Heck reactions using segmented flow conditions

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ARTICLE INFO

ABSTRACT

Various Heck couplings have been carried out using segmented flow conditions to accelerate the reactions. Aryl iodides and aryl bromides as well as anilines in diazonium-type Heck reactions have been used successfully.

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The Heck reaction is one of the best-known methods used in organic synthesis for formation of substituted alkenes by the coupling of two sp^2 carbon centres. Since discovered by Heck in the late 1960s,[1] the reaction has occupied a special place among metal-catalysed transformations along with Suzuki, Stille and Sonogashira reactions due to its versatility and applicability to a wide range of substrates. As a result, Heck coupling has become a popular transformation used in the synthesis of many structurally diverse compounds, such as Taxol,[2] morphine[3] and other macrocyclic compounds.[4] The Heck coupling normally takes place between an organohalide (aryl or vinyl) and an alkene typically in the presence of a zerovalent palladium catalyst. It is a very reliable reaction and many non-conventional methodologies have been exploited successfully.[5]

Currently there is high interest in continuous-flow processes and organic reactions performed in microfluidic systems.[6] This technology offers advantages over classical approaches by allowing miniaturisation of structural features up to the micrometre regime. Enhanced mass- and heat transfer due to a very large surface to volume ratio as well as regular flow profiles lead to higher yields with increased selectivities. The mixing of substrates and reagents can be performed under highly controlled conditions leading to improved protocols. Liquid–liquid biphasic reactions are routinely performed but microreactors can offer advantages by intense mixing of immiscible liquids.[7] We have already shown that ester hydrolysis performed under liquid–liquid biphasic reaction conditions can be accelerated in microreactors.[8] In such multiphase flow, mass transfer is accelerated by alternating immiscible fluid packets benefiting from having both (i) a continually refreshing interface between adjacent fluid packets, and (ii) a rapid vortex flow within a fluid packet.[9] One early study of the Heck reaction under biphasic conditions was reported by Arai et al. using toluene/ethylene glycol as a biphasic solvent system.[10] The best choice of catalyst under these conditions was $Pd(OAc)_2$. Keeping the catalyst separated from the reactants and product phase is a typical strategy used in biphasic catalysis giving the advantage of product/catalyst separation and recycling. Such a strategy has been adopted by Ryu et al. by dissolving the palladium catalyst in an ionic liquid. This allowed Heck reactions with an easy continuous recycling of the catalyst.[11]

Also, other research groups have investigated Heck reactions in flow using supported palladium catalysts. Kirschning et al.[12] used a monolith containing nanoparticular palladium while Garcia-Verdugo and Luis et al.[13] investigated an imidazolium-functionalised polystyrene monolith successfully for such cross-coupling reactions. Palladium-containing monoliths were also used by Ley et al. for Heck reactions carried out in superheated ethanol.[14] Seeberger and co-workers used palladium on charcoal as a catalyst for Heck reactions.[15] Jensen and Buchwald demonstrated an acceleration of such reactions when performed at elevated temperatures and pressures facilitated by microreactors.[16] A review on the use of transition metal-catalysed Heck reactions using microwave and microreactor technologies has appeared recently.[17]

Initially, the arylation of methyl acrylate **2a** and styrene **2b** with iodobenzene **1a** was performed using 10 mol % of a metal catalyst with 20 mol % triphenylphosphine in dimethylformamide (DMF) in the presence of triethylamine as a base to yield products **3a** and **3b** as shown in Scheme 1.

