Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6575

www.rsc.org/obc

PAPER

Continuous-flow, palladium-catalysed alkoxycarbonylation reactions using a prototype reactor in which it is possible to load gas and heat simultaneously†

Michael A. Mercadante and Nicholas E. Leadbeater*

Received 23rd May 2011, Accepted 1st July 2011
DOI: 10.1039/c1ob05808h

A prototype tube-in-tube reactor in which it is possible to load gas and heat simultaneously has been used in a continuous-flow approach to alkoxycarbonylation reactions of aryl iodides. In the stainless steel coil, liquid flows on the outside of a gas-permeable membrane. The coil can be heated and the temperature can be measured accurately *via* a probe touching the outer steel surface. A range of aryl iodides can be transformed to the corresponding esters in excellent conversion by reaction at 120 °C using 0.5 mol% palladium acetate as the catalyst with no additional ligand required. Small-scale optimization and substrate screening runs were followed by scale-up.

Introduction

Continuous-flow processing on micro- and mesoscale is currently a technology of considerable interest in the synthetic chemistry community.[1,2] It is possible to control reaction parameters very precisely and to perform chemistry across a wide temperature range very effectively. One class of reactions that has attracted is that involving reactive gases. Hydrogenation reactions can be performed using the now ubiquitous H-cube system.[3,4] Gases such as oxygen,[5] fluorine,[6] and dimethylsulfide[7] have also been used in flow. One of the key considerations when performing reactions involving gaseous reagents, is the ability to introduce the gas into the reaction mixture effectively. Typically this is achieved by plug flow or mixing of two phases.

Our laboratory recently took the plug flow approach to the palladium-mediated carbonylation of aryl iodides in ethanol to prepare ethyl esters.[8] Palladium acetate (0.5 mol%) was used as the catalyst with no additional ligand required. We introduced the carbon monoxide gas through a back-pressure regulator and at an angle of 90° to the liquid flow. The gas/liquid flow then entered a coiled tube reactor heated to 120 °C. An issue associated with this approach was the necessity to control very carefully the gas flow in order to obtain satisfactory product yields. In addition, a large excess of toxic carbon monoxide gas was used in the reaction.

Recently, a way to alleviate some operational issues with performing reactions involving gaseous reagents has been reported by Ley and co-workers.[9–11] They use a "tube in tube" approach (comprising of an outer PTFE tube in which a gas-permeable Teflon AF2400 tube is inserted) to load gas into either a solvent or reagent stream. This allows the flow of liquid within the membrane tubing while the gas fills the PTFE outer tubing and diffusion transfers the gas into the liquid stream. This approach has been successful for numerous reactions including the ozonolysis of alkenes,[9] carboxylation of Grignard reagents with carbon dioxide[10] and both homogeneous and heterogeneous hydrogenation reactions.[11] All reactions were performed at room temperature. In the case of ozonolysis, carboxylation and homogeneous hydrogenation, the reagents are flowed through the tube-in tube unit, loading gas and allowing the reaction to proceed. When performing heterogeneous hydrogenation reactions, the reagents are passed through the tube-in-tube unit to load the solution with hydrogen before passing into a cartridge of palladium on carbon. To convert all the starting material to product it was necessary to recycle the reagent mixture through the entire system a number of times.[11] This illustrates one of the limitations of the tube-in-tube approach in its current configuration. When passing reagents through either a supported catalyst/reagent bed or through a heated zone, the reaction is limited by the quantity of gas that can be loaded into the solution in the tube-in-tube unit beforehand. This necessitates running reactions at more dilute concentrations or else performing multiple passes through the entire system. Recently we have had access to a prototype tube-in-tube reactor in which it is possible to load gas into a heated reaction as it is consumed. In a proof-of-concept study we have used this to perform our palladium-catalysed alkoxycarbonylation reactions and present our results here.

