

**Novel Process Windows:
Reactions Using Tricky Reagents**



A Thesis Submitted to Cardiff University
in Fulfilment of the Requirements for the
Degree of Doctor of Philosophy
by Matthew John Hutchings

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List of Abbreviations

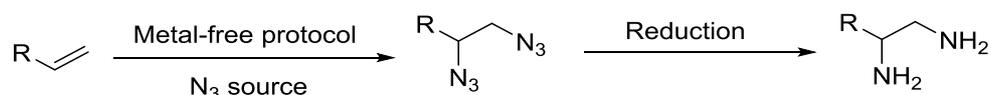
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|-------------------------|--|
| Å | Angström |
| Ac | Acetyl |
| AIBN | Azobisisobutyronitrile |
| Ar | Aryl |
| BPR | Back Pressure Regulator |
| CV | Column volumes |
| DBN | 1,5-Diazabicyclo(4.3.0)non-5-ene |
| DBU | 1,8-Diazabicycloundec-7-ene |
| (DHQ) ₂ PHAL | Hydroquinine 1,4-phthalazinediyl diether |
| DIAD | Diisopropyl azodicarboxylate |
| DIB | Diacetoxyiodobenzene |
| DMF | Dimethylformamide |
| DMP | Dess–Martin periodinane |
| DPPA | Diphenylphosphoryl azide |
| dppp | 1,3-Bis(diphenylphosphino)propane |
| DMSO | Dimethylsulfoxide |
| Et | Ethyl |
| FIBX | (2,4,5,6-Tetra -fluoro) 2-iodoxybenzoic acid |
| GPR | Gas Pressure Regulator |
| h | Hour/hours |
| HPLC | High pressure liquid chromatography |
| HRMS | High resolution mass spectrometry |
| IBX | 2-Iodoxybenzoic acid |
| <i>i</i> NOC | isonicotinyloxycarbonyl |
| IR | Infra-red |
| Hz | Hertz |
| mA | milliamp |
| µm | micrometre |
| <i>m</i> -CPBA | <i>m</i> -Chloroperoxybenzoic acid |

| | |
|------------------|--------------------------------------|
| Me | Methyl |
| MFC | Mass Flow Control |
| MHz | Megahertz |
| min | Minute |
| m.p. | Melting point |
| m/z | Mass over charge ratio |
| NIS | N-iodosuccinimide |
| NMR | Nuclear magnetic resonance |
| o.n. | overnight |
| PET | Positron emission tomography |
| PIFA | [Bis(trifluoroacetoxy)iodo]benzene |
| pKa | Acid dissociation constant |
| ppm | parts per million |
| Ph | Phenyl |
| Pr | Propyl |
| PTC | phase transfer catalysis/catalyst |
| Re | Reynold's Number |
| rt | Room temperature |
| T ₃ P | Propylphosphonic anhydride |
| TBD | 1,5,7-Triazabicyclo[4.4.0]dec-5-ene |
| <i>t</i> -Bu | <i>t</i> -Butyl |
| TEA | Triethylamine |
| TEMPO | 2,2,6,6-Tetramethyl-1-piperidinyloxy |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TMEDA | N,N,N',N'-Tetramethylethylenediamine |
| TMS | Trimethylsilyl |
| TTMS | Tetramethylsilane |

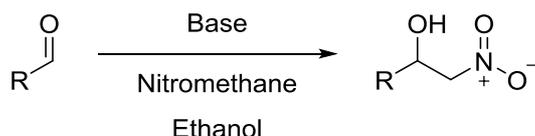
Abstract

Flow chemistry has been increasingly used in the last decade as an alternative method to batch chemistry. This methodology allows for conditions that would be unattainable under batch techniques due to the high temperature control, selectivity and safety that flow chemistry allows.

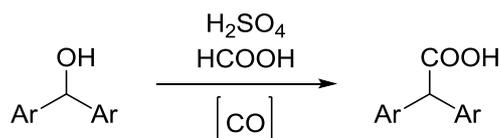
The diazidation of styrenes has been investigated under continuous flow conditions, where the inherent safety of flow chemistry allows the use of azides without the concerns usually associated with these reagents.



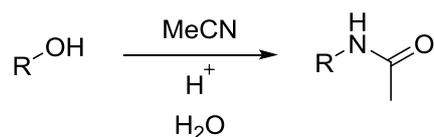
Secondly, the nitroaldol reaction has been transferred to flow conditions. This highlights the safety of continuous flow procedures, as the use of a highly energetic reagent such as nitromethane is easily possible..



The Koch-Haaf carbonylation reaction was investigated to demonstrate the use of gases in flow chemistry and the safe handling of toxic gases such as carbon monoxide.



Finally the Ritter reaction was used to further demonstrate the suitability of flow chemistry for highly exothermic reactions using concentrated acids; where the temperature control allows for high selectivities.



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1.1 Advantages of Flow Chemistry

The need for increased safety in chemical synthesis is always in demand and is under development by numerous research groups currently within the chemical industry. To address safety issues, many methods have been developed by the chemical industry, most notably flow and microreactor technologies. These offer a unique ability to allow reagents or intermediates, that were initially considered too dangerous for large scale production methods, to be used in a much less hazardous manner without detrimental effects to the reaction conditions.^[1-5]

Flow chemistry allows for many inherent benefits due to the multitude of effects caused by being at small volumes. Higher concentrations are substantially more applicable, mixing is drastically improved and a much better heating profile is possible due to the greatly increased surface-to-volume ratio. This then reduces localised “hot spots” which can either cause unwanted side products or worse adiabatic runaway potentially causing explosions. Furthermore, the likelihood of the aforementioned risks is lowered by the small volumes of reactive intermediates produced at any one time.

Mixing is important in all chemical reactions as it allows for rapid association of reagents at any given time. One of the biggest factors of mixing in solution phase is diffusion, which is most notable when reactions have a very low energy of activation. Conventionally for reactions of this type, cooling would have to be applied to have any control of the selectivity. Alternatively lower concentrations can be used; the high dilution of reactions can dramatically slow down the rate of reaction. Under highly concentrated conditions mixing must become faster than the reaction to reduce unwanted side products which is sometimes unachievable under batch conditions.

| Diffusion time (s) | distance |
|--------------------|-------------------|
| 0.0005 | 1 μm |
| 0.005 | 10 μm |
| 5 | 100 μm |
| 500 | 1 mm |

Table 1.1: Table showing the different diffusion times as related to distance travelled.^[6]

Flow chemistry relies directly on the low radial diffusion distance within microchannels. The time taken to travel across the channel is far lower than in a classical flask therefore diffusion speeds that are associated with flow cannot be reached in batch (without mixing) as shown in Table 1.1.

Highly efficient micromixers can be used as well as variation in flow rates to produce many different transport phenomena that can aid in mass transfer. This can range from a simple T-piece where flow rate can have a large effect on mixing properties, to specially designed mixers such as the Comet mixer or caterpillar mixers shown in Figure 1.1. Caterpillar type mixers work by multiple splitting and recombination of reagent streams. The streams are lifted up and down by the device, which then recombines the streams to form a single stream. This is repeated multiple times within the mixer to produce a near homogeneous solution. Comet mixers work with a similar method, using an arrangement of disks with varying through-put holes. The streams of reagents are continuously mixed to form an even distribution of reagents.

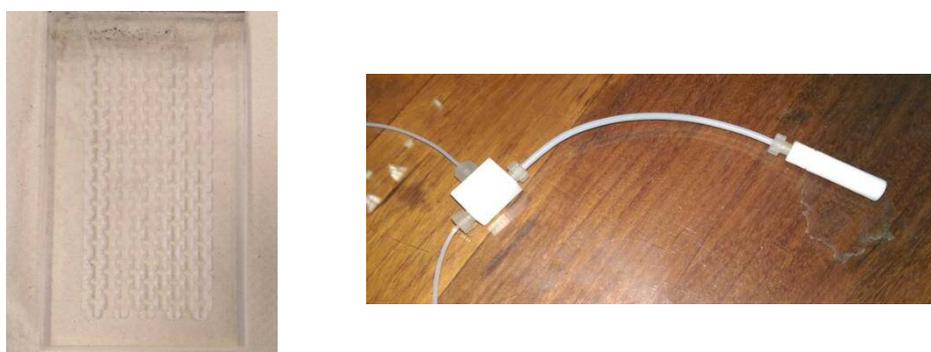


Figure 1.1: Picture of typical glass caterpillar mixer and a Comet™ mixer.

In general, in a flow system with a simple T-piece the mixing can be influenced directly by the flow rate and choice of tubing diameter. With the use of low flow rates and tubing in the micro range, a Laminar flow regime dominates. When switching to either larger tubing or when high flow rates are chosen, turbulent flow usually dominates.