The first microflow study we conducted on monophasic Heck coupling was carried out under laminar flow conditions, screening various metal catalysts in the reaction of iodobenzene and methyl acrylate. The monophasic reactions were performed using a very
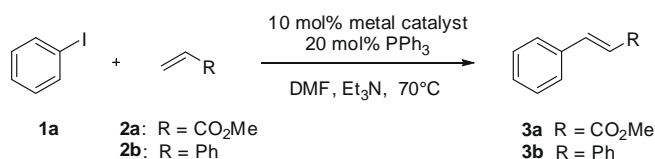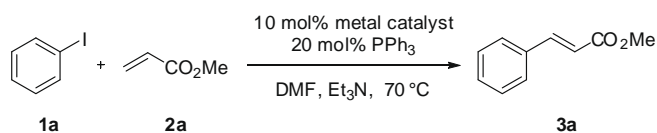
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		10 mol% metal catalyst		
1a	2a: R = CO₂Me	20 mol% PPh₃	3a R = CO₂Me	
	2b: R = Ph	DMF, Et₃N, 70°C	3b R = Ph	

1a   **2a**: R = CO₂Me   **3a** R = CO₂Me
          2b: R = Ph   **3b** R = Ph

Scheme 1.

Table 1
Homogeneous Heck reaction: conventional flask versus laminar flow

Entry	Metal catalyst	Flask reaction[a] yield **3a** (%)	PTFE microtubing[b] yield **3a** (%)
1	Pt(COD)Cl$_2$	8	21
2	CoCl$_2$	17	28
3	RuCl$_3$	12	45
4	Ni(OAc)$_2$	20	34
5	PdCl$_2$	30	47
6	Pd(OAc)$_2$	26	53
7	PdCl$_2$[c]	—	19
8	Pd(OAc)$_2$[c]	—	21
9	Pd(OAc)$_2$[d]	29	52
10	Pd(PPh$_3$)$_4$	—	62

[a] Reaction conditions: metal catalyst (10 mol %), PPh$_3$ (20 mol %), iodobenzene (0.2 mmol), methyl acrylate (0.2 mmol), Et$_3$N (0.2 mmol), in DMF, 70 °C (oil bath), reaction time: 35 min.
[b] Reaction conditions: metal catalyst (10 mol %), PPh$_3$ (20 mol %), iodobenzene (1.0 mmol), methyl acrylate (1.0 mmol), Et$_3$N (1.0 mmol), in DMF, 70 °C (oil bath), residence time: 35 min under laminar flow conditions.
[c] 1 mol % catalyst used.
[d] Pd(OAc)$_2$ (5 mol %), Et$_4$NCl (1.0 mmol), iodobenzene (1.0 mmol), methyl acrylate (1.0 mmol), K$_2$CO$_3$ (1.0 mmol), in DMF/ethylene glycol (4:1), 70 °C (oil bath), residence/reaction time: 50 min.

simple experimental set-up. Two solutions were introduced into the system via a syringe pump: (i) a solution of iodobenzene, methyl acrylate and triethylamine in DMF; and (ii) a solution of metal catalyst and PPh$_3$ in DMF. The two solutions were mixed in a T-inlet connected to PTFE microtubing (length: 2000 mm, internal diameter: 500 µm, reactor volume: 393 µl), which was immersed in an oil bath. The data in Table 1 demonstrate that the performance of the monophasic coupling reaction using the microflow system is better than that in a flask, and PdCl$_2$ and Pd(OAc)$_2$ showed better performance than other catalysts, both in flask and in microflow.

However, on many occasions when using Pd catalysts, we observed formation of a black particulate as a result of catalyst decomposition. A reduction of metal catalyst loading decreased the amount of particulate formed inside the microchannel, but at the same time lowered the reaction yields significantly (Table 1, entries 7 and 8). The ligand-free methodology employing Jeffery's conditions in Heck coupling[18] uses a combination of a divalent palladium with a quaternary ammonium salt in the presence of an inorganic base. The arylation of methyl acrylate was performed in the microchannel under Jeffery's conditions using tetraethylammonium chloride in the presence of Pd(OAc)$_2$ and potassium carbonate in a DMF/ethylene glycol solvent system. A 5 mol % loading of Pd(OAc)$_2$ resulted in slightly improved yields compared to that in the flask (Table 1, entry 9), while 10 mol % again led to particulate formation. Almost no particulate was formed when using Pd(PPh$_3$)$_4$ as catalyst (Table 1, entry 10) which improved the yield to 62%.

