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Flow Chemistry: Intelligent Processing of Gas–Liquid Transformations Using a Tube-in-Tube Reactor

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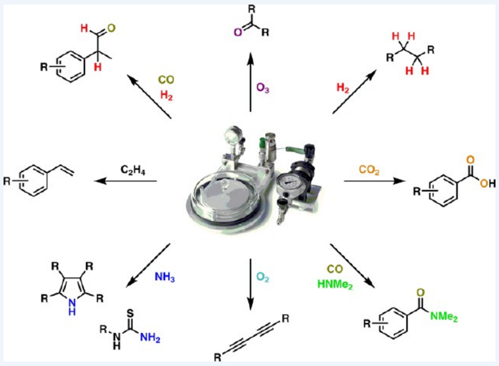
CONSPECTUS: The previous decade has witnessed the expeditious uptake of flow chemistry techniques in modern synthesis laboratories, and flow-based chemistry is poised to significantly impact our approach to chemical preparation. The advantages of moving from classical batch synthesis to flow mode, in order to address the limitations of traditional approaches, particularly within the context of organic synthesis are now well established. Flow chemistry methodology has led to measurable improvements in safety and reduced energy consumption and has enabled the expansion of available reaction conditions. Contributions from our own laboratories have focused on the establishment of flow chemistry methods to address challenges associated with the assembly of complex targets through the development of multistep methods employing supported reagents and in-line monitoring of reaction intermediates to ensure the delivery of high quality target compounds.

Recently, flow chemistry approaches have addressed the challenges associated with reactions utilizing reactive gases in classical batch synthesis. The small volumes of microreactors ameliorate the hazards of high-pressure gas reactions and enable improved mixing with the liquid phase. Established strategies for gas–liquid reactions in flow have relied on plug-flow (or segmented flow) regimes in which the gas plugs are introduced to a liquid stream and dissolution of gas relies on interfacial contact of the gas bubble with the liquid phase. This approach confers limited control over gas concentration within the liquid phase and is unsuitable for multistep methods requiring heterogeneous catalysis or solid supported reagents.

We have identified the use of a gas-permeable fluoropolymer, Teflon AF-2400, as a simple method of achieving efficient gas–liquid contact to afford homogeneous solutions of reactive gases in flow. The membrane permits the transport of a wide range of gases with significant control of the stoichiometry of reactive gas in a given reaction mixture. We have developed a tube-in-tube reactor device consisting of a pair of concentric capillaries in which pressurized gas permeates through an inner Teflon AF-2400 tube and reacts with dissolved substrate within a liquid phase that flows within a second gas impermeable tube.

This Account examines our efforts toward the development of a simple, unified methodology for the processing of gaseous reagents in flow by way of development of a tube-in-tube reactor device and applications to key C–C, C–N, and C–O bond forming and hydrogenation reactions. We further describe the application to multistep reactions using solid-supported reagents and extend the technology to processes utilizing multiple gas reagents. A key feature of our work is the development of computer-aided imaging techniques to allow automated in-line monitoring of gas concentration and stoichiometry in real time. We anticipate that this Account will illustrate the convenience and benefits of membrane tube-in-tube reactor technology to improve and concomitantly broaden the scope of gas/liquid/solid reactions in organic synthesis.



1. INTRODUCTION

Reactive gases are valuable reagents for a multitude of chemical transformations and serve as critical feedstocks for pharmaceuticals, crop-enhancing additives, polymers, and advanced materials. Gases are ideal reagents because reaction products can often be isolated by simply venting excess gas from the reaction vessel. Raising the pressure to provide a stoichiometric excess of reagent offers a simple means of driving a reaction to completion, with the low cost of gases readily enabling such an approach. High pressure reactions often necessitate expensive specialized equipment or purpose built facilities and additional safety precautions, while the use of toxic, flammable, and corrosive gases generates significant hazards that are intensified by scale.

To address these limitations, we and other groups have advocated the use of continuous flow techniques[1−4] to overcome the challenges associated with gas–liquid reactions. Small volume (microliter to milliliter) microreactors significantly reduce the hazards of high-pressure gas reactions, promote rapid interphase mixing, and improve mass- and thermal transfer with small channel diameters (micrometer to millimeter) of the microreactors conferring well-defined, large interfacial area.

Our initial contribution to the field began with the continuous flow hydrogenation of imines[5] utilizing an electrochemically generated hydrogen source (H-Cube).[6] Continuous flow processing has

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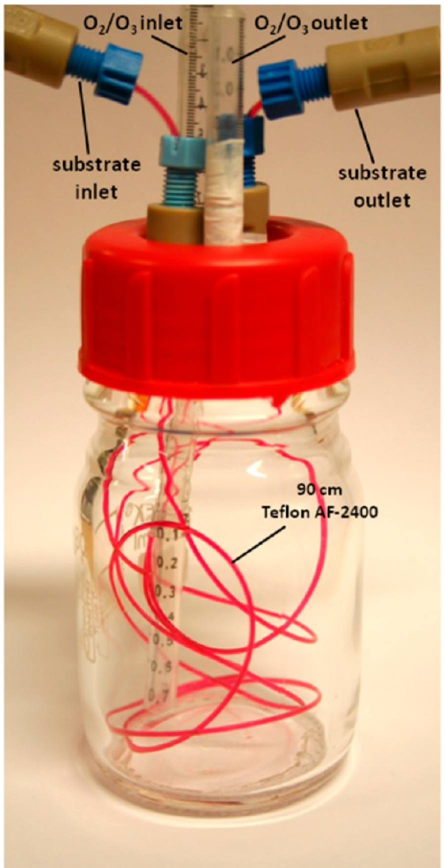


Figure 1. Proof-of-concept reactor.

Scheme 1. Flow Ozonolysis of Alkenes

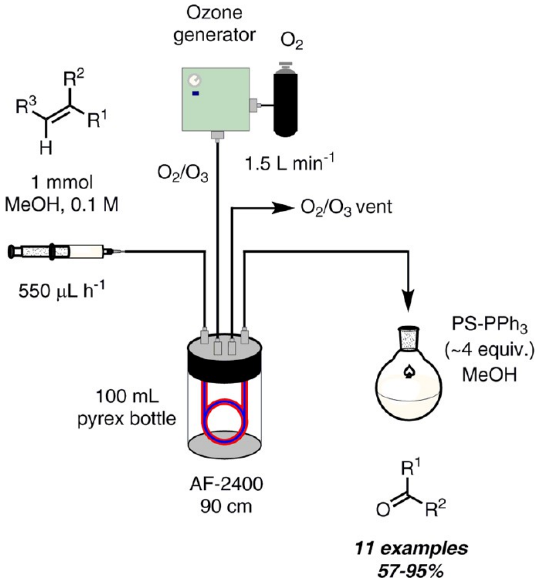
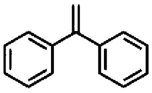
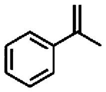
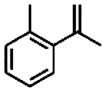
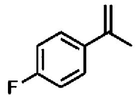
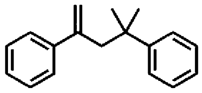
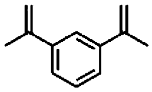
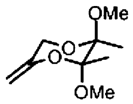
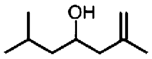
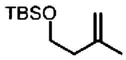
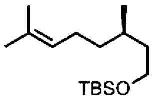
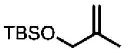


Table 1. Scope of Flow Ozonolysis

Substrate	Structure	Conv. (%)[a]	Yield (%)[b]
1a		100	87
1b		100	83
1c		100	93
1d		100	95
1e		100	88
1f		100	2[c] (75)[d]
1g		100	73
1h		100	90
1i		100	93
1j		100	57
1k		100	76

[a]Determined by ^{1}H NMR. [b]Isolated yields after column chromatography. [c]Monoketone product. [d]Bisketone product (5% dimethyl-acetal also formed).

also been applied to gas–liquid reactions such as carbonylation,[7] aerobic oxidation,[8] ozonolysis,[9] and fluorination.[10] These approaches have, however, generally relied on mechanical mixing of the two phases, leading to inefficient mixing. Microporous gas-permeable materials afford a practically simple method of achieving efficient gas–liquid contact by generating homogeneous solutions of gas.[11] Teflon AF-2400 is an amorphous glassy copolymer of fluoroethylene and perfluorodioxolane that displays high permeability to a range of gases while remaining impermeable to (nonfluorinated) liquids and resistant to a variety of corrosives.[12] We envisaged a device to modulate gas permeation across the membrane into a monophasic solution, thus, allowing precise control of reactive gas stoichiometry, which remains a significant challenge in multiphase reaction development.