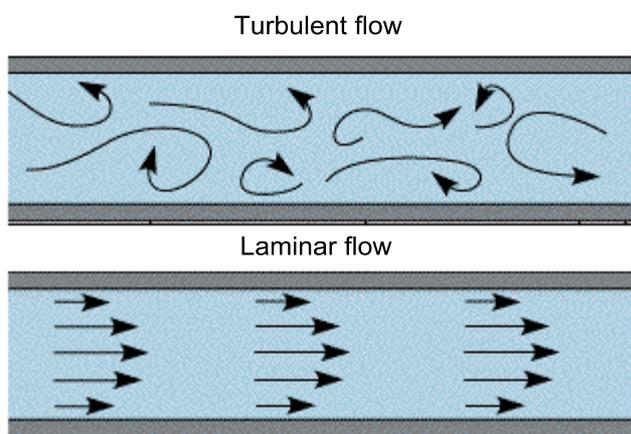


Figure 1.2: Laminar and turbulent flow in flow tubing. ^[7]

As shown in Figure 1.2, flow rates and flow area can have a large effect on mixing properties which are largely governed by the Reynolds numbers. The Reynolds number (Re) describes the relationship between the inertial forces and the viscous forces. This is represented in the following form:

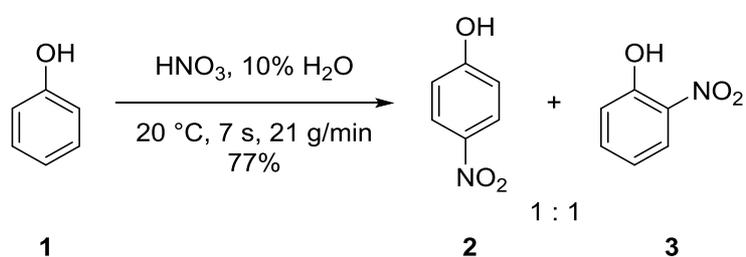
$$\text{Re} = \frac{\rho v D}{\mu}$$

At lower flow rates, viscous forces are dominant ($\text{Re} < 2000$) resulting in laminar flow. Turbulent flow is prevalent when the flow rates are higher and therefore inertial forces become a much larger factor ($\text{Re} > 3000$). Any value in between is then classified as transient flow.^[8]

1.2 Organic synthesis promoted by flow chemistry's properties

1.1.1 Single Phase Reactions

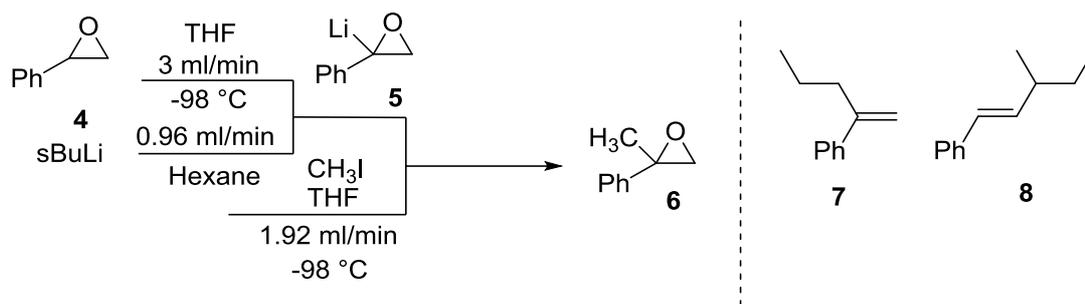
Single phase liquid reactions have been by far the largest area explored in flow chemistry. Many examples ranging from acid and base-promoted reactions to radical and metal-catalysed reactions have been studied. Generally due to the improved heat control in flow chemistry acid-catalysed reactions such as nitrations, which are highly exothermic, have been shown to benefit from this. Roberge *et al.* showed that nitrations, which were performed with excellent temperature control, led to a highly efficient and rapid synthesis (7 s) of nitrated phenols **2** and **3** (Scheme 1.1).^[9]



Scheme 1.1: Acid-catalysed nitration in continuous flow using a glass microreactor with a 10×0.5-mm channel width and 2.0 mL internal volume.

This is a great example of how the increased surface-to-volume ratio can allow for great control of heat exchange within flow chemistry compared to batch chemistry where controlling a temperature of 20 °C in such an exothermic reaction is challenging and yields of only 32% were achievable.

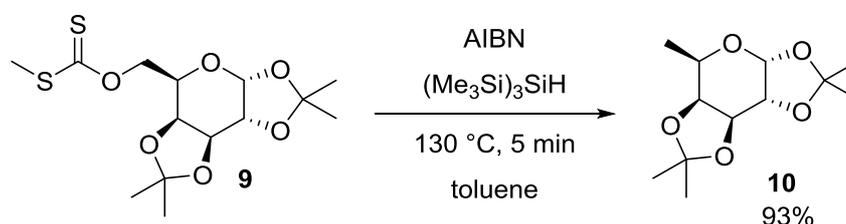
Many base controlled reactions have been performed in flow systems ranging from simple organic bases^[10] to alkyl lithium bases, addressing the dangers and selectivity associated with using lithiated bases. Yoshida and co-workers have been at the forefront of alkyl lithium chemistry in flow for a number of years, using the temperature control and increased mixing of flow chemistry to allow for selective reactions, even with such highly reactive compounds. Reaction times can be in the orders of milliseconds and the area has thus been termed as flash chemistry.^[6,11–14] Their work shows the ability to control reactions extremely effectively where the speed of the reaction is faster than that of mixing and consequently with the small diffusion distances in microreactors selectivity is easily obtained. An example of this is shown in Scheme 1.2:



Scheme 1.2: Lithiation of styrene epoxide followed by quenching with MeI in a microreactor.

Yoshida^[15] showed that the use of microreactor technologies could allow for a huge increase in selectivity, avoiding the side products **7** and **8**. The small diffusion distances allow for sufficient concentrations of MeI to interact with the lithiated species **5** and therefore yields of up to 88% in reaction times in the order of seconds. This was achieved without the use of TMEDA (tetramethylethylenediamine) needed for high selectivity in batch procedures. They compared their results to a batch procedure where to obtain the same conversions to that of the flow procedure it was necessary to allow the reaction to proceed for 60 min.

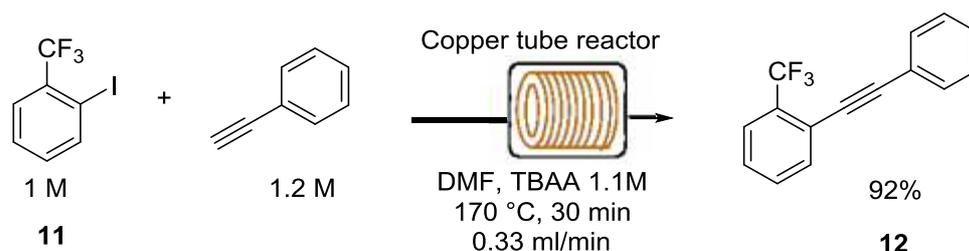
Radical reactions have been shown to be highly efficient within flow. Most examples generally contain trialkyltin hydride with azobisisobutyronitrile (AIBN), and have been shown to proceed in a rapid and highly selective manner.^[16] An example of this has been demonstrated by Seeberger and co-workers as shown in Scheme 1.3. A radical based reduction method was shown in a glass-chip reactor with a 1 mL volume using a combination of AIBN and TTMS. Using this Barton-McCombie deoxygenation protocol they were able to deoxygenate xanthate derivative **9** to form deoxy-D-galactose **10** (Scheme 1.3). The use of the glass reactor in combination with a BPR allowed for superheating of the reaction solvent and therefore a rapid and efficient procedure.



Scheme 1.3: Radical deoxygenation of diacetone-D-glucose derivative **9** using AIBN and TTMS in a glass flow reactor.

Metal catalysed reactions have been intensively studied using microreactor technologies. These include cross coupling reactions^[17], metathesis^[18] and Lewis acid catalysis^[19] using transition metals to name but a few. Methods have sought to use some of the physical

properties of microreactors to develop synthetic protocols for these reactions. Solid-supported reagents have been used as precatalysts and some groups have even specifically designed tubing with catalytic properties. An example of the latter has been shown in a cross coupling reaction such as the Sonogashira coupling of 2-trifluoromethyliodobenzene **11** with phenyl acetylene using a copper tube flow reactor.^[20] Mainolfi *et al.* established conditions where, in a 30 min residence time, the coupling could be achieved with a 92% yield of **12** at 170 °C without the need for palladium. (Scheme 1.4).



Scheme 1.4: Copper tube catalysed Sonogashira cross coupling in flow. TBAA = tetra-*n*-butylammonium acetate.

This shows a large benefit compared to traditional copper-catalysed syntheses due to the nature of the chosen reactor. The need to separate the copper from the reaction mixture is eliminated and, combined with the reusable nature of such tubing, allows for a much more efficient synthesis.