A segmented flow technique was then applied to reactions previously carried out under laminar flow conditions in order to achieve further optimisation. We transformed the laminar flow into segmented flow by introducing an immiscible inert liquid into the laminar flow as shown in Figure 1. We aimed to exploit the advantages of segmentation, that is, the generation of internal circulation within segments leading to improved mixing compared to laminar diffusion. Besides, having to be immiscible with the reaction phase, the segmented phase must not interfere with, or dissolve any of the reaction components, and must have a boiling point compatible with the reaction conditions.
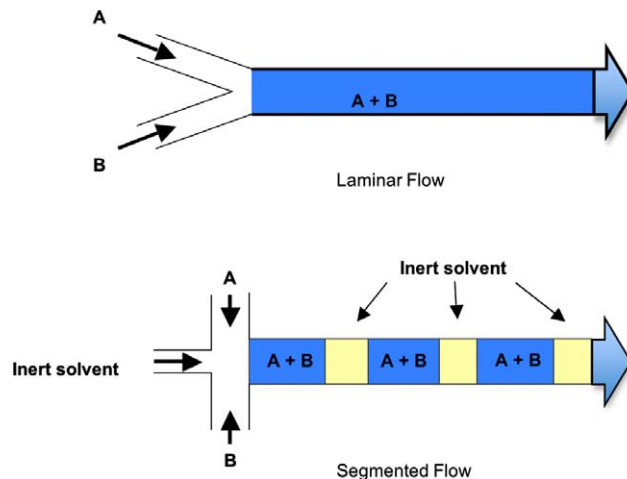
Figure 1. Laminar and segmented flows.

Table 2
Laminar versus segmented flow applied to Heck coupling of iodobenzene **1a** with methyl acrylate **2a** to form methyl cinnamate **3a** or with styrene **2b** to form stilbene **3b**

Entry	Catalyst Pd(PPh$_3$)$_4$ (mol %)	Laminar flow[a] yield (%)	Segmented flow[a] yield (%)
1[b]	5	**3a**: 36	**3a**: 65
2[b]	10	**3a**: 53	**3a**: 76
3[c]	5	**3b**: 38	**3b**: 57
4[c]	10	**3b**: 43	**3b**: 59

[a] Reaction conditions: Pd(PPh$_3$)$_4$ (5 or 10 mol %), iodobenzene (1 mmol), methyl acrylate or styrene (1 mmol), Et$_3$N (1 mmol), in DMF, 70 °C (oil bath).
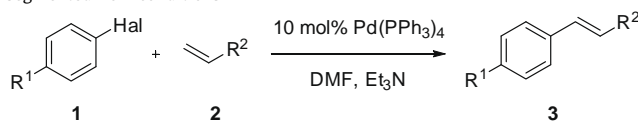[b] Residence time: 35 min.
[c] Residence time: 45 min.

In addition, in some cases where heating was applied, the inert phase such as decane homogenised with the reaction phase causing loss of segmentation resulting in the formation of laminar flow. Segmentation by an inert gas presented intrinsic problems in the control of the flow rate requiring different equipment. Perfluorinated solvents, such as perfluorodecalin, were found to be immiscible with DMF even at high temperatures (120 °C), hence it was used as the segmentating phase. As shown in Table 2, significant improvements in reaction yields of methyl cinnamate **1** and stilbene **2** were obtained as a result of introducing segmentation, showing that high conversions were achievable with a relatively low loading of catalyst. The temperature dependence of potential partially miscible solvents has not been investigated. Also segment sizes have not been varied in the experiments described here.