In this Account, we will discuss the development of such a reactor device and accompanying continuous flow methodology to a range of organic transformations. We also describe the integration of the flow reactor technology into multistep processes in conjunction with solid-supported reagents for purification and computer-aided imaging methods for real time in-line gas quantitation.

2. GAS–LIQUID REACTIONS BASED ON TEFLON AF-2400

2.1. Proof-of-Concept

Our initial interest in gas–liquid flow chemistry was inspired by the ubiquity of ozonolysis in synthesis.[13] A continuous flow method would imbue an improved safety profile through the use of reduced volumes of gas. By continuous quenching of the

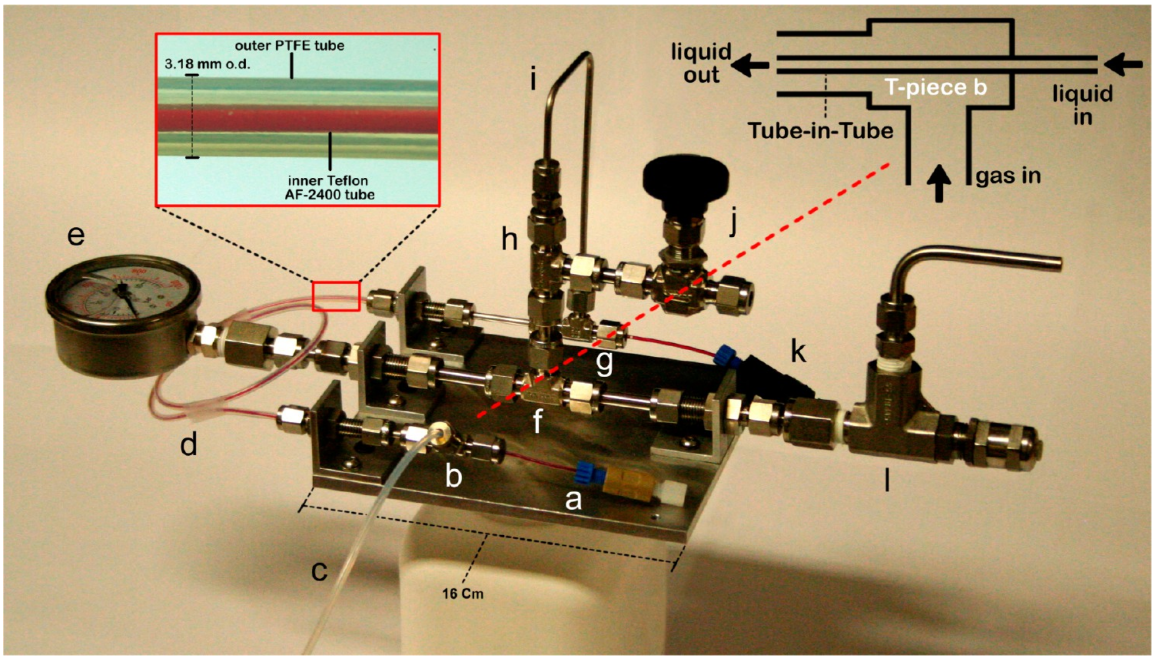
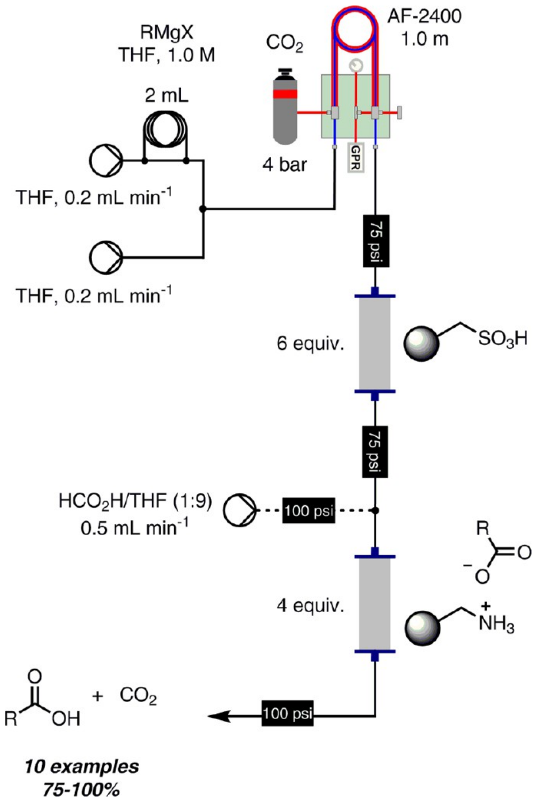
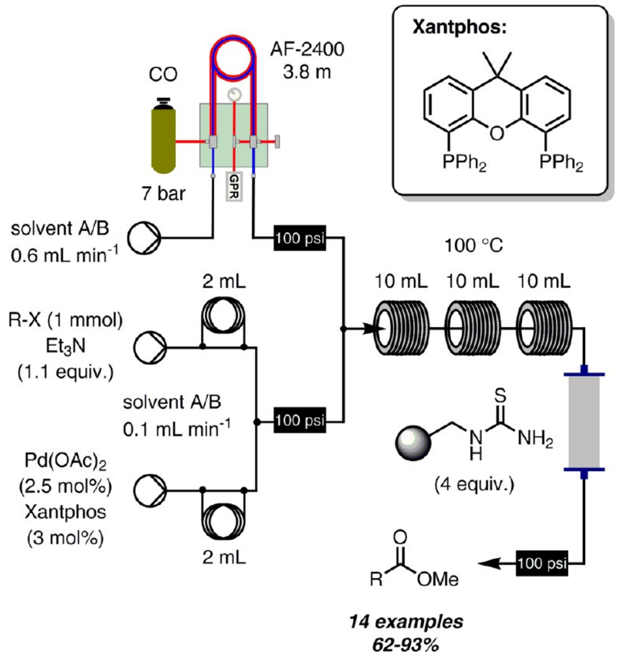


Figure 2. Prototype reactor: (a) solution inlet; (b) T-piece; (c) gas inlet; (d) tube-in-tube (inner tube, 0.8 mm od Teflon AF-2400; outer tube, 1/8 in. od PTFE); (e) pressure gauge; (f, g, h) T-piece; (i) 1/8 in. connector; (j) needle valve; (k) solution outlet; (l) pressure relief valve. Left inset, tube-in-tube internal configuration. Right inset, schematic of T-piece connection.

Scheme 2. Flow Carboxylation of Grignard Reagents



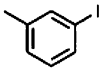
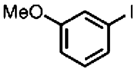
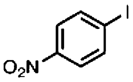
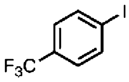
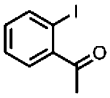
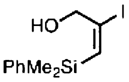
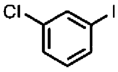
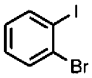
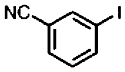
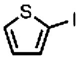
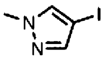
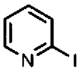
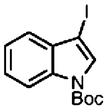
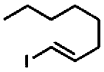
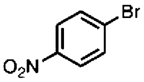
Scheme 3. Continuous Flow Methoxycarboxylation[a]



[a] Solvent A = PhMe/MeOH/DMF (45:45:10); solvent B = 1,4-dioxane/MeOH (1:1).

ozonide intermediates, the concentration of these hazardous species is kept to a minimum. In 2010, we described a bespoke apparatus that permitted flow ozonolysis reactions to be conducted in a convenient and safe manner.[14] The apparatus consisted of a length of Teflon AF-2400 tubing passed through a chamber supplied with ozone (diluted with oxygen) (Figure 1). Permeation of O_3 across the membrane was demonstrated by bleaching a 1 mM dye solution. Initial experiments determined that exposing a 0.1 M flow stream of 1,1-diphenylethene in methanol to O_3 for 1 h readily effected alkene cleavage. A series of alkenes were ozonolyzed by passage through the gas–liquid reactor, which was supplied with O_3 at a rate of 1.5 L min^{-1}, and then quenched into polymer-supported PPh_3 (Scheme 1). A 1 h residence time effected 100% conversion for all substrates with good to excellent isolated yields (Table 1).