1.1.2 Liquid-Liquid Biphasic Reactions

Many other benefits can be attributed to the effects of flow chemistry when using varied conditions that have been used in batch chemistry for decades. Biphasic reactions which one associates with poor mass transfer can be improved by the mixing properties of flow chemistry. Again, by using a simple T-piece and two immiscible solvents, a phenomenon known as segmented flow can be achieved when defined plugs of segregated reactants are formed. Unlike in batch chemistry, where the interface between the large defined phases is small; the large number of small segments within the flow reactor has a substantially larger interface due to the large surface-to-volume ratio achieved. This is a huge advantage in cases where diffusion is a limiting factor. Not only is there a larger interfacial relationship but due to the interaction with the tube wall whilst in flow, axial forces cause an internal mixing as shown in Figure 1.3, consequently leading to much higher rates of reaction.^[21]

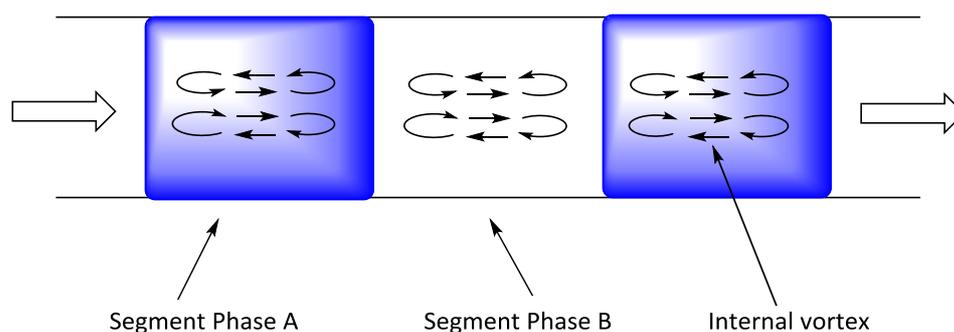
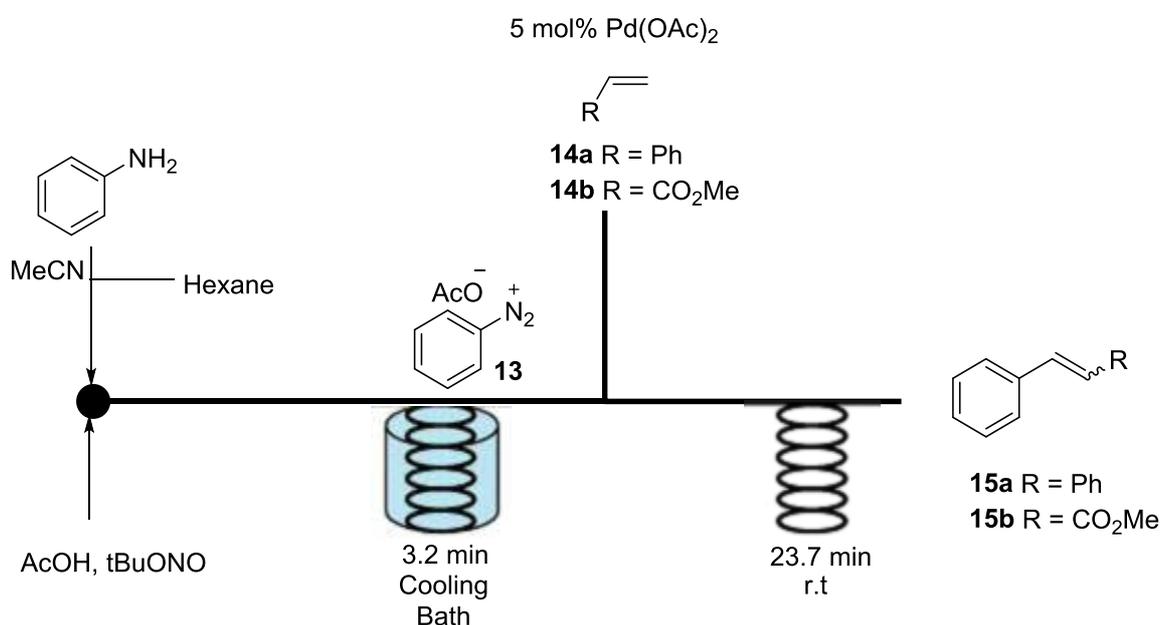


Figure 1.3: Internal vortex formation shown in each phase during segmented flow conditions.

An early example of this was shown by Wirth and co-workers where a Heck coupling with diazonium salts was dramatically promoted by segmented flow.^{[21][22]} Starting from aniline they could oxidise to the diazonium salt **13** with *t*BuONO. Pd(OAc)₂ and the alkene **14** were then added via a second T-piece to form the product **15** (Scheme 1.5) Using the immiscibility of hexane and MeCN the formation of segments could be achieved as in Fig 1.3. This in turn creates a vortex mixing effect allowing increased rate of reaction. Therefore by dissolving the reagents in MeCN whilst flowing an inert hexane solution through a T-piece the overall yields could be increased.



Scheme 1.5: Tandem diazotation/Heck reaction in segmented flow conditions.

Yields ranged from 64-98% through ten examples with a much higher reaction rate than that of laminar flow conditions and traditional batch methods.

1.3 Heterogeneous conditions

1.1.3 Gas liquid conditions

The use of gases in continuous flow gains an added advantage in a closed system, with the aid of a BPR (back pressure regulator). The formation or addition of gases in continuous flow can be advantageous as gases are unable to escape into the head space found within conventional batch reactors. In general there are two methods for the use of gases in continuous flow: A biphasic flow of gas-liquid^[23] and a saturation of solvent with the gas in pressurised systems^[24] through semi-permeable membranes; each having their advantages and disadvantages.

Biphasic gas liquid methods have a number of subcategories within continuous flow reactors. An example is falling film microreactors, where a falling film of liquid controlled by gravity is brought into contact with an opposite stream of gas.^[25] Mesh reactors use partially segmented channels that are overlapped and are open to interaction between the gas and the liquid; and dispersed-phase microreactors, which work by allowing separate streams of gas and liquid to be introduced at the inlet.^[26]

Within dispersed phase systems the most common flow regime is Taylor flow Figure 1.4

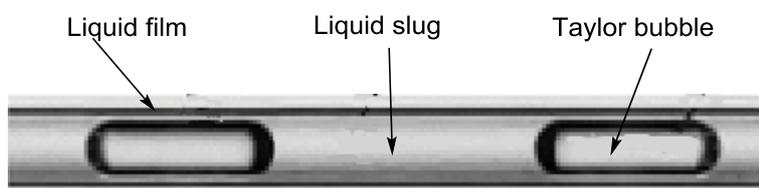


Figure 1.4: Taylor flow within a tube reactor.

When this is adopted in microstructured devices the reactions normally take place within the liquid slug or in a film at the tube walls. This technique is not only used for reactions with the gas itself but as with liquid-liquid biphasic systems the same axial effects are observed and therefore an inert carrier gas can be introduced to form vortex mixing.

A recent example of gas liquid flow has been described by Vilar and colleagues.^[27] They used a gas liquid flow regime for the screening of Pd catalysed carbonylations comparing annular flow with segmented flow. Using aryl iodides, amines and CO gas they were able to demonstrate a reliable system for the Heck type carbonylation. When comparing segmented to annular flow they noted that more control was possible with segmented compared to annular flow. Lower flow rates are more achievable and therefore reactions can be given time to go to full

conversion. Yields of up to 96% were achieved within 10 min of residence time and, if allowed to react for longer, yields of 99% could be achieved in 1 h for some substrates.

A further example of gas liquid flow within tubing is annular flow. This is a regime where a flow of gas is sent at such a high flow rate as to form a core through the centre of the tubing, which is surrounded by the liquid phase as a film on the tube wall. A recent example of this technique was used to strip a side product from the product mixture to drive the equilibrium towards the product has been developed by Kappe *et al.* [28]

Kappe showed that stripping the carbon monoxide (CO) from the reaction mixture prevented the poisoning of the catalyst. This allowed lower catalyst loadings and a drastic increase in reaction rate. Using nitrogen gas to produce the annular flow, the decarbonylation of aldehydes to alkanes could be achieved by stripping away the CO by-product (Figure 1.5). This allowed for a reduction in reaction time reducing from 16 h to 8 min in some cases, as compared to conventional batch and flow techniques that cannot allow for the escape of gas at such an efficient rate.

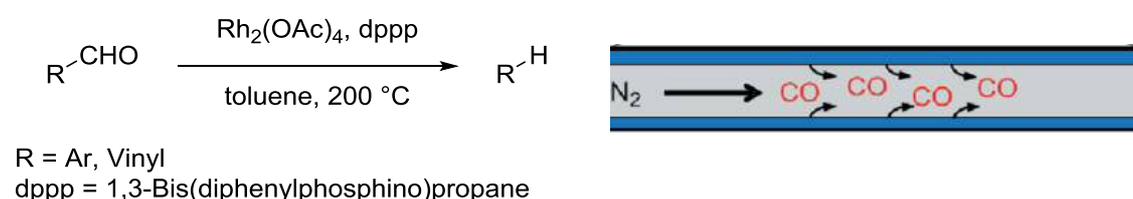


Figure 1.5: Use of annular flow for the stripping of CO gas from the reaction mixture.