On the basis of these encouraging results obtained in the first attempts to synthesise **3a** and **3b**, the study was extended to a variety of Heck coupling substrates, leading to the successful reaction of substituted iodobenzenes and bromobenzenes with a variety of alkenes as shown in Table 3 (entries 1–9). As expected, iodobenzene showed generally higher reactivity, whereas bromobenzene required longer residence times or higher temperatures. Further optimisation studies on the coupling between iodobenzene and methyl acrylate showed that by decreasing the concentration of iodobenzene from 0.2 M to 0.09 M and increasing the temperature to 85 °C in the presence of 10 mol % of Pd(PPh$_3$)$_4$, the reaction rate was increased remarkably allowing a shorter residence time of approximately 1 min to produce methyl cinnamate **3a** in 97% yield (Table 3, entry 10). We then applied the segmented flow method to another type of Heck coupling of alkenes using arene-diazonium salts instead of aryl halides as shown in Table 4.[19] Once the

Table 3
Heck coupling of aryl halides to alkenes under segmented flow conditions

$$\text{R}^1\text{—C}_6\text{H}_4\text{—Hal} \quad + \quad \diagup\diagdown\text{R}^2 \quad \xrightarrow[\text{DMF, Et}_3\text{N}]{10 \text{ mol}\% \text{ Pd(PPh}_3)_4} \quad \text{R}^1\text{—C}_6\text{H}_4\text{—CH=CH—R}^2$$

| | | | | | |
| **1** | | **2** | | | **3** |

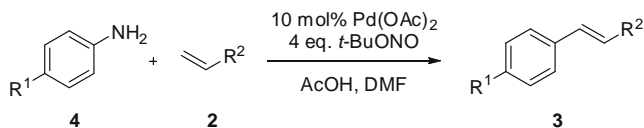| Entry	R^1	R^2	Product[a]	Hal = Br[b] yield (%)	Hal = I[c] yield (%)
1	H (**1a**)	CO_2Me (**2a**)	**3a**[20]	51	68
2	H (**1a**)	Ph (**2b**)	**3b**[21]	25	57
3	H (**1a**)	$4\text{-CF}_3\text{C}_6\text{H}_4$ (**2c**)	**3c**[22]	38	63
4	H (**1a**)	$4\text{-FC}_6\text{H}_4$ (**2d**)	**3d**[23]	22	60
5	H (**1a**)	$3\text{-NO}_2\text{C}_6\text{H}_4$ (**2e**)	**3e**[24]	21	35
6	Me (**1b**)	$4\text{-CF}_3\text{C}_6\text{H}_4$ (**2c**)	**3f**[22]	32	49
7	Me (**1b**)	$4\text{-MeC}_6\text{H}_4$ (**2f**)	**3g**[22]	29	47
8	Me (**1b**)	$3\text{-NO}_2\text{C}_6\text{H}_4$ (**2e**)	**3h**[25]	19	44
9	NO_2 (**1c**)	Ph (**2b**)	**3i**[24]	65	—
10[d]	H (**1a**)	CO_2Me (**2a**)	**3a**	—	97

[a] Reaction conditions: Pd(PPh$_3$)$_4$ (10 mol %), aryl halide (1 mmol), alkene (1 mmol), Et$_3$N (1 mmol), in DMF, residence time: 40 min.
[b] 130 °C (oil bath).
[c] 70 °C (oil bath).
[d] 85 °C (oil bath), residence time: 1 min.

Table 4
Diazonium Heck coupling of aniline derivatives **4**

$$\text{R}^1\text{—C}_6\text{H}_4\text{—NH}_2 \quad + \quad \diagup\diagdown\text{R}^2 \quad \xrightarrow[\text{AcOH, DMF}]{\substack{10 \text{ mol}\% \text{ Pd(OAc)}_2 \\ 4 \text{ eq. } t\text{-BuONO}}} \quad \text{R}^1\text{—C}_6\text{H}_4\text{—CH=CH—R}^2$$

| | | | |
| **4** | | **2** | **3** |

Entry	R^1	R^2	Product[a]	Yield (%)
1	H (**4a**)	CO_2Me (**2a**)	**3a**	54
2	H (**4a**)	Ph (**2b**)	**3b**	66
3	H (**4a**)	$4\text{-FC}_6\text{H}_4$ (**2d**)	**3d**	72
4	OMe (**4b**)	CO_2Me (**2a**)	**3j**[25]	27
5	OMe (**4b**)	Ph (**2b**)	**3k**[25]	33
6	OMe (**4b**)	$3\text{-NO}_2\text{C}_6\text{H}_4$ (**2e**)	**3l**[26]	18
7	Cl (**4c**)	CO_2Me (**2a**)	**3m**[29]	62
8	I (**4d**)	CO_2Me (**2a**)	**3n**[27]	90