Results and discussion

Our prototype reactor comprises of a coil of stainless steel tubing through which liquid flows on the outside of a gas-permeable inner membrane. The fact that the coil is made of stainless steel and that the liquid is in contact with the outer wall means that the coil (a) is rugged, (b) can be heated or cooled and (c) the liquid temperature can be measured accurately *via* a probe touching the

---

Department of Chemistry, University of Connecticut, 55 North Eagleville Rd, Storrs, CT, 06269-3060, USA. E-mail: nicholas.leadbeater@uconn.edu; Fax: +1 860 486 2981; Tel: +1 860 486 5076

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05808h

Table 1 Optimisation of conditions for the alkoxycarbonylation reaction

Entry	Reaction conditions[a,b]	Conversion (%)[b]
1	Pass through one coil at 0.5 mL min^{-1}	38
2	Pass through one coil at 0.25 mL min^{-1}	46
3	Pass through two coils at 0.5 mL min^{-1}	60
4	Pass through two coils at 0.25 mL min^{-1}	97

[a] Reactions were performed on the 5 mmol scale at 1 M concentration, 0.5 mol% Pd(OAc)$_2$ as catalyst, 1.1 eq DBU as base, a gas pressure of 180 psi and a reagent flow rate of 0.25 mL min^{-1} through two ~15 mL liquid volume coils heated to 120 °C and exiting through a 250 psi back-pressure regulator. [b] Determined using ^{1}H NMR spectroscopy.

outer steel surface. The reactor has a working liquid volume of approximately 15 mL when the inner gas tube is inflated. Gas and reagents enter the coil in a counter-current manner, the gas coming in where the reagents exit and *vice versa*. Our first step was to find suitable conditions for the alkoxycarbonylation reaction, the results being shown in Table 1. We initially passed ethanol through the coil and out through a 250 psi back-pressure regulator at a flow rate of 0.5 mL/min. We gradually increased the gas pressure to 180 psi and then heated the coil to 120 °C. Once stabilized we saw a constant stream of bubbles after the back-pressure regulator but none before it indicating the carbon monoxide was indeed dissolving in the ethanol as desired. We then flowed the reagents through the coil at 0.5 ml min^{-1} maintaining the gas pressure at 180 psi. We used 4-iodotoluene (5 mmol) as our aryl halide starting material, ethanol as the nucleophile and solvent (5 mL), DBU (1.1 eq) as base and 0.5 mol% Pd(OAc)$_2$ as catalyst. Following the stream of reagents we again passed ethanol through the reactor. As the product mixture began to emerge through the back-pressure regulator at the end of the reactor, we observed that the gas bubbles initially subsided and then stopped entirely. Towards the time that the product stream was fully exiting the coil the bubbles started appearing again after the back-pressure regulator. This told us that the reaction was gas-limited and this was exemplified by the 38% conversion to product that we obtained (Table 1, entry 1). We performed a second trial, this time reducing the flow rate to 0.25 mL/min. While this resulted in a somewhat improved conversion of 46%, the reaction was still gas limited (Table 1, entry 2). We turned next to running two gas reactors in series. Working at 0.5 mL min^{-1} we obtained a 60% conversion but running at 0.25 mL min^{-1} increased this to 97% (Table 1, entries 3 and 4). In addition, we saw bubbles of CO after the back-pressure regulator throughout the run, showing us that the reaction was no longer gas-limited. Thus, our optimised reaction conditions were: 1 M aryl iodide in ethanol, 0.5 mol% Pd(OAc)$_2$ as catalyst, 1.1 eq DBU as base, a gas pressure of 180 psi and a reagent flow rate of 0.25 mL min^{-1}, through two ~15 mL liquid volume coils heated to 120 °C and exiting through a 250 psi back-pressure regulator. A pictorial representation of our optimised configuration is shown in Fig. 1.