Another method for introducing gases into flow devices has been developed recently. The use of gas-permeable membranes has been shown to be a useful method for delivering reagent gases in synthetic transformations, the main difference of this technique being that the gas is dissolved into the liquid phase under pressure to afford a saturated solution which can then be used in a reaction, featuring a tube in tube reactor consisting of a gas permeable inner tube of AF 2400 Teflon tubing and a wider diameter non permeable tubing surrounding this. Therefore a liquid stream can then be pumped through either tube, and a gas through the other to saturate the liquid stream as shown in Figure 1.6,

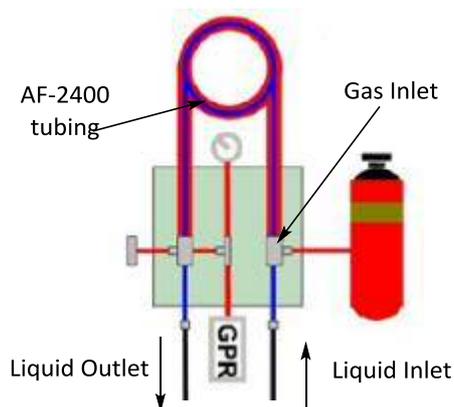


Figure 1.6: Tube in tube reactor schematic. GPR = gas pressure regulator adapted from ^[29].

As well as being used for methods of introducing gases this concept has also been used to make gases *in situ* from a solution phase to be passed through to the additional non permeable tubing. This can be useful when a gas that would otherwise be unfavourable to use due to its toxicity or explosive nature. The conditions used to make the gas can therefore be disposed of without interfering with the subsequent reaction steps.

Very recently Kappe and co-workers used this method to generate anhydrous diazomethane in flow (Figure 1.7).^[30]

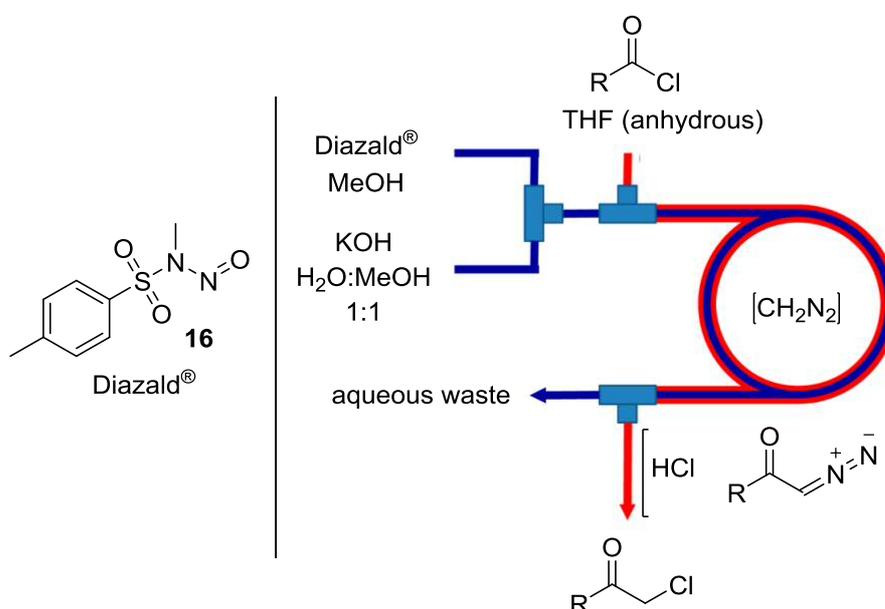


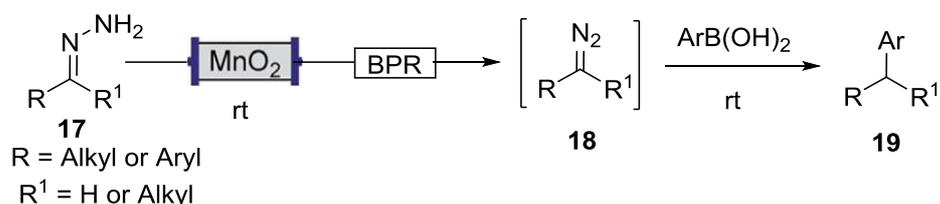
Figure 1.7: Use of AF2400 tubing for the production of diazomethane in-situ, from Diazald.®

The precursor Diazald® **16** is introduced to a base through the inner tubing which produces the gaseous diazomethane. Diazomethane then passes through the permeable membrane to the outer tubing where the acyl chloride is waiting in anhydrous THF. The side products from the diazomethane are safely disposed of from the inner tubing and the diazo compound produced is then transferred for a further reaction, in this case for the synthesis of α -haloketones. Additionally it was shown that subsequent methylations, [2+3] cycloadditions and cyclopropanations were possible using this method of diazomethane generation.

1.1.4 Solid liquid conditions

Heterogeneous conditions not only exist between gas and liquid, but solids can be used in continuous flow in the form of cartridges containing a solid reagent. The use of solids in continuous flow may sound strange, due to the associated risks of blocking in microreactor technologies, but methods using cartridge-based reagents have been developed.^[31] These reagents can generally be resin supported catalysts such as chiral ligand complexes and organocatalysts or stoichiometric reactants like amberlyst exchange resins; to non-resin bonding supports such as Pd/C or Fetizons reagent (Ag_2CO_3 on Celite®). Flow chemistry again offers a large benefit of increased surface interaction with the solid with minimal to no separation of the solid particulates at the end of the reaction.

Ley and co-workers here worked extensively in this area and has shown many novel processes using such techniques. A recent example has shown the use of manganese dioxide as a solid oxide for the generation of diazo compounds **18** from hydrazones **17** which are subsequently reacted with boronic acids in an $\text{sp}^2\text{-sp}^3$ cross coupling to form products **19** in yields of up to 95% (Scheme 1.6).^[32]



Scheme 1.6: Generation and subsequent reaction of in-situ generated diazo compounds.

As well as being used as reagents, cartridge type chemistry has been applied in many other practical applications. Purification techniques have been developed where removal of unwanted reactants from previous inline steps can be accomplished by trapping, via scavengers. Systems in which solubilized reagents are trapped onto monolith based reagents have also been developed. Known as a “catch and release” protocol, the reactant is fed into

the monolith, trapped via a weak interaction i.e. a salt formation, and then subjected to the reaction conditions, washed to remove unreacted reagents and side-products. It is then finally released to afford the product with minimal work-up and purification.

The success of such flow techniques has led to commercialised products becoming available most notably the Thales Nano H-Cube and Omnifit glass columns.

As stated the idea of continuous flow with solid particulates sounds challenging but some methods provide solutions to this problem. Using ultrasound is one method for this. Buchwald *et al.* showed that a palladium-catalysed amination reactions can be achieved in continuous flow Figure 1.8.^[33] They observed clogging of the channels under standard flow conditions stopping the overall system.

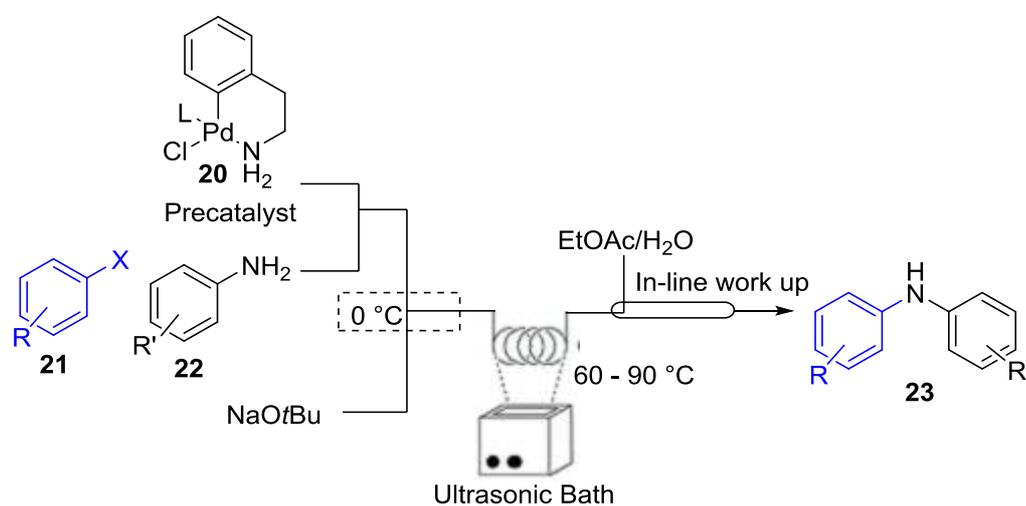


Figure 1.8: Pd coupling of aryl halides with anilines in flow assisted by ultrasonic radiation. L = BrettPhos. This was solved by acoustic irradiation. The sonication of the reactor coil then allowed a rapid synthesis of substrates ranging from 20 s to 10 min of residence time.