[a] Reaction conditions: Pd(OAc)$_2$ (10 mol %), aniline derivative **4** (1 mmol), alkene **2** (1 mmol), t-BuONO (4 mmol), AcOH, DMF, 0–25 °C, residence time: 27 min.[28]

diazonium salt is formed in situ from an aniline derivative under acidic conditions, decomposition follows with rapid elimination of nitrogen gas. As a consequence, diazonium salts may give rapid

and uncontrolled explosions, making their use generally hazardous in conventional flask chemistry especially on large scale. One of the greatest advantages of microflow systems is the safe generation of reactive hazardous intermediates in a continuous flow due to the handling of only very small volumes within a contained environment.

The microflow system set-up for the Heck diazonium reaction was modified as shown in Figure 2 to allow the in situ diazotisation prior to the Pd-catalysed coupling. The aniline derivative **4** was converted into the diazonium intermediate by pumping a mixture of t-butyl nitrite (t-BuONO) with excess of acetic acid and aniline at low temperatures (0 °C) through Section 1. A solution of Pd(OAc)$_2$ and the alkene is then introduced and the Heck reaction can take place in Section 2 at room temperature. A variety of aniline derivatives were reacted with several alkenes using 10 mol % of Pd(OAc)$_2$ successfully as shown in Table 4. Reasonable conversions were initially obtained when a diluted solution of t-BuONO and a standard solution of acetic acid in DMF were used. The reactivity of the diazonium intermediate, largely influenced by the nature of the aniline substrate, has a noticeable effect on the reaction yields. The presence of electron-withdrawing substituents activates the diazonium intermediate whereas electron-donating
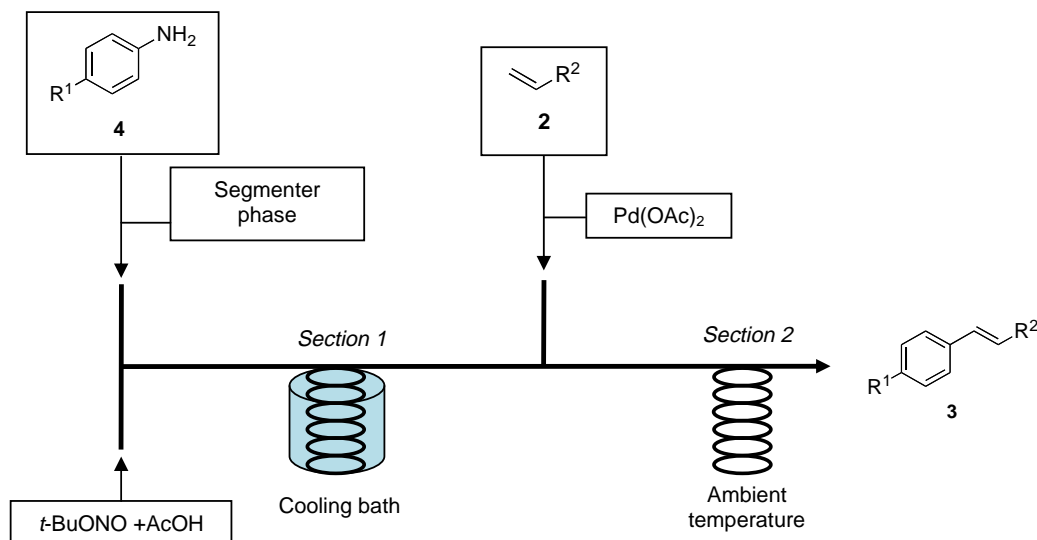
Figure 2. Experimental set-up.