Table 2. Scope of Continuous Flow Methoxycarbonylation

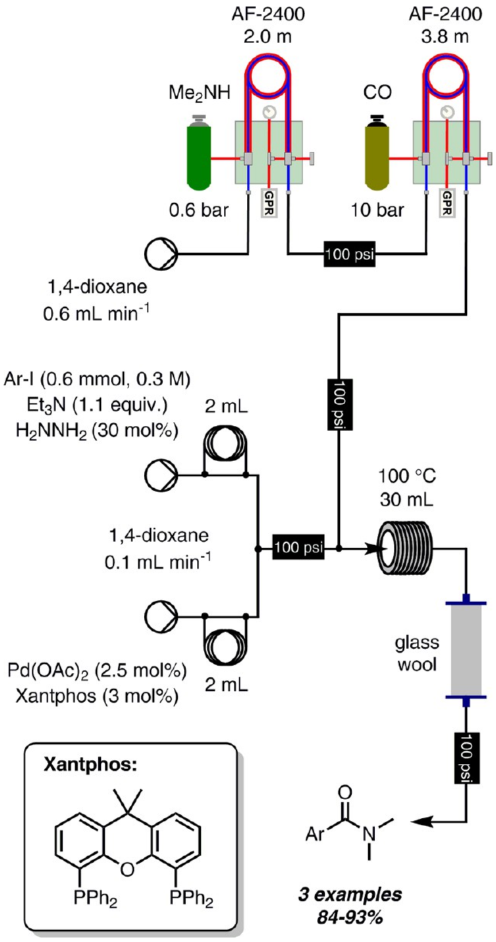
Substrate	Structure	Solvent[a]	Yield (%)[b] (Conv.) (%)[c]
2a		A	70 (85)
2b		A	63 (78)
2c		A	81 (95)[d]
2d		A	88 (95)
2e		A	(11)[e]
2f		A B	38 (95)[f] 83 (100)[g,h]
2g		A	93 (95)
2h		B	69 (77)[h,i,j]
2i		A	72 (90)
2j		A	71 (85)
2k		A B	43 (60)[e] 65 (73)[h,j]
2l		B	62 (88)[h,j]
2m		B	62 (100)[j]
2n		B	81 (100)[i,k]
2o		B	72 (94)[h,i,j,l] 77 (90)[h,i,j]

[a] Solvent A = PhMe/MeOH/DMF (45:45:10); solvent B = 1,4-dioxane/MeOH (1:1). [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR. [d] Substrate/base introduced in DMF. [e] Rapid Pd(0) precipitation. [f] 50 °C. [g] $Pd(OAc)_2$ (5 mol %), no Xantphos, CO (15 bar), 25 °C. [h] No thiourea cartridge. [i] $Pd(OAc)_2$ (5 mol %), Xantphos (6 mol %). [j] Hydrazine (30 mol %, 1.0 M THF solution), CO (15 bar). [k] CO (15 bar), 25 °C. [l] 120 °C.

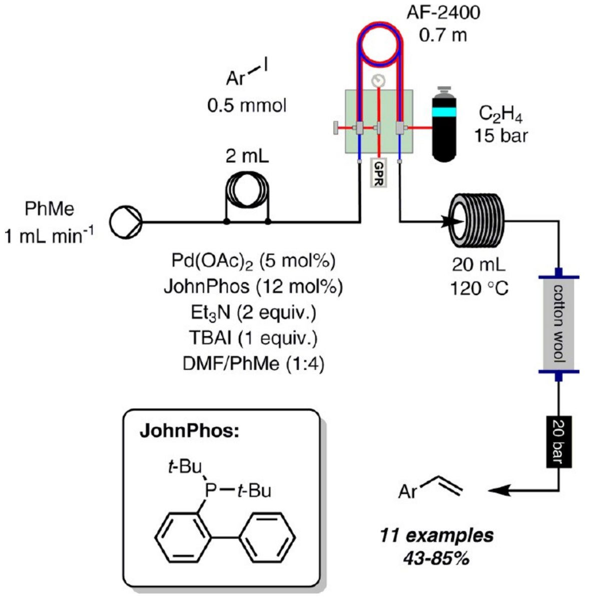
2.2. The Development of a Prototype Reactor

Following the successful proof-of-concept study, we developed a prototype reactor that enabled variable temperature and pressure control (Figure 2). The reactor was configured so that the substrate stream passed through a length of Teflon AF-2400 tubing that was fixed within larger diameter PTFE tubing filled with reactive gas. The inner and outer tubing was separated by Swagelok T-pieces that allowed for precise control of the pressure and flow rate of both of the inputs. The reactor contained a maximum gas volume of 1.5 mL per meter of tubing, offering a safe and convenient means of handling pressurized gases.

Scheme 4. Continuous Flow Dimethylaminocarbonylation



Scheme 5. Continuous Flow Heck Vinylation



The application of the prototype reactor was exemplified by the carboxylation of Grignard reagents.[15] Gaseous carbon dioxide (CO_2) is an attractive feedstock because it is a nontoxic,

Scheme 6. Continuous Flow Hydroformylation

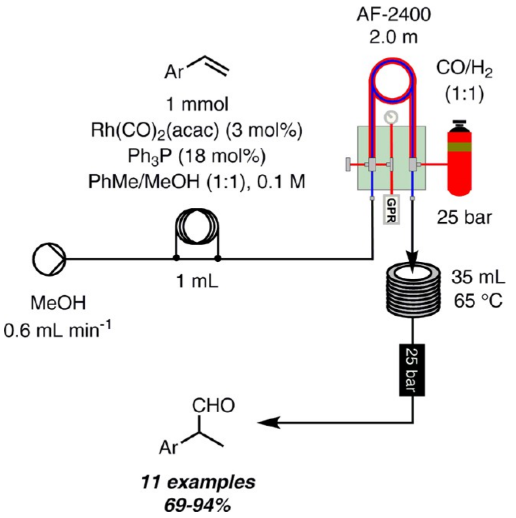
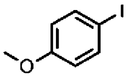
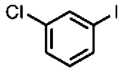
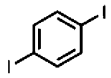
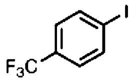
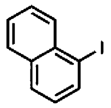
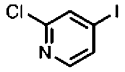
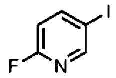
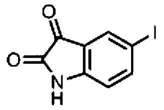
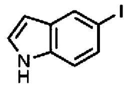
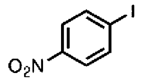
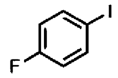
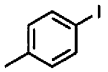


Table 3. Substrate Scope for Modified Heck Vinylation Conditions[a]

Substrate	Structure	Yield (%)[b] (Conv.) (%)[c]
3a		84[d] (92)
3b		82 (89)
3c		95 (99)
3d		90 (99)
3e		90 (99)
3f		68[g,h] (82)
3g		–[e,g,h] (99)
3h		95[f,h] (99)
3i		95[h] (97)
3j		95[h] (97)
3k		91 (99)
3l		–[e] (97)

[a] See Scheme 5 for flow configuration. Reaction conditions: iodide (0.3 mmol, 0.5 M), Cy_2NMe (1.2 equiv), $Pd(OAc)_2$ (1 mol %), t-$Bu_3P{\cdot}HF_4$ (2 mol %), TBAI (0.1 equiv), MeOH/PhMe (1:9), 130 °C, T_R = 20 min, ethylene (10 bar), AF-2400 (l = 0.7 m). [b] Isolated yield after distillation. [c] Determined by GC-MS. [d] Scale, 0.12 mol; $Pd(OAc)_2$ (0.5 mol %), DMF/PhMe (1:4), C_2H_4 (15 bar), 130 °C. [e] Volatile. [f] Insoluble. [g] Acidic workup not possible. [h] Purified by column chromatography.

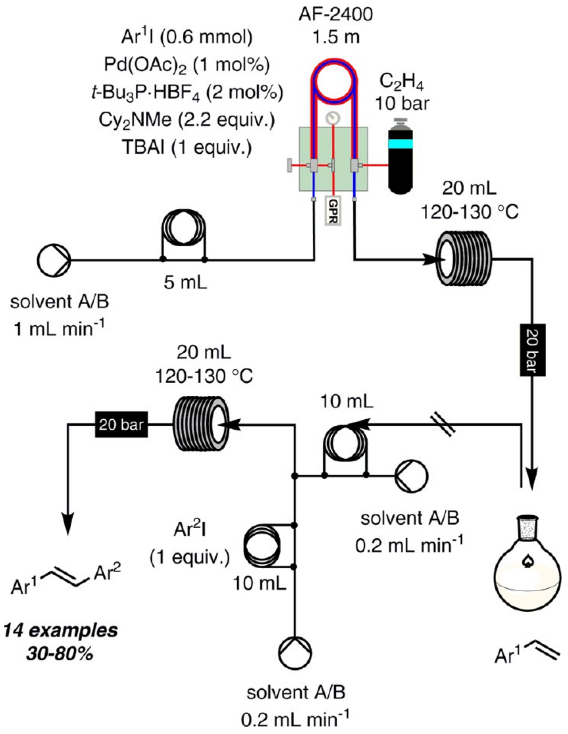
renewable, and highly abundant source of high oxidation state carbon. A Vaportec R2+ pumping module was used to pump a stream of Grignard reagent through the tube-in-tube reactor pressurized with 4 bar of CO_2 (Scheme 2). Placement of a back-pressure regulator (BPR) downstream of the tube-in-tube device prevented premature outgassing and maintained a homogeneous solution. Optimization experiments showed that a flow rate of 400 μL min^{-1} gave high conversions at very short residence times (42 s). Upon exiting the reactor, the crude carboxylate stream was treated with polymer-supported sulfonic acid (QP-SA) to simultaneously protonate the carboxylate product and remove magnesium salt coproducts. Purification was performed in a "catch-and-release" fashion by trapping the product on polymer-supported ammonium hydroxide (A-900), washing with THF and then releasing the acid product from the resin with HCO_2H. A range of alkyl, aryl, heteroaryl, and alkynyl carboxylic acids were synthesized in high yields and high purity (>97% by ^1H NMR) after simply concentrating the reaction output. Importantly, we successfully demonstrated the preparative scale (20 mmol) synthesis of 2,4,6-trimethylbenzoic acid with no significant difference in yield observed.