1.4 Miscellaneous techniques

The benefit of a closed flow system can allow for extreme changes in reaction conditions. By just an addition of a BPR, Figure 1.9^[34] solvents can then be heated to temperatures well above their boiling points in a safe and facile manner. Solvents can therefore be used in a subcritical or even supercritical state with added benefits of increased solubility and reactivity. These harsh conditions can then be applied safely as they are only exerted over a smaller volume compared to that of a traditional batch reactor.

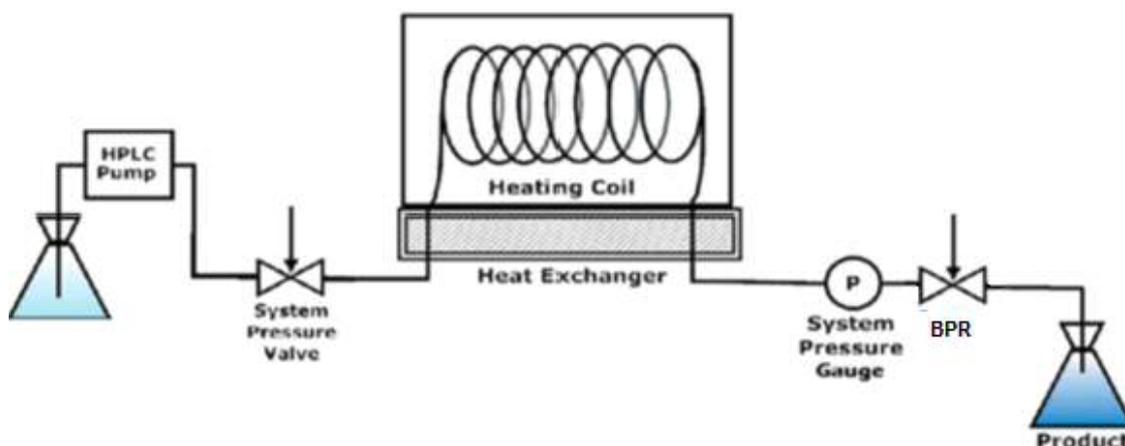


Figure 1.9: Schematic diagram of a pressurised flow reactor. Adapted from^[35].

A system as shown in Figure 1.9 has been used by Wirth and co-workers.^[36] They showed the synthesis of amides with varying functionality with cheap commercially available reagents at temperatures of 200 °C and pressures of 20 MPa. Yields were very good ranging from 55-97% in 5 min as shown in Scheme 1.7 compared to the reaction time in the batch protocol (150 °C, 48 h).



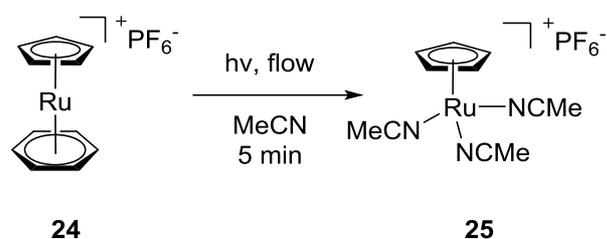
R = Aryl, Alkyl, Heteroaryl

Scheme 1.7: Synthesis of amides from aldehydes using a high temperature pressure flow reactor (steel tubing reactor (length: 1 m, internal diameter: 1.6 mm) in a GC oven) analogous to the system in Figure 1.9

Not only has the aforementioned technique been adopted for continuous flow, but many other batch type techniques have been adapted to take advantage. The numerous inherent benefits at working at small volumes and larger surface areas allow for increased efficiency some of which are listed below.

Photochemical microreactors use the huge increase in surface area to dramatically reduce the path length of the irradiation through the solvent. Thus a much more efficient irradiation can be achieved, decreasing reaction time and increasing selectivity. When moving to larger scale reactions, the power of the light source does not have to be changed and this can reduce costs significantly. A general reactor is essentially designed in the same manner as a conventional batch reactor with a jacketed UV lamp but with the addition of the coiled reactor around the jacket. This can be used to cause transformations solely or together with a photocatalyst. The photocatalyst can be introduced in two distinct ways: in solution like a conventional system or as a coating on the tubing which is beneficial for catalysts that are not readily soluble.

One such method described by Jamison *et al.* ^[37] shows the dramatic effects of an increased surface area allowing for a much more efficient irradiation and therefore, in this case, rate of reaction. The ligand exchange reaction of **24** to **25** that usually takes 36 h to go to completion was enhanced to 5 min in continuous flow as shown in Scheme 1.8.



Scheme 1.8: Synthesis of CpRu(MeCN)₃PF₆ in a photochemical flow reactor.

Although still in its infancy another technique for flow synthesis is the use of electrochemistry reactors. Again there are problems associated with scale up in batch chemistry, such as large volume of electrolyte and therefore it is hoped that flow chemistry can solve this. Addressing the problems of an inhomogeneous electric field and the loss of energy associated with Joule heating can hopefully lead to this being a viable technique within fine chemical processing due to its “green” nature.

Wirth *et al.* showed a recent example of deprotection of phenols and thiophenols using a continuous flow microreactor. The deprotection of the iNoc-group was accomplished in 92 s.

With the addition of 50 mM of TBAI and a current of 30 mA yields of up to 61% in DMF/H₂O were obtained.^[38]

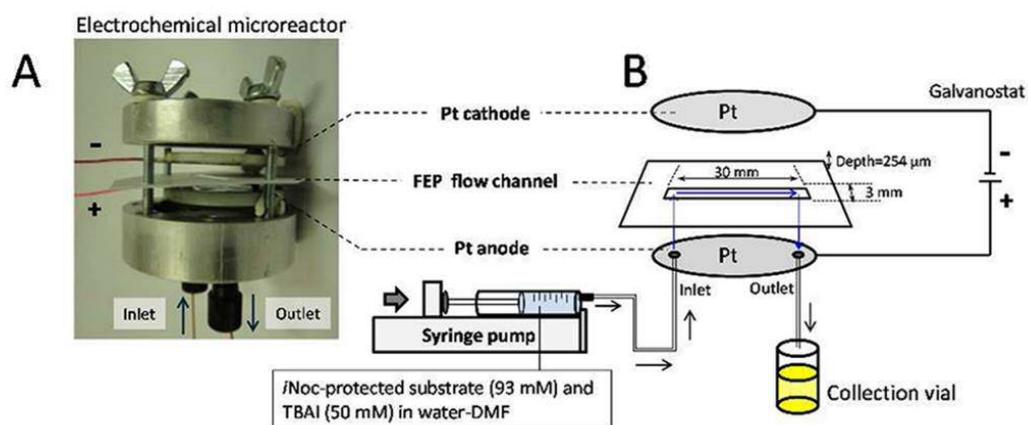


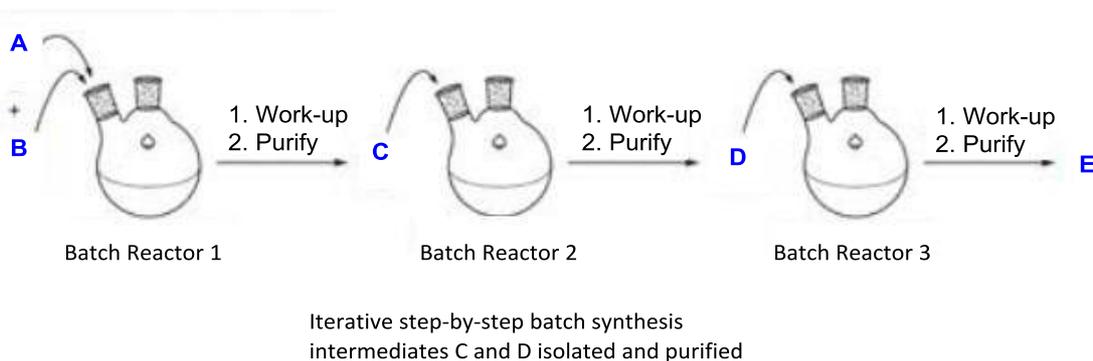
Figure 1.10: Schematic of the electrochemical reactor used in the deprotection of iNoc-groups.^[38]

The benefit of using such a purposely designed reactor is within the fabrication. With only an internal volume of 23 μl the distance between each electrode is minimal (100 μm) which allows for the absence of an electrolyte (Figure 1.10). This obviously has the potential to be highly advantageous in terms of cost when moving to a preparative scale.

1.5 Multi-Step Synthesis

With the move towards process engineering, and with flow chemical techniques ever growing, the idea of multi-step synthesis for production of more complex target molecules has become within reach. The traditional method of synthesis of C from reagents A and B followed by purification has been used for decades.

(a) Traditional multi-step synthesis



(b) Continuous flow multi-step synthesis

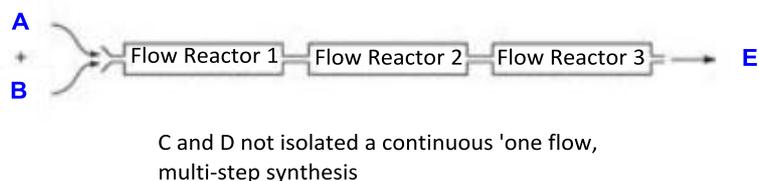


Figure 1.11: Multi-step synthesis strategies in batch and continuous flow (adapted from Jamison *et al.* [37]).