Table 5
Heck coupling of preformed diazonium salt **5** with alkenes **2**
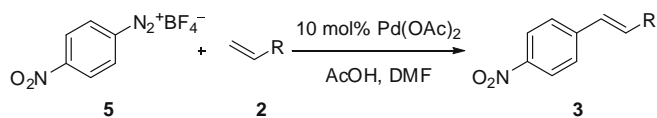
Entry	R	Product[a]	Yield (%)
1	CO$_2$Me (**2a**)	**3o**[29]	64
2	Ph (**2b**)	**3i**	42
3	4-CF$_3$C$_6$H$_4$ (**2c**)	**3p**[30]	57
4	3-NO$_2$C$_6$H$_4$ (**2e**)	**3q**[31]	49
5	4-BrC$_6$H$_4$ (**2g**)	**3r**[32]	61

[a] Reaction conditions: Pd(OAc)$_2$ (10 mol %), aniline derivative **4** (1 mmol), alkene **2** (1 mmol), t-BuONO (4 mmol), AcOH, DMF, 0–5 °C, residence time: 27 min.

substituents make them unreactive, as reflected in the very low yields given by substrates such as *p*-methoxyaniline **4b**, in contrast to the very good conversions achieved using substrates such as *p*-iodoaniline **4d**.

For comparison, we also performed a series of reactions using commercially available *p*-nitrobenzenediazonium tetrafluoroborate **5** to provide an alternative viable route with relatively high product yields as shown in Table 5. By the direct use of an isolated intermediate one could expect cleaner reactions and better yields. However, only small improvements were seen meaning that the in situ production of the diazonium compounds in the microchannel worked rather well.

In conclusion, by utilising the large specific interfacial area provided by the microreactor under segmented flow, the Heck reaction of aryl halides and diazonium intermediates was found to be more efficient than in parallel flow and under conventional (batch) conditions in a flask. This demonstrates that even homogeneous reactions can be enhanced by using the segmented flow technique.