To demonstrate the generality of the tube-in-tube reactor, we sought to extend its use to other gases that are often avoided at laboratory scale due to potential handling hazards. From 2011 onward, we developed flow syntheses incorporating CO, H_2, NH_3, O_2, CO_2, ethylene (C_2H_4), syngas (1:1 CO/H_2), and dimethylamine (Me_2NH). The following sections detail our efforts in exploring the scope of gas–liquid flow reactions and are arranged by reaction type.

2.3. C–C Bond Formation

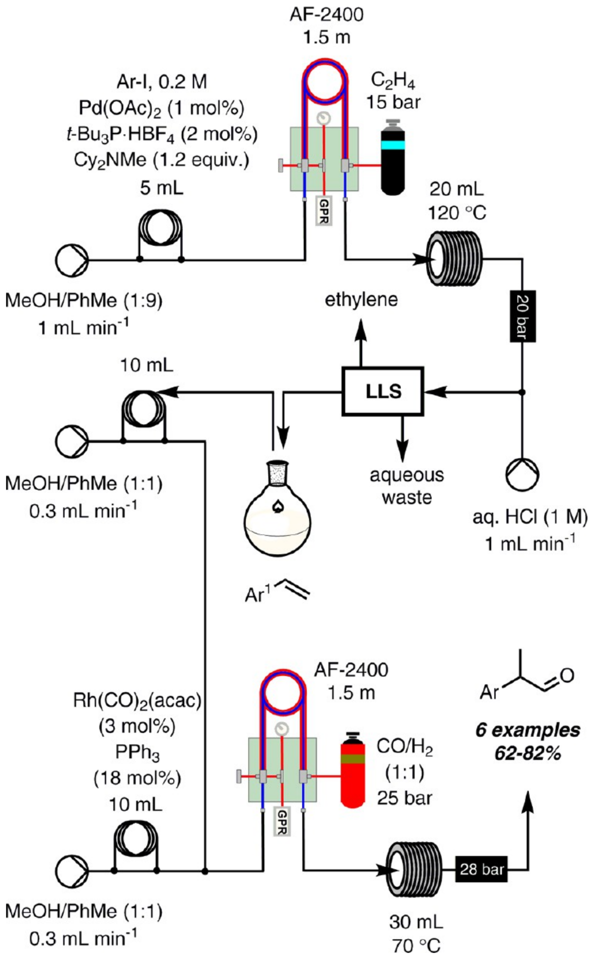
Seeking to demonstrate the safe handling of hazardous gases, we investigated CO-mediated methoxycarbonylation reactions.[16] Carbonyl compounds are of high importance because they readily offer access to a range of diverse functional groups and oxidation states. The high abundance of CO in Nature makes it an ideal carbonyl source, yet it is often avoided due to the significant hazards it poses for research laboratories. Employing the tube-in-tube reactor with 3.8 m of Teflon AF-2400 tubing, we carried out the methoxycarbonylation of aryl, heteroaryl, and vinyl halides with a maximum of 5.6 mL of CO occupying the reactor at any one time (Scheme 3). Solutions of substrate/base and catalyst/ligand were mixed at a T-piece and then merged with a CO-enriched solvent stream. This configuration avoided blockage of the reactor by Pd(0), which was observed during optimization. A BPR downstream of the gas–liquid reactor was found to be essential to avoid in-line degassing. The reaction stream was directed through a heated coil section, followed by polymer-supported thiourea (QP-TU), which removed palladium residues, to afford the methyl ester products (Table 2). Modified conditions were required in several cases because some substrates displayed instability to the thiourea resin or the phosphine ligand. We also demonstrated that dissolved gases could be removed from a flow stream by applying vacuum (10 mbar) to a second, serially positioned gas–liquid reactor. *This technique enhances the prospect of multistep transformations in flow with multiple gases.*

Scheme 7. Tandem Heck−Heck Sequence[a]



[a]Solvent A = DMF/PhMe (1:4); solvent B = MeOH/PhMe (1:9). No TBAI required when solvent B was employed.

Scheme 8. Tandem Heck-Hydroformylation Sequence[a]



[a]LLS = liquid−liquid separator.

Recently, we disclosed a follow up study on flow carbonylation where we sought to explore the diversity of possible nucleophiles.[17] Aryl iodides with pendant amino or hydroxy groups were trapped intramolecularly to give lactams and lactones in excellent yields. The addition of H_2O or amine additives gave carboxylic acids and amides, respectively. Gaseous nucleophiles could be successfully implemented as illustrated by the use of Me_2NH in a dual gas process (Scheme 4).

Continuing our work on palladium catalysis, we applied the tube-in-tube reactor to Heck vinylation of aryl iodides with C_2H_4 gas (Scheme 5).[18] The reactants were pumped sequentially through the gas−liquid reactor, a heated reaction coil, and then a plug of cotton wool to capture minor amounts of Pd(0). With this configuration, both electron-rich and electron-deficient iodides were amenable to the reaction conditions. In this study we demonstrated that vinylation products could be telescoped into a second Heck reaction, yielding unsymmetrical stilbenes without intermediate isolation or the addition of further catalyst.

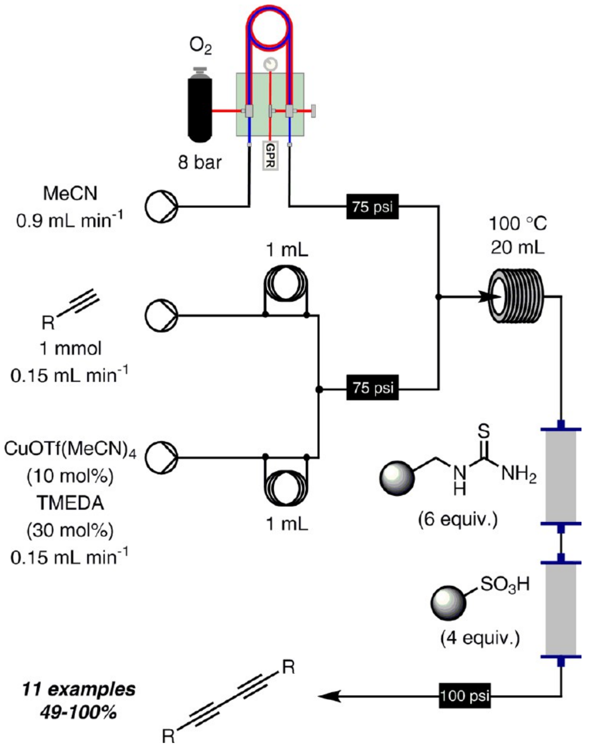
Concurrent to our vinylation investigation, we reported the flow hydroformylation of styrenes.[19] Hydroformylation was achieved by enrichment of a solution of substrate/catalyst with syngas and then passage through a heated reaction coil (Scheme 6). Reaction optimization revealed that a rhodium catalyst at 25 bar gave high conversions and good to excellent yields of branched aldehydes. In parallel with previous vinylation work, we detailed a telescoped Heck-hydroformylation sequence of 4-iodoanisole that gave 58% conversion to 2-(4-methoxyphenyl)propanal. This multistep flow sequence permitted the use of *three reactive gases* for the construction of two new carbon−carbon bonds.

Subsequent studies focused on increasing the throughput of the Heck vinylation for further tandem processes.[20] The formation of Pd(0) was eliminated by the use of *t*-Bu$_3$P·HBF$_4$ as the ligand and Cy$_2$NMe as base. These modifications permitted increased reaction concentration and reduced catalyst/TBAI loadings, giving a second series of styrenes in high yields (Table 3). Large scale (0.12 mol, 28 g) vinylation of 4-iodoanisole gave the styrene product in 84% yield, and an improved Heck−Heck sequence afforded a range of unsymmetrical stilbenes with high selectivity for the *trans*-1,2-diaryl products (Scheme 7).