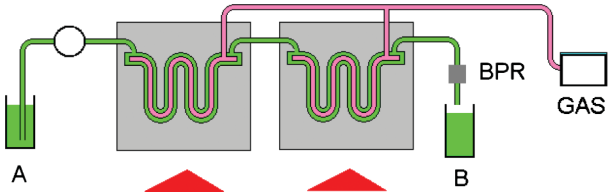
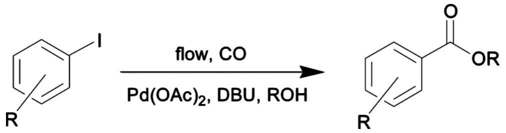
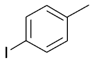
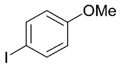
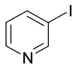
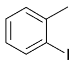
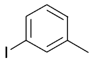
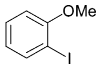
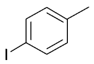
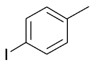


Fig. 1 Optimised flow configuration.

Table 2 Alkoxycarbonylation of aryl halides[a]



Entry	Aryl halide	Alcohol	Conversion (%)[b,c]
1		EtOH	91
2		EtOH	98
3		EtOH	95
4		EtOH	98
5		EtOH	98
6		EtOH	95
7		*n*-PrOH	99
8		*i*-PrOH	99

[a] Reactions were performed on the 5 mmol scale at 1 M concentration, 0.5 mol% Pd(OAc)$_2$ as catalyst, 1.1 eq DBU as base, a gas pressure of 180 psi and a reagent flow rate of 0.25 mL min^{-1} through two ~15 mL liquid volume coils heated to 120 °C and exiting through a 250 psi back-pressure regulator. [b] Determined using ^{1}H NMR spectroscopy. [c] Our earlier work, both using batch microwave heating[12] and continuous plug-flow[8] has shown that product conversion is a very close measure for isolated product yields for these alkoxycarbonylation reactions.

With the optimised conditions in hand, we screened a range of aryl iodides to probe substrate scope. Our results are shown in Table 2. On the 5 mmol scale, working at a reagent concentration of 1 M, a range of aryl iodides could be converted to the ethyl esters including *ortho*-substituted examples (Table 2, entries 4 and 6). A representative heteroaromatic substrate, 3-iodopyridine, gave a good conversion of the desired ester (Table 2, entry 3). Both 1-propanol and 2-propanol can be used as the alcohol for the reaction (Table 2, entries 7 and 8). Product conversions were as good, and in many cases better, than those obtained in our previous plug-flow approach.[8]

Our next objective was to determine the scalability of the reaction. It occurred to us that as we were passing relatively small portions of reagents through the coils during our reaction optimization and substrate screening studies, there may be some considerable dispersion in the length of the two reactors. Therefore, although we were passing reagents into the flow reactor at a concentration of 1 M, it may be that steady-state is not achieved and that the concentration of the reaction mixture as it passes through the length of the two coils may be lower. To probe this, we performed the reaction using 4-iodotoluene on the 25 mmol scale, therefore passing 50 mL of reaction mixture through the system. As the product mixture exited the flow reactor, we collected fractions of 10 mL. Immediately noticeable was that in the middle of the run we saw no gas bubbles emerging beyond the back-pressure regulator, this suggesting that the reaction may have become gas limited when the reagents had reached a steady-state concentration in the reactors. Analysis of representative fractions from the product stream confirmed this. While at the start of the run and towards the end we obtained conversion of 98%, during the middle this dropped to 77%. We repeated the 50 mL run but this time inputting a reagent solution that was 0.75 M in iodoarene. Again at the start and the end of the run we obtained near-quantitative conversion. An improvement was observed during the middle of the run (86% conversion), but the reaction was still gas limited. Performing the 50 mL run inputting a reagent solution that was 0.5 M in iodoarene led to a 98% conversion throughout and gas bubbles were clearly seen after the back-pressure regulator. This shows that, due to dispersion factors, while smaller-scale trails can be performed at higher input reagent concentrations, scale-up may require operating at more dilute conditions.