Multi-step synthesis in continuous flow has sought to circumnavigate this by in-line quenching, purification and analysis without the need for isolation (Figure 1.11). Therefore the idea that more complex molecules can be made in flow synthesis is being realised. Multiple examples of this have been reported in the literature.^[37]

A good example of multi-step synthesis in continuous flow has been described by Jamison *et al.*^[39] The synthesis of Ibuprofen **29** was completed in three steps including an in-flow extraction from readily available starting materials (**26** & **27**) in 3 min of residence time (Figure 1.12). They showed that 8.09 g of Ibuprofen **29** could be synthesised every hour making this technique a powerful tool for chemical processing.

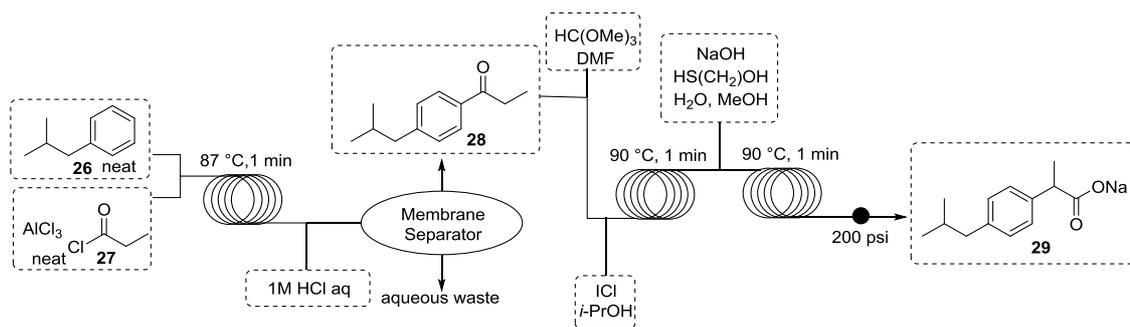


Figure 1.12: Multi step flow synthesis of Ibuprofen demonstrated by Jamison.

One large step in the pursuit of multi-step synthesis in continuous flow has been the production of “in-line work ups”. These systems work by using a hydrophobic membrane separating two channels, one channel for the organic phase and another for the aqueous phase. The reaction mixture is then introduced to an extraction solvent and an aqueous wash, usually with mixing, via two separate pumps. The unwanted side products are removed in the aqueous extraction and the product mixture is allowed to pass through the membrane into the organic phase. This can then be eluted or continued, by clever choice of solvent, onto the next reaction step. An example of this has been shown in the previous example by Jamison where the side products from the Friedal Crafts reaction are separated before the organic product is continued onto the second transformation.

Other examples consist of gravity type in-line separators where a column containing an aqueous solution is suspended via a clamp. The reaction mixture is then fed into the column via an exit tube which is submerged into the aqueous solution. Above this aqueous solution is an organic extraction solvent which is introduced via a secondary pump. The density difference then allows the reaction mixture to rise through the aqueous solvent into the organic phase which can then be pumped out via a third pump.

1.6 In-line Analysis and automated control

In recent work methods to monitor reactions in-line have been extensively produced. Unlike a batch style reaction, where thin layer chromatography can be used to monitor the progress, this cannot be done with continuous flow technologies part way through the reaction. It has therefore been the work of some research groups to find a way of monitoring reactions inline. Multiple methods have since been used such as infra-red spectroscopy (IR), GC, HPLC and even NMR.

IR spectroscopy has been used widely in the last couple of years for the in-line monitoring of reactions. Ley and colleagues^[40] showed that this process can be used to monitor the formation of arylmagnesium reagents **31** in-line (Figure 1.13). It was demonstrated that the concentration of the formed Grignard reagent could be observed over time and therefore the residence time could be tuned to allow for maximum conversion to the Grignard. Once these conditions have then been optimised a second step can then be coupled to quench the Grignard, in this case by an aldehyde.

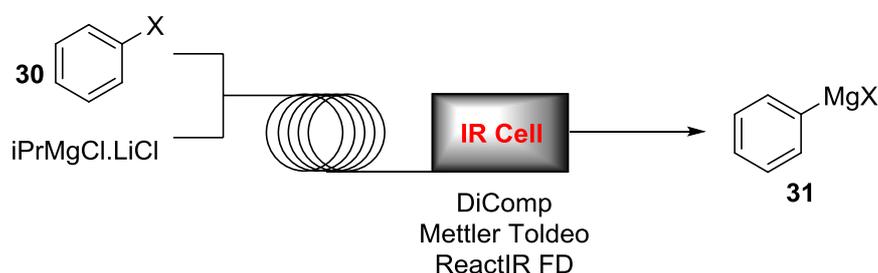
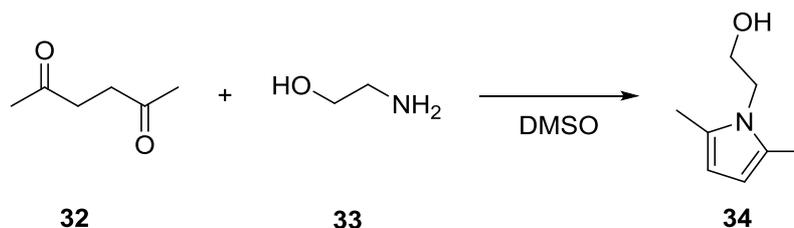


Figure 1.13: In-line IR cell used to monitor the production of Grignard reagents in-situ.

This data gathered by these spectroscopic techniques has allowed for the collected data to be reviewed by being fed to a computer. The system can, with the correct software, interpret, analyse and react to tune the reaction conditions without the need for human control. Again multiple groups have established such protocols.

One such example has been developed by Jensen *et al.* using a similar ReactIR protocol.^[41]

The system involved Paal–Knorr reaction of 2,5-hexanedione **32** and ethanolamine **33** in dimethyl sulfoxide (DMSO) (Scheme 1.9) which they used to demonstrate a multitrajectory optimisation strategy to maximise the rate of production by reaching the optimised conditions as efficiently as possible.



Scheme 1.9: Synthesis of pyrole **34** using a multi-trajectory flow system for rapid optimisation of conditions.

The IR cell was used to monitor the mixture continuously and when paired with a microstructured device, the use of reagents was kept to a minimum by making sure that steady state was reached before moving to the next condition Figure 1.14.^[41]

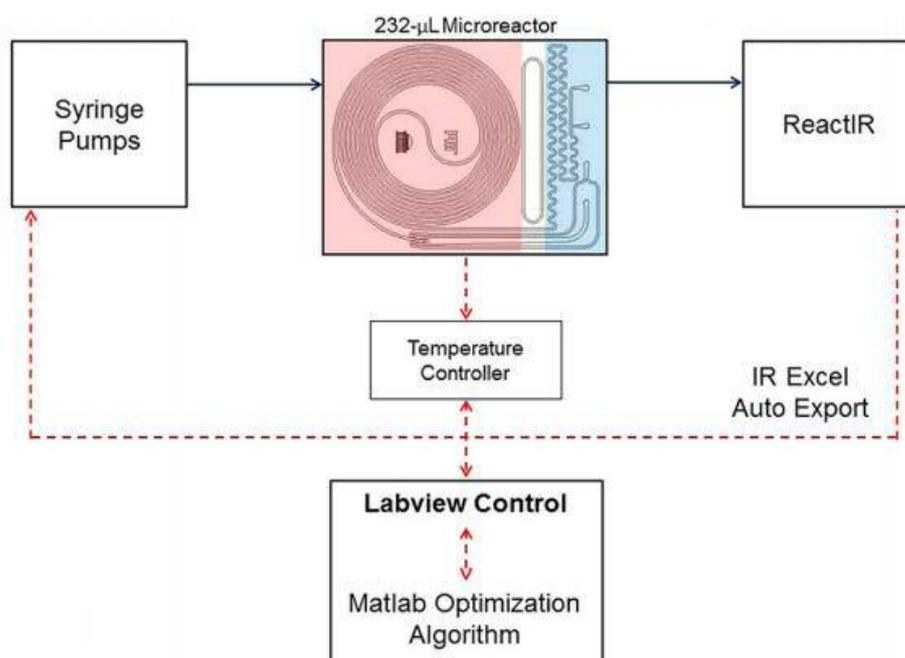
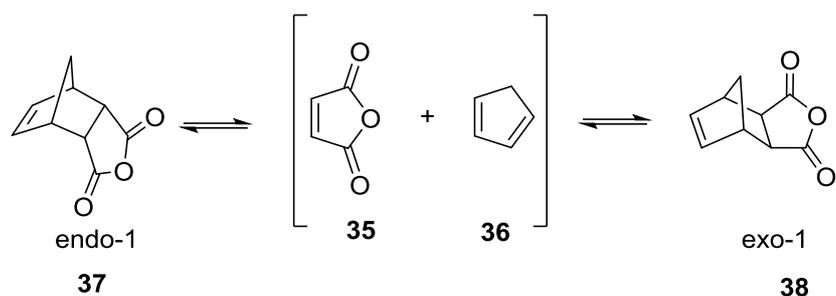


Figure 1.14: Multitrajectory optimisation strategy for rapid optimization of reaction conditions. Adapted from ^[41].