Our prior work verified an opportunity for tandem Heck-hydroformylation reactions, but control experiments revealed that both DMF and TBAI were detrimental to the hydroformylation step. A solvent switch to 1:9 MeOH/PhMe gave comparable conversions and eliminated the need for TBAI addition altogether. Despite these changes, inhibition of the hydroformylation reaction remained, which was attributed to the formation of $Cy_2NMeH^+I^-$, necessitating an aqueous acid wash. Incorporation of our recently developed in-line liquid−liquid separator enabled the sequence to be executed as a truly continuous telescoped process (Scheme 8). In this work >400 separate experiments were conducted without any detectable mechanical failure of the Teflon AF-2400 membrane, demonstrating the robustness and reuse capabilities of the reactor.

Molecular oxygen has recently emerged as a green oxidant especially in transition metal-catalyzed reactions.[21,22] We have illustrated the use of O_2 in flow via a Glaser−Hay coupling.[23] A solvent stream was oxygenated and then merged with a solution of alkyne, CuOTf(MeCN)$_4$, and TMEDA in acetonitrile (Scheme 9).

Scheme 9. Continuous Flow Glaser–Hay Coupling



Passage through polymer-supported thiourea and sulfonic acid (QP-SA) resins removed copper residues and TMEDA, and the 1,3-butadiyne products were obtained in good yields following concentration (Table 4). A gram scale reaction of **4a** (17.4 mmol, 2.3 g) gave an 84% isolated yield without chromatography, highlighting the relevance of the process to preparative scales.

We have also utilized O_2 as the terminal oxidant in an iron-catalyzed nitro-Mannich reaction of *N*-aryl tetrahydroisoquinolines.[24] Optimization studies revealed that substrate conversion was strongly dependent on O_2 pressure (Scheme 10).

2.4. C–N Bond Formation

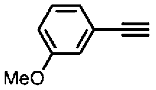
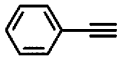
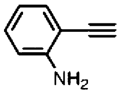
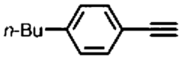
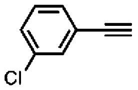
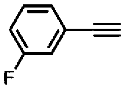
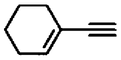
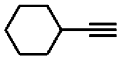
The formation of C–N bonds is of particular significance, because it provides access to a diversity of natural products, pharmaceuticals, agrochemicals, and other bioactives. Our contributing work relates to the use of gaseous NH_3 in the Paal–Knorr reaction.[25] The tube-in-tube reactor configuration was reversed (inner tube = gas, outer tube = liquid) to allow rapid heat transfer by placing the reactor in a heating/cooling bath. Optimization studies revealed that gas loading at 0 °C prior to heating gave quantitative conversions to pure products (Scheme 11).

The tube-in-tube reactor facilitated the formation of thioureas by controlled addition of gaseous NH_3 to isothiocyanates.[26] The reactor was configured with the gas stream in the inner tube as per the Paal–Knorr synthesis. Rapid serial optimization established conditions that gave analytically pure thiourea product after solvent removal (Scheme 12). Increased reaction temperatures and residence times were required for alkyl substrates. In an extension of this work we disclosed a two-step synthesis of the anti-inflammatory agent fanetizole, which provided 70 g over a period of 7 h (Scheme 13).[27]

2.5. C–O Bond Formation

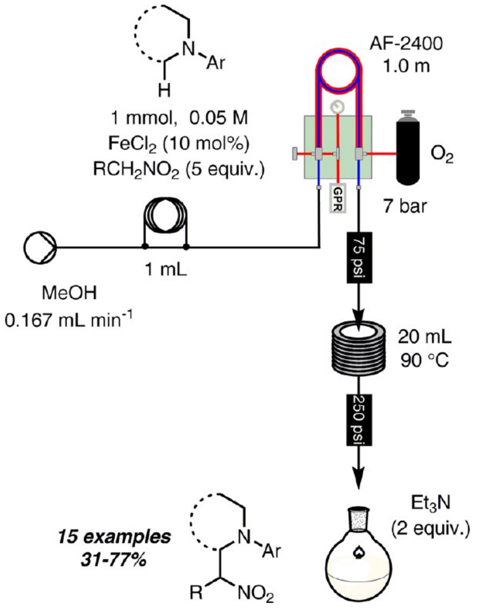
Extending the gas–liquid processes to C–O bond formation, we detailed a continuous flow Wacker oxidation of styrenes with high selectivity for the anti-Markovnikov arylacetylaldehydes (Scheme 14).[28] Both electron-rich and electron-poor styrenes were oxidized under the optimized conditions, giving the bisulfite adducts in 56–80% isolated yields. Modified conditions for a scale-up process were established that allowed for increased reaction concentration (0.3 M) and flow rate (1.2 mL min^{-1}),

Table 4. Scope of Continuous Flow Glaser–Hay Coupling[a]

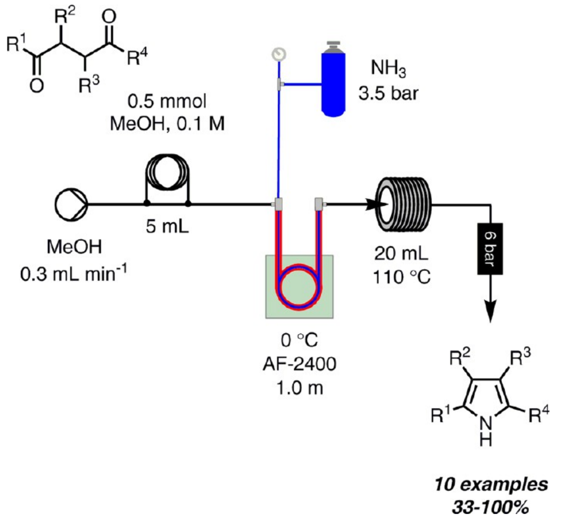
Substrate	Structure	Yield (%)[b]
4a		99 84[c]
4b		96
4c		65[d]
4d		87
4e		96
4f		100
4g		49[e]
4h		94[e,f]
4i		92[e,f]
4j	$i\text{-Pr}_3\text{Si}-\equiv$	65[f]
4k		88[f]

[a]Scale, 1.0 mmol unless stated otherwise. [b]Isolated yield after solvent removal. [c]Scale, 17.4 mmol (2.3 g). [d]Purified by column chromatography; 91% conversion by ^{1}H NMR. [e]PhMe used as solvent. [f]DBU (25 mol %).

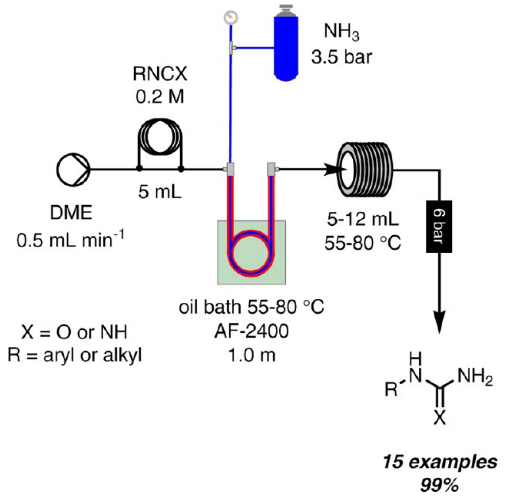
Scheme 10. Continuous Flow Oxidative Nitro-Mannich Reaction



Scheme 11. Flow Paal–Knorr Pyrrole Synthesis



Scheme 12. Flow Synthesis of Iso(thio)ureas



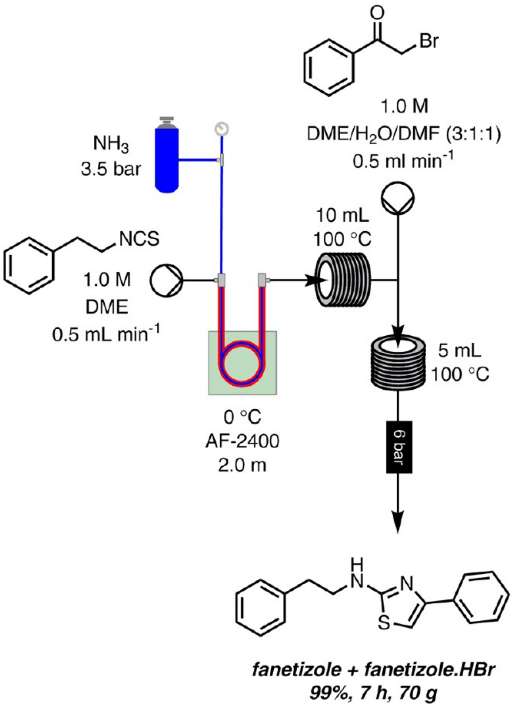
giving a 7-fold improvement in throughput (3 mmol h^{-1} to 21.6 mmol h^{-1}).

