SDS in 2.00 g of water with 0.0600 g hexadecane as co-surfactant/hydrophobe for 24 h.

[B] Hydrodynamic diameter ($D_H$) of the miniemulsion after ultrasonication measured by DLS at 25°C.

[C] Polydispersity index (PDI) of the particle size distribution in miniemulsion after ultrasonication measured by DLS at 25°C.

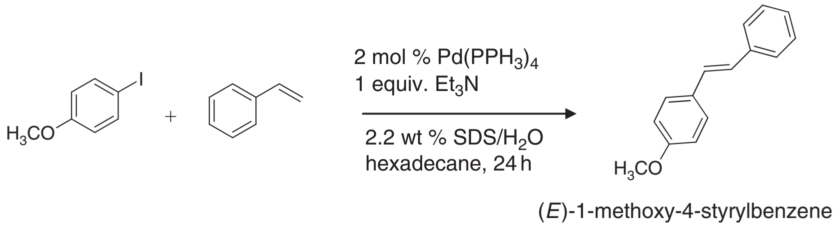
[D] Determined by $^1$H NMR spectroscopy.

[E] Determined by GC-MS.

and 96 % *E* formation (entry 1, Table 2) was obtained as determined by $^1$H NMR spectral analysis. In an effort to increase the conversion, a 2 mol % loading of $Pd(PPh_3)_4$ was used at the same temperature. This reaction resulted in an increase in the conversion to 81 % ($E = 96$ %, entry 2, Table 2). However, at temperatures below 50°C, there was little or no conversion (entries 3 and 4, Table 2). The initial droplet diameters after sonication at room temperature ranged between 34 and 42 nm, which was slightly larger compared with the sizes found in Table 1. The reason for the larger initial size of 93 nm at 1 mol % loading is unclear, but suggests that the greater amount of catalyst acts to further stabilize the droplets.

The Heck reaction of 4-methoxyiodobenzene with styrene showed an increase in the conversion from 41 to 76 % when the temperature was increased from 40 to 70°C (Table 3). Over the three temperatures used, the initial droplet sizes were similar, ranging between 30 and 40 nm. The formation of the trans-product was greater than 90 %. The *para*-methoxy group on iodobenzene seemed to inhibit the reaction with styrene as compared with unsubstituted iodobenzene (Table 1), whereas its reaction with a *tert*-butyl acrylate (Table 2) gave a slightly faster rate. Even though we use an inexpensive commercially available catalyst, $Pd(PPh_3)_4$, and SDS, we obtain similar results to those found in the literature.[10,11]

**Table 3. Heck cross-coupling reaction of 4-methoxyiodobenzene and styrene in miniemulsion at different temperatures for 24 h**



| Entry[A] | $D_H$ [nm][B] *(PDI)*[C] | Reaction temperature [°C] | Catalyst loading [mol %] | Conversion of 4-methoxyiodobenzene [%][D] *(E %)*[E] |
|---|---|---|---|---|
| 1 | 30 *(0.257)* | 70 | 2 | 76 *(97)* |
| 2 | 39 *(0.254)* | 50 | 2 | 74 *(92)* |
| 3 | 35 *(0.232)* | 40 | 2 | 41*(90)* |

[A] Reactions are carried out using styrene (0.0024 mol), iodobenzene (0.0024 mol), triethylamine (0.0024 mol) and $Pd(PPh_3)_4$ (2 mol %) in 0.0450 g SDS in 2.00 g of water with 0.0600 g hexadecane as co-surfactant/hydrophobe for 24 h.
[B] Hydrodynamic diameter ($D_H$) of the miniemulsion after ultrasonication measured by DLS.
[C] Polydispersity index (PDI) of the particle size distribution in miniemulsion after ultrasonication measured by DLS.
[D] Determined by $^1H$ NMR spectroscopy.
[E] Determined by GC-MS.

## Conclusion

In conclusion, we have successfully demonstrated the use of miniemulsion in a palladium catalysed Heck cross-coupling reaction of aryliodides and olefins from 40 to 70°C. The catalyst chosen was the inexpensive, commercially available $Pd(PPh_3)_4$, resulting in high yields of product with good control of the stereochemistry. The remarkably high stability displayed by the miniemulsions and the excellent solubility of the catalyst in the reagents provided proof of the successful encapsulation of the hydrophobic reactants and catalyst in the system. This ensured that catalysis occurred within the generated miniemulsion nanodroplets, resulting in high yields as compared with the low yields found when the catalyst was poorly solvated in either toluene or DMF. As a result, this work highlights the potential for conducting Heck reactions in miniemulsions and opens up the possibilities for extending this process to other palladium-catalyzed cross-coupling reactions, including Suzuki-Miyaura or Sonogashira reactions for organic synthesis and polymerization reactions.

## Experimental

### Materials

Styrene (99 %, Sigma-Aldrich), *tert*-butylacrylate (98 %, Sigma-Aldrich) and iodobenzene (98 %, Sigma-Aldrich) were passed through a column of basic alumina before use. 4-Methoxyiodobenzene (98 %, Sigma-Aldrich), $Pd(PPh_3)_4$ (99 %, Sigma-Aldrich), triethylamine (Merck), hexadecane (99 %, Sigma-Aldrich), sodium dodecyl sulfate (ultra-pure, ICN Biomedicals Inc.) and dichloromethane were used as received. Milli-Q water ($18.2\,M\Omega\,cm^{-1}$) was generated using a MilliQ Academic water purification system.

### Heck Cross-Coupling Reaction in Miniemulsion

A typical Heck cross-coupling reaction in miniemulsion was conducted as follows: styrene (0.2500 g, 0.0024 mol), iodobenzene (0.4898 g, 0.0024 mol), triethylamine (0.2429 g, 0.0024 mol), hexadecane (0.0150 g) and $Pd(PPh_3)_4$ (0.0277 g, $2.4 \times 10^{-5}$ mol) were mixed and added dropwise to a solution of SDS (0.0045 g) in water (2.00 g). The mixture was stirred vigorously (1600 rpm) for 1 h at room temperature and ultrasonicated for 30 min with pulses of 50 s and pauses of 10 s at 35 % amplitude (Sonics Vibra Cell 750, 750 W, 3 mm tapered microtip) under ice cooling. The miniemulsion was transferred to a Schlenk tube, sealed and purged with argon for 30 min under ice cooling and placed in an oil bath at 70°C for 24 h.

### Dynamic Light Scattering (DLS)

Dynamic light scattering measurements were performed using a Malvern Zetasizer 3000HS. A droplet from the miniemulsion was diluted in Milli-Q water and filtered before DLS measurement at 25°C. The sample refractive index (RI) was set at 1.59 for polystyrene. The dispersant viscosity and RI were set to $0.89\,Ns\,m^{-2}$ and 1.33, respectively.

### Nuclear Magnetic Resonance (NMR) Spectroscopy

All NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer using an external lock ($CDCl_3$) and utilizing the solvent peak as an internal reference.

### Gas Chromatography-Mass Spectrometry (GC-MS)

The *cis* : *trans* ratio of the products was determined by GC-MS (Shimadzu) using a 30 m × 0.32 mm × 0.25 μm Altech column. Conditions: injection temperature 275°C; initial temperature: 40°C, 1.5 min hold time; ramp to 275°C (20°C $min^{-1}$), 4 min hold time.

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