Experimental section

General experimental

All aryl iodides were obtained from commercial suppliers and used without further purification. For the alcohol substrates: ethanol used was 200 proof (anhydrous); commercially available anhydrous 1-propanol and 2-propanol were used. Reactions were run without the need for exclusion of air. ^{1}H-NMR spectra were recorded at 293 K on either a 300 MHz or 400 MHz spectrometer, products being characterized by comparison with literature data or in-house samples.

Apparatus

Experiments were performed on a Vapourtec R series.[13] The system was equipped with two gas loading reactor coils. The "reagent out" port on the first reactor coil was connected to the second reactor coil "reagent in" port using a 32 mm length of tubing. The "reagent out" port of the second reactor was equipped with a 250 psi back pressure regulator after which a length of tubing led to a waste or collection flask. To load the reagent gas to each reactor, the tubing from the gas tank was equipped with a T-piece and connected to the "gas in" ports on each reactor coil. The "gas out" ports were plugged. At this point the system was then primed and flushed with anhydrous ethanol for ~5 min at 8 mL min^{-1}. The pump was turned off to prime the gas line. The plugs on the "gas out" were loosened and the carbon monoxide tank, was fitted with a regulator capable of delivering pressures of up to 250 psi, was opened at 180 psi. CAUTION: Make sure the "gas out" apertures vent into a fumehood since carbon monoxide is toxic and may be fatal if inhaled in significant quantities. After 10 s of venting, the gas flow was turned off while continuing to vent into the hood. The "gas out" plugs were then closed. Next, the system pump was set to "solvent" and the flow rate set to 0.250 mL min^{-1} while heating each reactor to 120 °C. Once the system pressure reached ~60 psi (~4 bar) the gas was turned on at 180 psi for the duration of the experiment. The system was then allowed to continue to pressurize from liquid flow, until it reached 250–275 psi (~19 bar). At this pressure, gas bubbles are present after the back pressure regulator. Once a constant bubble stream is seen, the system is ready for loading the reagents.

General procedure for alkoxycarbonylation reactions on the 5 mmol scale: The ethoxycarbonylation of 4-iodotoluene

To a 10 mL test tube was added anhydrous ethanol (5 mL), followed by DBU (0.820 mL, 5.5 mmol, 1.1 equiv.). The solution was thoroughly mixed before adding $Pd(OAc)_2$ (5.0 mg, 0.022 mmol). The solution was again mixed thoroughly. If upon examining the test tube particulate matter remained, the mixture was gently heated until no particles remained.

With this solution prepared, the flow reactor was readied. Once this was complete, 4-iodotoluene (1.09 g, 5 mmol) was added to the test tube containing the other reaction components and mixed thoroughly. The reagent line was then placed inside the prepared solution, reaching the bottom of the tube. The line was secured to the test tube and the reactor pump switched from "solvent" to "reagent". Product collection was commenced immediately after this switch. After the reaction mixture had been completely inputted into the reactor, the reactor pump was turned back to "solvent".

To the product mixture was added diethyl ether (50 mL) followed by a volume (about 80 mL) of brine and the biphasic mixture transferred to a 500 mL separatory funnel. The layers were separated and the aqueous layer was re-extracted with diethyl ether 3 times (equal volumes, about 80 mL each). The combined organic layers were then mixed with an equal volume (about 300 mL) of hexanes. This facilitated removal of ethanol from the diethyl ether layer. After waiting about 10 min the ethanol layer was removed. The diethyl ether layer was then dried with Na_2SO_4 and filtered. The solvent was removed by rotary evaporation and the product conversion determined by ^{1}H-NMR spectroscopy.[14,15]

General procedure for alkoxycarbonylation reactions on the 25 mmol scale: The ethoxycarbonylation of 4-iodotoluene

To a 125 mL Erlenmeyer flask was added anhydrous ethanol (50 mL), followed by DBU (4.1 mL, 27.5 mmol, 1.1 equiv.). The solution was thoroughly mixed before adding $Pd(OAc)_2$ (28 mg, 0.125 mmol, 0.5 mol%). The solution was again mixed thoroughly. If upon examining the test tube particulate matter remained, the mixture was gently heated until no particles remained.