Another example of such a method has been developed by Welch and co-workers.^[42] They showed that a microflow HPLC (Figure 1.15) could be used to monitor the reaction in-line. The Diels-Alder reaction of maleic anhydride **35** with cyclopentadiene **36** was used to show the versatility of such a system Scheme 1.10.



Scheme 1.10: Isomerisation of **35** and **36** via a Diels-Alder reaction.

By changing the flow rates and switching to the HPLC at different residence times, they could model the isomerisation within the reaction as a ratio of starting materials to product at their specific retention times of each isomer, exo **38** and endo **37**.

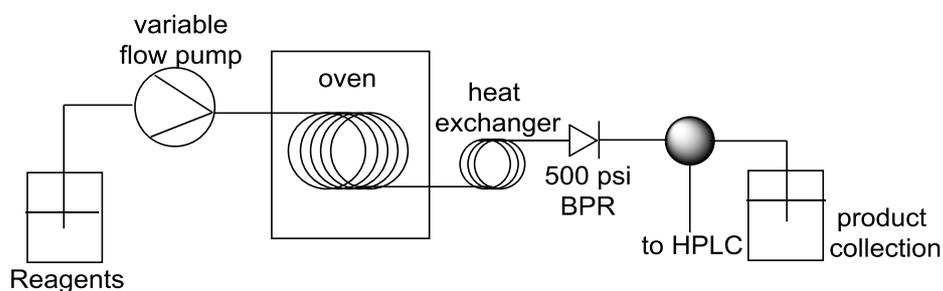


Figure 1.15: Schematic diagram of inline HPLC analyse for the Diels-Alder reaction of cyclopentadiene and maleic anhydride.

By monitoring the different temperature profiles and residence times a 3 dimensional plot could be obtained to profile the reaction and thus choose the optimal conditions for the each isomer., with longer residence times (10 min) being optimal for the exo isomer and shorter (0.2 min) for the endo.

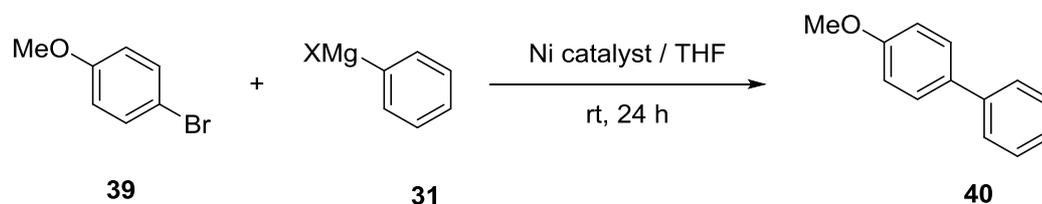
1.7 Scaling up

One of the many challenges associated with chemical processes and their use within industry is scaling up. When moving to pilot scale or production scale away from the laboratory, a number of issues have to be resolved to allow for the same yields, selectivity and safety. As mentioned before when scaling up safety concerns become a problem when dealing with reactions that are highly exothermic. Adiabatic runaway, although not an issue within a lab, could become a serious problem in large scale batch reactors. Furthermore when scaling up to large scale reactors mixing time can become significantly longer than the reaction rate and therefore this could lead to “overcooking” of a reaction. A few methods have been devised to try and solve these problems within flow chemistry, these being: increasing reactor size, numbering up and scaling out.^[43]

The most logical and simplest method is to increase the tubing diameter and therefore the reactor volumes. This can be useful for reactions that are not highly dependent on heat transfer and diffusion where mixers can be used to partially control this.

Numbering up or parallelization consists of numerous reactors being placed in parallel therefore running the same system without changing concentration, residence times or heat transfer. This is obviously advantageous as original conditions have no need to be modified, although, the drawback is the significant costs where multiple pumps are needed.^[44]

Finally, the third method that is being conducted within industrial processes is scaling out.^[45] This means that a reactor is left to run for a much longer time. Instead of creating, for instance, a milligram quantity within minutes, gram quantities could be synthesised within hours, although this is not the most efficient process. An example of this method in use has been demonstrated by Styring (Scheme 1.11).^[46]



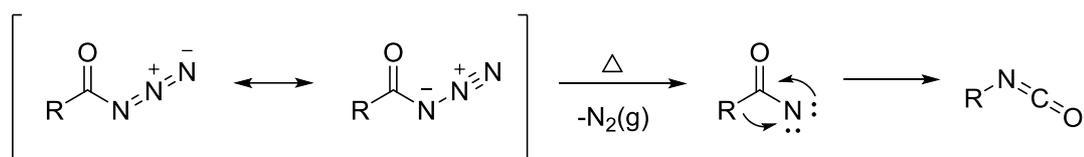
Scheme 1.11: Kumada coupling of 4-bromoanisole with phenylmagnesium halide to form 3-methoxybiphenyl **40** under Ni catalysis in flow.

They demonstrated a Kumada coupling of 4-bromoanisole **39** with aryl magnesium halides **31** within a meso flow reactor under Ni catalysis. By running the reactor for 24 h they were able to produce 137 g of product yield **40**. This was all done without the need for changing the reactor size, as running for longer circumvented the need to scale-up.

2.1 Introduction to diazidation reactions

2.1.1 Azides in organic synthesis

The first preparation of an organic azide was reported by Griebner in 1864 where he produced phenyl azide by diazotization of phenylhydrazine with nitrous acid.^[47] Since then further work has been done by Curtius when he produced hydrazoic acid and applied it to what is now known as the Curtius rearrangement, the formation of isocyanates from acyl azides (Scheme 2.1).^[48,49]



Scheme 2.1: The Curtius rearrangement of acyl azides to form isocyanates.

The first interpretation of the structure for an azide moiety was devised by Curtius and Hantzsch where a 3-membered ring, 1*H* triazirine was suggested, Figure 2.1 a).^[48-50] This has since been revised to the current system of a linear structure, Figure b). The nature of the N₃ π-bond is the reason for such energetic properties as these bonds can be very easily polarised leading to the release of nitrogen.^[47]

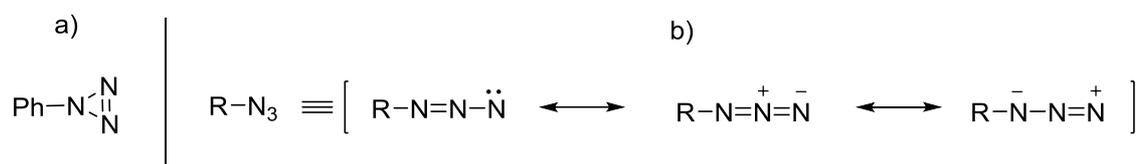


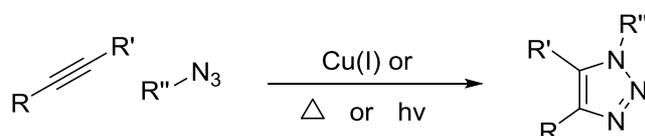
Figure 2.1: a) First proposed structure of an azide compared to b) modern interpretation.

Azide chemistry has had a huge increase in interest in the last couple of decades after previous neglect until the 1960s.^[51-54] This has been due to the large increase in safety aspects permitted by modern technological advancements. Azides pose a substantial risk compared to other functional groups. The extremely high energy that organic and inorganic azides possess can therefore lead to explosive properties.

Azides are highly energetic on cleavage and after cleavage a very reactive nitrene group is left behind. Generally, the addition of an azide group to an organic compound increases its energetic property by approximately 290-355 kJ/mol.^[55] This shows why it is considered to be

a hazardous group but also how applicable it can be in energetic polymers, propellants and other high energy density materials. ^[56,57]

Azides have been used extensively in organic synthesis due to their versatility and ease in access to many nitrogen containing compounds such as aziridines,^[58] azirines,^[59] triazoles^[60] and tetrazoles.^[61] Most notably, and recently, a large amount of work has been described for their access to nitrenes^[62] and even formation of diazo compounds leading to carbenes.^[63] Furthermore, azide groups can be easily reduced to amines^[64] through a number of methods leading to their huge utility in natural product synthesis.^[65] Due to the rapid addition to other dipoles they have also seen great interest in a modern type of chemistry that is “Click Chemistry” (Scheme 2.2). ^[66]



Scheme 2.2: Click chemistry of azides with acetylenes to form triazoles.

2.1.2 Azide chemistry in microreactors

Equipment that has allowed for the safe use of azides in synthesis has been microreactor technology and many articles have been published in the last two decades on the subject.^[67] Their ability to allow for small amounts of reactive intermediates to either be produced at a given time or for hazardous groups to be subjected to extreme conditions has garnered much attention.