2.6. Hydrogenation Reactions

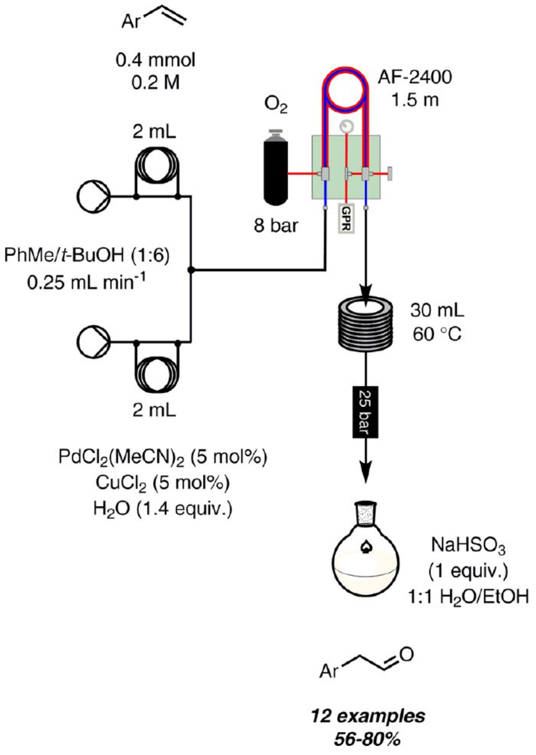
Different approaches to achieving gas–liquid contact in flow hydrogenation include plug flow, mechanical mixing, and the H-cube apparatus. The tube-in-tube reactor proved to be an effective means of carrying out catalytic hydrogenation at elevated pressure.[29] The concentration of H_2 can be controlled with high precision, signifying a major advancement over the other methods. Homogeneous hydrogenation was achieved by exposing a flow stream of alkene and Crabtree's catalyst to 25 bar of H_2 (Scheme 15). Quantitative conversion was achieved for all substrates within 93 s. Heterogeneous hydrogenation was performed using a cartridge of 10% Pd/C (Scheme 16). Low conversions were obtained for single-pass runs and a closed-loop process was employed in preference to increasing pressure or catalyst loading. Alkene substrates were reduced within 2 h and alkynes within 4 h.

This methodology has been extended to asymmetric hydrogenation of trisubstituted olefins with chiral iridium- and rhodium-based catalysts.[30] Reaction parameter screening was accelerated by injecting reaction plugs periodically so that multiple plugs were processed on a single machine simultaneously. Full conversion of the α,β-unsaturated ester **5a** was attained after 80 min, with high diastereoselectivity for the (2*S*)-diastereomer (Scheme 17). This work was key to the total synthesis of polyketides spirangien A methyl ester and spirodienal A (Figure 3), the majority of which was performed in flow.[31]

Scheme 13. Telescoped Fanetizole Process

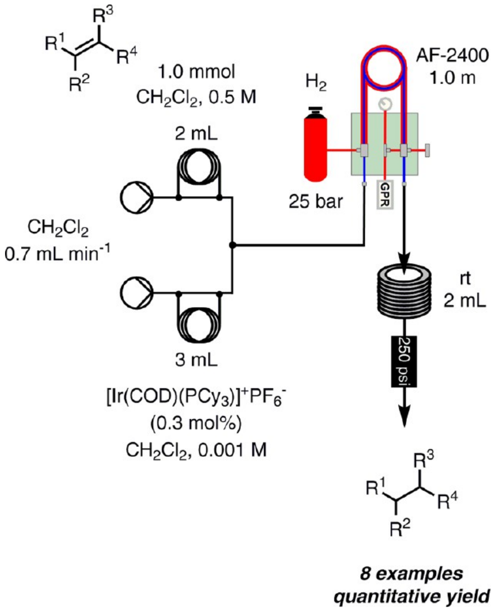


Scheme 14. Continuous Flow Wacker Oxidation[a]

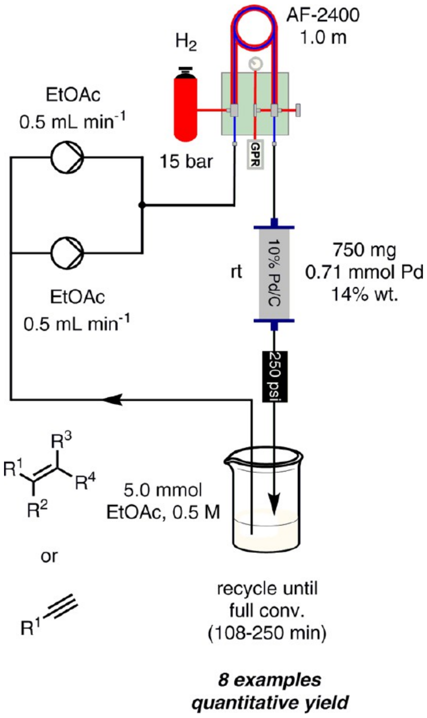


[a] Products isolated as the bisulfite adducts.

Scheme 15. Flow Homogeneous Hydrogenation

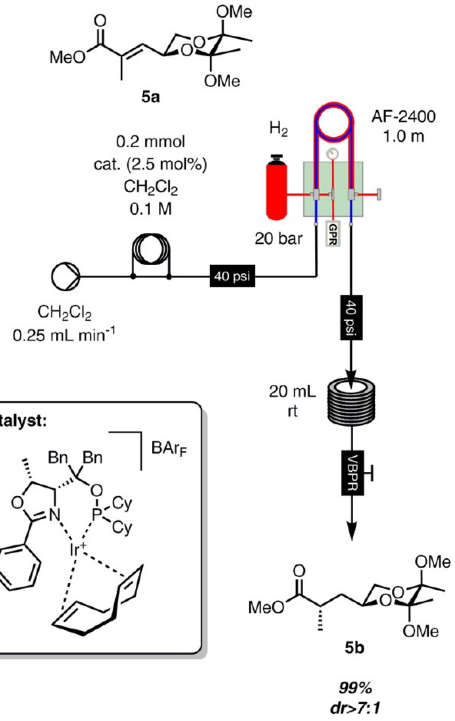


Scheme 16. Flow Heterogeneous Hydrogenation



3. IN-LINE ANALYSIS OF DISSOLVED GASES

Scheme 17. Continuous Flow Asymmetric Hydrogenation of 5a



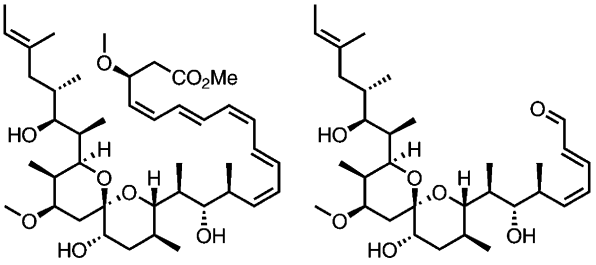
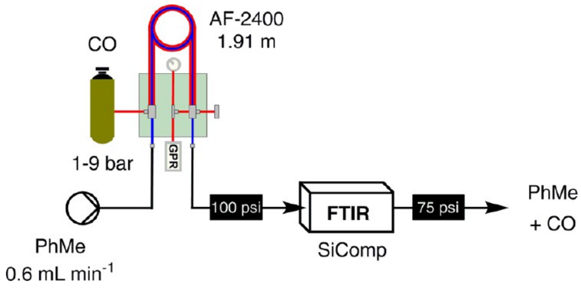


Figure 3. Spirangien A methyl ester (left) and spirodienal A (right).