Acknowledgements

References and notes

1. (a) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322; (b) Heck, R. F. *Org. React.* **1982**, *27*, 345–390; (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (d) Knowles, J. P.; Withing, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44; (e) *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009.
2. Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723–1726.
3. Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.
4. Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035–4040.
5. Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835.
6. (a) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008; (b) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem. Eur. J.* **2008**, *14*, 7450–7459; (c) Watts, P.; Wiles, C. *Org. Biomol. Chem.* **2007**, *5*, 727–732; (d) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740; (e) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318.
7. Ahmed-Omer, B.; Wirth, T. In *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008; pp 122–139.
8. (a) Ahmed, B.; Barrow, D.; Wirth, T. *Adv. Synth. Catal.* **2006**, *348*, 1043–1048; (b) Ahmed-Omer, B.; Barrow, D.; Wirth, T. *Chem. Eng. J.* **2008**, *135S*, S280–S283.
9. Harries, N.; Burns, J. R.; Barrow, D. A.; Ramshaw, C. *J. Heat Mass Transfer* **2003**, *46*, 3313–3322.
10. Bhanage, B. M.; Zhao, F.-G.; Shirai, M.; Arai, M. *Tetrahedron Lett.* **1998**, *39*, 9509–9512.
11. (a) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Synlett* **2004**, 1814–1816; (b) Liu, S.; Fukuyama, T.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477–481.
12. Solodenko, W.; Wen, H.; Leue, S.; Stuhlmann, F.; Sourkouni-Argirusi, G.; Jas, G.; Schönfeld, H.; Kunz, U.; Kirschning, A. *Eur. J. Org. Chem.* **2004**, 3601–3610.
13. Karbass, N.; Sans, V.; Garcia-Verdugo, E.; Burguete, M. I.; Luis, S. V. *Chem. Commun.* **2006**, 3095–3097.
14. Nikbin, N.; Ladlow, M.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 458–462.
15. Snyder, D. A.; Noti, C.; Seeberger, P. H.; Schael, F.; Bieber, T.; Rimmel, G.; Ehrfeld, W. *Helv. Chim. Acta* **2005**, *88*, 1–9.
16. Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1734–1737.
17. Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. *Org. Process Res. Dev.* **2008**, *12*, 468–474.
18. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.
19. Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622–4643.
20. Zhou, P.; Li, Y.; Sun, P.; Zhou, J.; Bao, J. *Chem. Commun.* **2007**, 1418–1420.
21. (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; (b) Wang, J. X.; Wang, K.; Zhao, L.; Li, H.; Fu, Y.; Hu, Y. *Adv. Synth. Catal.* **2006**, *348*, 1262–1270.
22. (a) Mu, B.; Li, T.; Xu, W.; Zeng, G.; Liu, P.; Wu, Y. *Tetrahedron* **2007**, *63*, 11475–11488; (b) Warner, P.; Sutherland, R. *J. Org. Chem.* **1992**, *57*, 6294–6300.
23. (a) Pews, R. G.; Ojha, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 5769–5773; (b) Djakovitch, L.; Heise, H.; Kohler, K. *J. Organomet. Chem.* **1999**, *584*, 16–26.
24. Cai, M.; Huang, Y.; Zhao, H.; Song, C. *J. Organomet. Chem.* **2003**, *682*, 20–25.
25. Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2003**, *687*, 269–279.
26. Anstead, G. M.; Katzenellenbogen, J. A. *J. Phys. Chem.* **1988**, *92*, 6249–6258.
27. Brunner, H.; de Courcy, N. L. C.; Genêt, J. P. *Tetrahedron Lett.* **1999**, *40*, 4815–4818.
28. Representative experimental procedure: Stock solutions were prepared in individual Schlenk tubes under inert atmosphere. In a typical experiment, solutions were prepared as follows: (A) 0.1 m solution of aniline (93 mg, 1 mmol) in DMF (10 mL); (B) 0.005 m solution of Pd(OAc)$_2$ (22.4 mg, 0.1 mmol) in DMF (20 mL); (C) 0.2 m solution of alkene (1 mmol) in DMF (5 mL); (D) 0.8m solution of t-BuONO (4 mmol) and AcOH (1.25 mL) in DMF (5 mL); and (E) pure hydrocarbon solvent (hexane, heptane, nonane or decane) used as a segmenting phase. Each solution was loaded individually into gas-tight glass syringes which were then connected onto the microflow system (PTFE) through a designated inlet using a T-connector. Tubing length 2920 mm (section 1 150 mm, residence time 3.2 min) + (section 2 - 2770 mm, residence time 23.7 min), internal diameter 500 μm, and system volume 573 μl. The solutions were then delivered into the microchannel at the required flow rates, in a continuous segmented flow manner using *KD Scientific* syringe pumps. First the diazotisation of aniline was carried out in section 1 at 0 °C by pumping solution (A) along with solutions (D) and (E), while in section 2 solutions (B) and (C) were introduced then mixed with the diazotised flow from section 1 at ambient temperature to carry out the Heck coupling. The reactions were run for the appropriate total residence time of approximately 27 min. After collecting the output of the reaction, the crude mixture was first washed with water followed by 5% aq. sodium bicarbonate solution. After drying the mixture with sodium sulfate, the solvent was removed under reduced pressure. Finally, the product was isolated by preparative TLC / column chromatography on silica gel using an appropriate solvent system.
29. Zhang, Z.; Wang, Z. *J. Org. Chem.* **2006**, *71*, 7485–7487.
30. Hanna, P. E.; Gammans, R. E.; Sehon, R. D.; Lee, M. K. *J. Med. Chem.* **1980**, *23*, 1038–1044.
31. Ling, C.; Minato, M.; Lahti, P. M.; Willigen, H. V. *J. Am. Chem. Soc.* **1992**, *114*, 9959–9969.
32. Choudary, B. M.; Kantam, M. L.; Reddy, N. M.; Gupta, N. M. *Catal. Lett.* **2002**, *82*, 79–83.