With this solution prepared, the flow reactor was readied. Once this was complete, 4-iodotoluene (5.45 g, 25 mmol) was added to the flask containing the other reaction components and mixed thoroughly. The reagent line was then placed inside the prepared solution, reaching the bottom of the flask. The line was secured to the flask and the reactor pump switched from "solvent" to "reagent". Aliquots of 10 mL exiting the reactor were collected and then the product mixture isolated and analyzed using the same procedure as for the smaller-scale trials.

Conclusion

In summary, a prototype tube-in-tube reactor in which it is possible to load gas and heat simultaneously has been used for continuous-flow alkoxycarbonylation reactions of aryl iodides. A range of aryl iodides can be transformed to the corresponding esters in excellent conversion by reaction at 120 °C using 0.5 mol% palladium acetate as the catalyst with no additional ligand required. Small-scale optimization and substrate screening runs were followed by scale-up. Due to dispersion factors, while smaller-scale trails can be performed at 1 M input reagent concentrations, scale-up required operating at 0.5 M. The methodology using the heated tube-in-tube reactor was found to be operationally far superior to a plug-flow approach. No longer was it necessary to painstakingly optimize bubble size and use a significant excess of carbon monoxide gas. An additional benefit was that the significant build up of palladium black at the point of exit through the back-pressure regulator that occurred with the plug-flow approach due to excess CO poisoning the catalyst was no longer an issue when using the heated tube-in-tube reactor. Work is now underway to use the reactor for other chemical transformations, including expanding the substrate scope of the alkyoxycarbonylation methodology to aryl bromides and chlorides by using a phosphine-ligated palladium complex as the catalyst.

Acknowledgements

Vapourtec is thanked for equipment support. David Griffin and Duncan Guthrie are particularly thanked for their input. Funding from the National Science Foundation (CAREER award CHE-0847262) is acknowledged.

Notes and references

1 For an overview see: *Chemical Reactions and Processes under Flow Conditions*, S. V. Luis and E. Garcia-Verdugo, ed., Royal Society of Chemistry, Cambridge UK, 2010.

2 For recent reviews see: (*a*) C. Wiles and P. Watts, *Chem. Commun.*, 2011, **47**, 6512, DOI: 10.1039/c1cc00089f; (*b*) J. Wegner, S. Ceylan and A. Kirschning, *Chem. Commun.*, 2011, **47**, 4583–4592; T. Razzaq and C. O. Kappe, *Chem. Asian J.*, 2010, **5**, 1274; (*c*) D. Mark, S. Haeberle, G. Roth, F. von Stetten and R. Zengerle, *Chem. Soc. Rev.*, 2010, **39**, 1153; (*d*) N. Kockmann and D. M. Roberge, *Chem. Eng. Technol.*, 2009, **32**, 1682; (*e*) C. Wiles and P. Watts, *Eur. J. Org. Chem.*, 2008, 1655.

3 http://www.thalesnano.com/products/h-cube.

4 For selected recent examples see: (*a*) M. Baumann, I. R. Baxendale and S. V. Ley, *Synlett*, 2010, **5**, 749; (*b*) B. Clapham, N. S. Wilson, M. J. Michmerhuizen, D. P. Blanchard, D. M. Dingle, T. A. Nemcek, J. Y. Pan and D. R. Sauer, *J. Comb. Chem.*, 2008, **10**, 88; (*c*) H. H. Horvath, G. Papp, C. Csajagi and F. Joo, *Catal. Commun.*, 2007, **8**, 442; (*d*) G. Szoellosi, B. Herman, F. Fulop and M. Bartok, *React. Kinet. Catal. Lett.*, 2006, **88**, 391; (*e*) V. Franckevicius, K. R. Knudsen, M. Ladlow, D. A. Longbottom and S. V. Ley, *Synlett*, 2006, **6**, 889; (*f*) R. V. Jones, L. Godorhazy, N. Varga, D. Szalay, L. Urge and F. Darvas, *J. Comb. Chem.*, 2006, **8**, 110.