Scheme 18. In-Line Real-Time FTIR CO Monitoring



The quantitative analysis of dissolved gases is an important part of process development and can greatly assist in the optimization of reaction parameters. We have endeavored to incorporate real-time monitoring of dissolved gas concentration, with the aim of fully automated gas–liquid flow processes. In our methoxycarbonylation work,[16] we implemented real-time FTIR analysis to quantitate the uptake of CO by monitoring the intensity of the CO IR stretching frequency at 2133 cm^{-1} (Scheme 18). A linear relationship between relative peak intensity and CO pressure was observed and confirmed by gas buret measurements. The ReactIR flow cell was also used in our Heck coupling investigations to determine C_2H_4 concentration based on the asymmetric CH_2 stretching frequency.[18]

A computer-assisted "bubble counting" technique was developed for in-line H_2 quantitation.[29] A length of tubing was wrapped around a support in view of a digital camera and the apparatus was placed downstream of a back-pressure regulator where plugs of outgassed H_2 were observed. Red dye was added to the solution and digital images were captured and processed by a Python script that converted pixels to pure red or pure white and then calculated the concentration of gas against a calibration image (Figure 4). Saturation concentrations were achieved

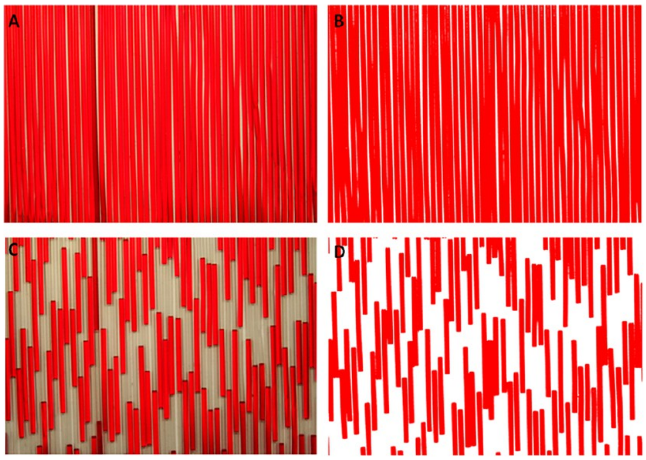
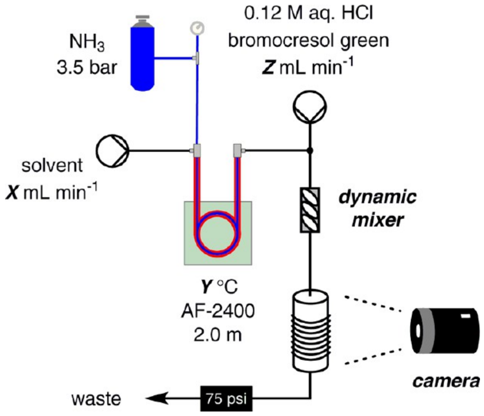


Figure 4. Bubble counting technique: (A) calibration run, reactor not pressurized with hydrogen; (B) corresponding processed image with pure red and pure white pixels; (C) outgassed reaction stream; (d) Corresponding processed image for quantitation of outgassed hydrogen.

within a residence time of 5 s and were found to be proportional to external H_2 pressure, in accordance with Henry's law.

A novel colorimetric flow titration was implemented during our work with NH_3 gas.[25−27,32] An NH_3-enriched solvent stream was merged with an aqueous HCl stream containing added pH indicator (Scheme 19). The flow stream was then passed though a dynamic mixer and an observation coil, where a digital camera captured the indicator color. By varying the flow rate of the acidic stream, the concentration of dissolved NH_3 could be determined based on the titration end point (Figure 5). This method was used to evaluate the influence of solvent, flow rate, and gas loading temperature on the molar ratio of NH_3 present in solution.

Scheme 19. In-Line Colorimetric Flow Titration



The use of real-time, quantitative gas analysis affords the potential to rapidly evaluate and optimize the processing parameters of a given reaction. Further developments in analysis methods will help to imbue greater control of gaseous transformations.

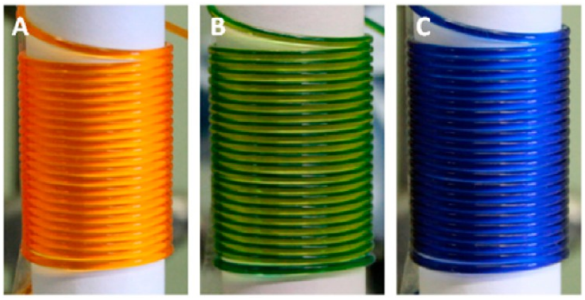
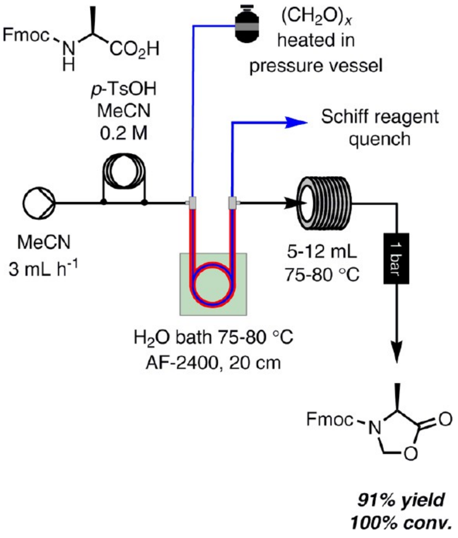
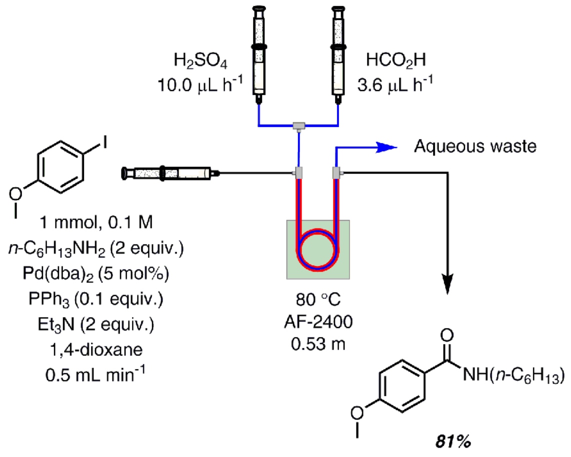


Figure 5. In-line colorimetric flow titration. Pictures of the observation coil at different pH values: (A) pH < 3.8; (B) intermediate pH; (C) pH > 5.4.

Scheme 20. Continuous Flow Synthesis of *N*-Fmoc-L-4-methyl-oxazolidin-5-one



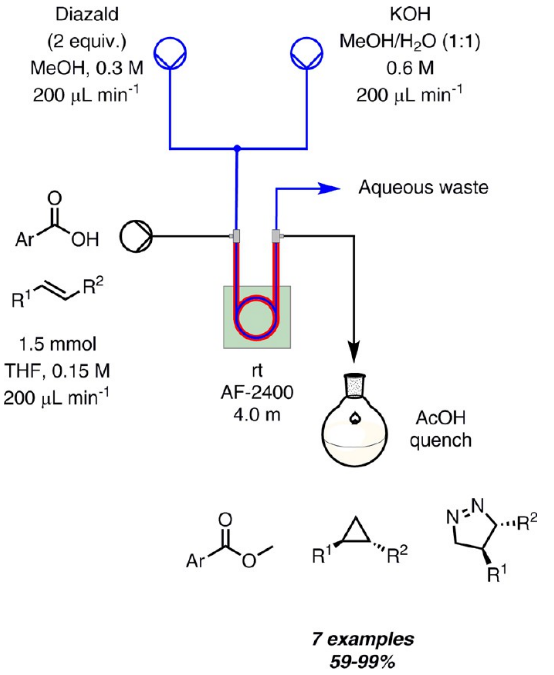
Scheme 21. Continuous Flow Heck Aminocarbonylation



4. EXPANDING THE CAPABILITIES OF THE TUBE-IN-TUBE DESIGN

The following section will detail investigations by groups who have utilized our tube-in-tube technology. Kunz and co-workers recently described the use of a tube-in-tube reactor for the flow synthesis of *N*-methyl amino acids.[33] *N*-Fmoc-L-alanine was converted to the corresponding oxazolidinone by treating a stream of the substrate and catalytic *p*-TsOH in acetonitrile with gaseous formaldehyde that was generated by heating paraformaldehyde in a pressure-resistant vessel (Scheme 20). It was necessary to maintain the tube-in-tube reactor at a temperature

Scheme 22. *Ex Situ* Generation of Anhydrous Diazomethane



above 75 °C to avoid precipitation of solid paraformaldehyde onto the membrane surface.

Investigations into low-pressure aminocarbonylation led the Ryu group to the *ex situ* formation of CO by the dehydration of HCO_2H with H_2SO_4 (Scheme 21).[34] A tube-in-tube reactor was used to preclude the mixing of H_2SO_4 and Et_3N with the amide product obtained in isolated yields comparable to the batch procedure.

We have previously reported a method for the *in situ* generation of diazomethane in flow.[35] More recently, Kappe and co-workers have generated anhydrous diazomethane in an *ex situ* manner using the tube-in-tube device.[36] By merging a methanolic stream of Diazald with KOH in 1:1 $MeOH/H_2O$ in the gas–liquid reactor, anhydrous diazomethane was liberated and rapidly diffused to the outer tube containing substrate in THF (Scheme 22). This process was applied to the methylation of benzoic acids and tetrazoles, [2 + 3] cycloadditions, and Pd-catalyzed cyclopropanation of alkenes.

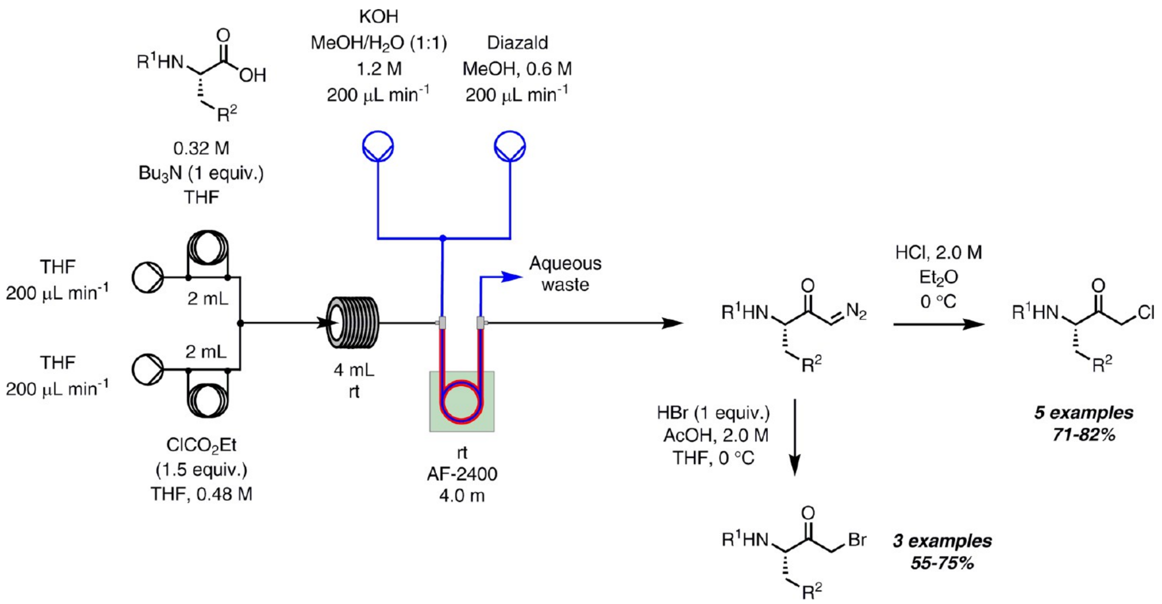
Kappe's *ex situ* diazomethane generation was applied to the flow synthesis of a number of α-halo ketones (Scheme 23).[37] A gram-scale halomethylation of *N*-Cbz-L-phenylalanine gave the enantiopure α-chloro ketone product in 87% yield with a throughput of 1.25 mmol/h.

The efficiency of olefin metathesis reactions that generate C_2H_4 as a coproduct have been shown to be significantly lower in flow compared with batch.[38,39] This issue has been ascribed to inefficient removal of C_2H_4, which decomposes the intermediate ruthenium methylidene species.[40] Skowerski et al. showed that removing C_2H_4 by applying vacuum to a tube-in-tube reactor gave equivalent or better results for continuous flow conditions olefin metathesis reactions.[41]

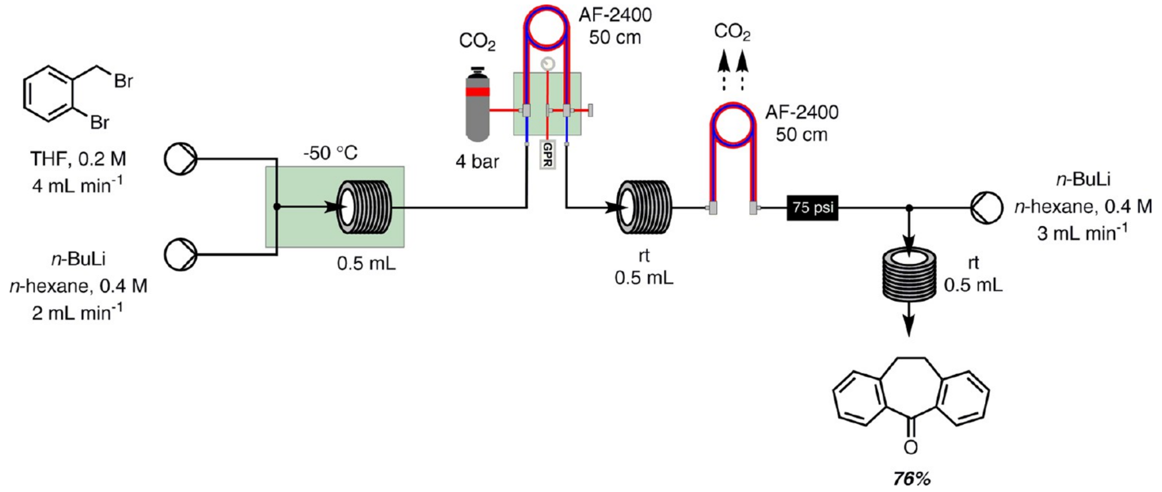
Krischning and co-workers have disclosed a two-stage multistep flow synthesis of the tricyclic antidepressant amitripyline employing the tube-in-tube reactor (Scheme 24).[42] A one-pot Parham cyclization was performed with gaseous CO_2, the excess of which was removed by a second tube-in-tube device prior to the final lithiation step. This process gave a 76% isolated yield of the ketone product in an overall residence time of ~33 s, a significant improvement over the batch procedure (38–56% yield after 2 h at −100 °C).

Since the development of the initial prototype, a commercial tube-in-tube gas–liquid reactor has been made commercially available.[43] The commercial reactor is specified as being functional up to 25 bar pressure and at flow rates of 10 mL min^{-1} with membrane lengths of 1–4 m. Teflon AF-2400 displays high thermal stability (glass transition temperature = 240 °C)[44] and high chemical resistance, giving the tube-in-tube reactor wide operational limits. Jensen has published a study where quantitative models for predicting gas and substrate concentration profiles within reactor were developed and found to accurately model mass transfer performance.[45] Strategies for increasing volumetric flow rate were investigated and an increase in the tube diameter was ineffective, with a drop in saturation fraction observed due to gradient-driven diffusion being the major transport mechanism. Increasing tube

Scheme 23. Continuous Flow Synthesis of α-Halo ketones



Scheme 24. Stage One of Multistep Flow Synthesis of Amitripyline



length with parallelization would effectively maintain the saturation fraction at flow rates of 50 mL min^{-1}, although this approach would be cost prohibitive. This investigation of the scalability of the reactor highlights the broader interest in expanding the technology beyond preparative laboratory syntheses into process scale chemistry. Beyond current applications, future challenges will center on evolving the technology to accommodate larger scale synthesis for process chemical manufacture.

5. CONCLUSIONS AND FUTURE DIRECTIONS

This Account has highlighted our development of tube-in-tube reactors based on Teflon AF-2400 membrane tubing and how such devices have greatly improved the accessibility of continuous flow gas−liquid reactions. Because only a small volume (1−2 mL) of pressurized gas occupies the reactor at any one time, toxic and flammable gases can be handled in a much safer and more efficient manner in comparison to high-pressure batch or continuous plug flow operations. We have shown the utility of tube-in-tube reactors in processing a range of reactive gases and developed intelligent real-time monitoring techniques such as “bubble counting” and colorimetric flow titration. We anticipate that this Account will help stimulate further research into the selective transfer of gaseous reagents across semipermeable membrane tube-in-tube reactors in flow synthesis.

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Notes

The authors declare no competing financial interest.

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Dr. Mathew O’Brien carried out Ph.D. studies with Prof. Eric J. Thomas (University of Manchester) and postdoctoral studies with Prof. Ian Paterson, FRS (University of Cambridge). After serving as Kinerton Lecturer of Organic Chemistry at Trinity College, Dublin, he returned to Cambridge as a Research Associate with Steven V. Ley, FRS, where he was elected to Fellowship of Pembroke College (2008) and Director-of-Studies for Natural Sciences (2011). In 2012, he was appointed Lecturer in organic chemistry at Keele University.

Professor Steven Ley completed his Ph.D. under Prof. Harry Heaney (Loughborough University) before undertaking postdoctoral studies with Prof. Leo Paquette (The Ohio State University) and Prof. Sir Derek Barton (Imperial College). He was promoted to Lecturer (1975), Professor (1983), and then Head of Department (1989) at Imperial College and elected to the Royal Society (London) in 1990. He has been the BP (1702) Professor of Chemistry at the University of Cambridge since 1992 and was the President of the Royal Society of Chemistry from 2000 to 2002.

Dr Anastasios (Tash) Polyzos received his Ph.D. from La Trobe University (Prof. A. B. Hughes) and was appointed as Research Fellow at CSIRO in 2005. In 2008, he commenced postdoctoral studies with Steven V. Ley, FRS (University of Cambridge). He is currently a Senior Research Scientist and Julius Fellow at CSIRO.

■ ABBREVIATIONS

DBU: 1,8-diazabicyclo-[5.4.0]-undec-7-ene
DMF: *N*,*N*-dimethylformamide
TBAI: tetra-*n*-butylammonium iodide
THF: tetrahydrofuran
TMEDA: *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine

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