5 For selected recent examples see: (*a*) X. Ye, M. D. Johnson, T. Diao, M. H. Yates and S. S. Stahl, *Green Chem.*, 2010, **12**, 1180; (*b*) S. Hübner, U. Bentrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Küpper and K. Jähnisch, *Org. Process Res. Dev.*, 2009, **13**, 952; (*c*) B. N. Zope and R. J. Davis, *Top. Catal.*, 2009, **52**, 269; (*d*) A. Lapkin, B. Bozkaya and P. K. Plucinski, *Ind. Eng. Chem. Res.*, 2006, **45**, 2220.

6 (*a*) K. Jahnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Lowe, C. Wille and A. Guber, *J. Fluorine Chem.*, 2000, **105**, 117; (*b*) C. B. McPake, C. B. Murray and G. Sandford, *Tetrahedron Lett.*, 2009, **50**, 1674.

7 A. Kumar, T. Chilongo, J. Dewulf, S. J. Ergas and H. Van Langenhove, *Bioresour. Technol.*, 2010, **101**, 8955.

8 C. B. Kelly, C. Lee, M. A. Mercadante and N. E. Leadbeater, *Org. Process Res. Dev.*, 2011, **15**, 717–720.

9 M. O'Brien, I. R. Baxendale and S. V. Ley, *Org. Lett.*, 2010, **12**, 1596.

10 A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale and S. V. Ley, *Angew. Chem., Int. Ed.*, 2011, **50**, 1190.

11 M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, 2011, **2**, 1250–1257.

12 (*a*) C. M. Kormos and N. E. Leadbeater, *Org. Biomol. Chem.*, 2007, **5**, 65; (*b*) M. D. Bowman, J. R. Schmink, C. M. McGowan, C. M. Kormos and N. E. Leadbeater, *Org. Process Res. Dev.*, 2008, **12**, 1078; (*c*) M. Iannelli, F. Bergamelli, C. M. Kormos, S. Paravisi and N. E. Leadbeater, *Org. Process Res. Dev.*, 2009, **13**, 634.

13 http://www.vapourtec.co.uk/.

14 Literature data for compounds prepared in this study – Table 2, entries 1–6: R. Shang, Y. Fu, J. B. Li, S. L. Zhang, Q. X. Guo and L. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 5738 Table 2, entry 8: Q. Liu, G. Li, J. He, J. Liu, P. Li and A. Lei, *Angew. Chem. Int. Ed. Engl*, 2010, **49**, 3371.

15 Table 2, entry 7 – Propyl-4-methylbenzoate: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (t, J = 7.51 Hz, 3 H) 1.79 (m, J = 7.17 Hz, 2 H) 2.40 (s, 3 H) 4.26 (t, J = 6.66 Hz, 2 H) 7.23 (d, J = 7.85 Hz, 1 H) 7.94 (d, J = 8.19 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 10.78, 21.88, 22.39, 66.59, 128.06, 129.28, 129.81, 143.66, 167.01. MS (EI): 178 (M+, 6%), 136 (71%), 119 (100%), 91 (45%), 65 (15%), 39 (4%). HRMS (ESI+), calcd for $C_{11}H_{14}O_2$[M]+: 179.1072, found 179.1055. FTIR (cm^{-1}, neat, ATR) 3039 (w), 2965 (m), 2878 (w), 1713 (s), 1613 (m), 1461 (w), 1265 (vs), 1174 (m), 1104 (s), 748 (s).