To demonstrate this approach multiple groups have shown the Curtius rearrangement in continuous flow. Jensen and co-workers showed a highly efficient system of the Curtius rearrangement under multi-step phase transfer conditions (Figure 2.2).^[68] The formation of the acyl azide **42** was shown using heterogeneous liquid-liquid conditions and the organic phase separated in-line removing the aqueous by-products. The rearrangement was then achieved in the following reactor whereupon formation of the isocyanate **43**, nitrogen gas was expelled. The N₂ gas was then separated in a second separation method in-line.

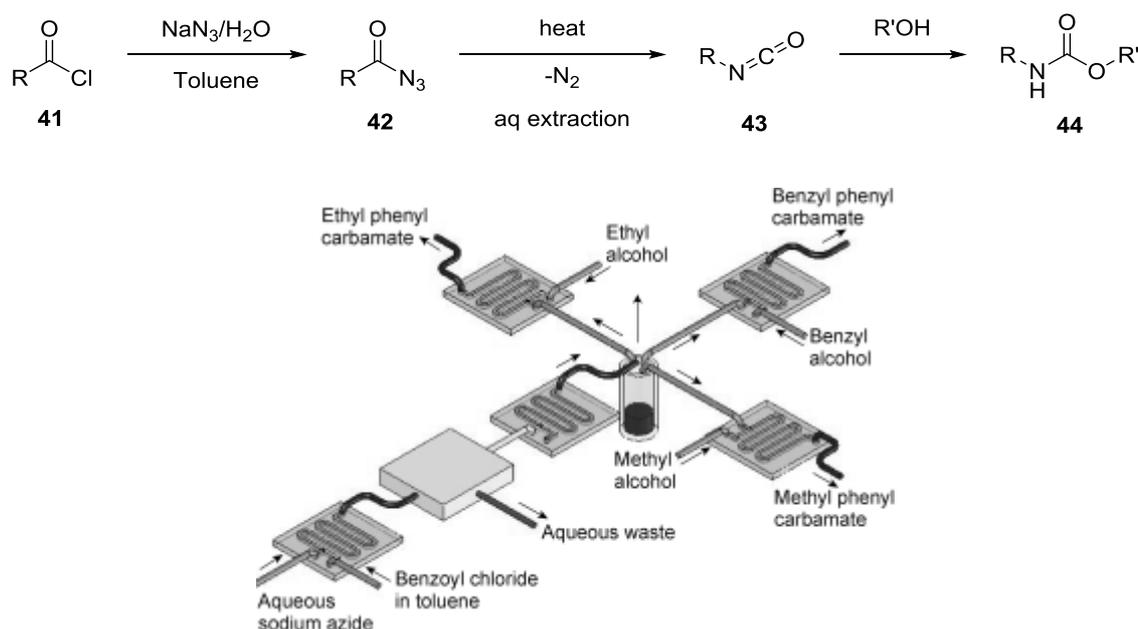


Figure 2.2: Multi-step flow Curtius rearrangement demonstrated by Jensen *et al.*

Ley *et al.* demonstrated two distinct methods of azide sources in flow.^[69] A homogeneous method of DPPA (diphenylphosphoryl azide) **45** was used in combination with triethylamine to transform a carboxylic acid into the desired isocyanate and subsequent urea or carbamate (Figure 2.3). The reagents were mixed prior to heating within a cartridge containing magnesium sulphate and heated to 120 °C using a microwave heater. High yields of 75-90% were produced

with purities of >90%. This was due to the scavenging of the side products (TEA and phosphoric acid) by the Amberlyst 21 and 15 cartridges in succession post to the reaction.

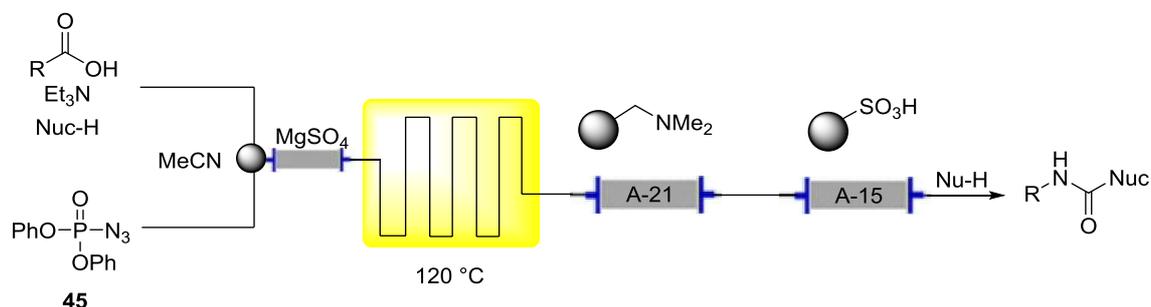


Figure 2.3: Flow based Curtius rearrangement showing in-line cartridge based purifications.

A heterogeneous method was described where the azide source could be preloaded onto a quaternary amine in a cartridge which upon reaction with the acyl chloride is then exposed to the high temperature of 120 °C required in a secondary coil Figure 2.4.^[70]

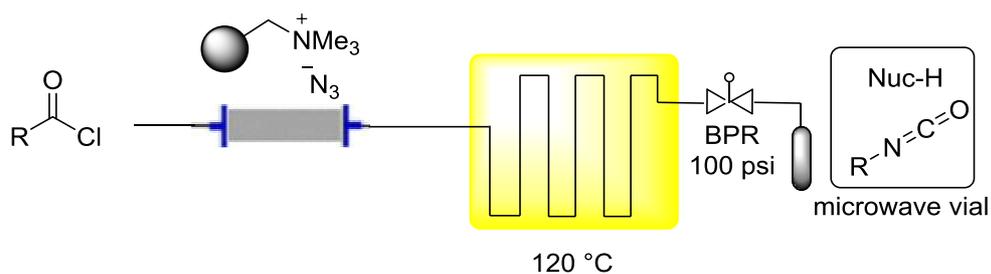


Figure 2.4: Formation of isocyanates using supported azide reagent from acyl chlorides.

This is highly beneficial as the unreacted source of azide is not involved with the second step and therefore reduces the inherent risk of heating larger concentrations of azide. The monolith can be reused multiple times and produced the isocyanates in good yields. The isocyanates were then further reacted with nucleophiles such as alcohols or amines to produce carbamates or ureas respectively. Thirdly due to the distinctive signal produced by the azide group, Ley has demonstrated an in-line IR method for the detection of the acyl azide generated in flow by monitoring the evidence of HN_3 .^[71] This can allow for an easy method of manipulation to optimise conditions rapidly.

The Curtius rearrangement was one of the first reactions discovered using azides but since then many more have been demonstrated. Flow chemistry has followed this path and other reactions using azides have been developed taking advantage of the properties of flow chemistry. The Huisgen cyclization is notable for the high temperatures needed to form a

triazole from an alkyl azide and an alkyne. More recently copper catalysis has been used to allow for reduced temperatures, but still in most cases higher temperatures are needed. Bogdan *et al* demonstrated a copper-catalysed cycloaddition of alkyl azide **48** with alkyne **46** using copper tubing as the catalyst at 150 °C (Figure 2.5).^[72] The intermediate organic azide was generated *in situ* from **47** and NaN₃ and then directly reacted with the alkyne in one continuous flow setup. Yields ranged from 26 to 88% in a 5 min residence time.

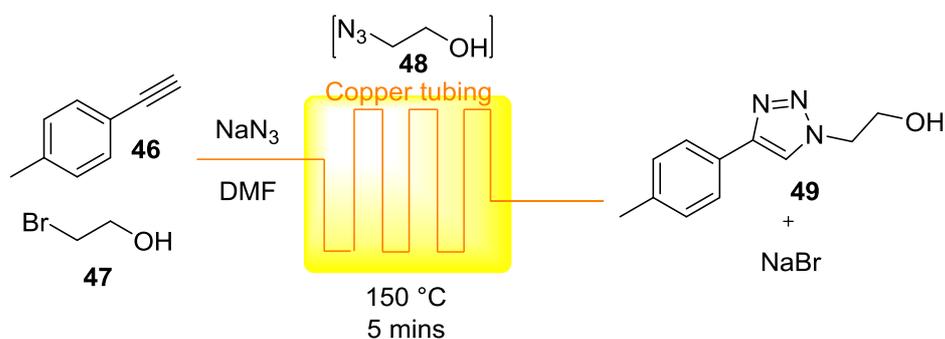


Figure 2.5: Triazole formation via the Huisgen click reaction catalysed by copper tubing.

Since this work many other reports have shown the usefulness of continuous flow for the formation of triazoles. The same authors demonstrated further application for the system described where excellent regioselectivity was attained for the synthesis of large ring sized macrocycles containing a 5-iodo-1,2,3-triazole. A second step of a Pd-catalysed coupling after the addition of the alkyl azide to an alkynyl halide fashioned a large library of easily accessible macrocycles in a two set-up flow synthesis.^[73]

A report from Kirschning showed the formation of vinyl azides **52** and their subsequent cycloaddition to form triazoles **54** (Figure 2.6).^[74]

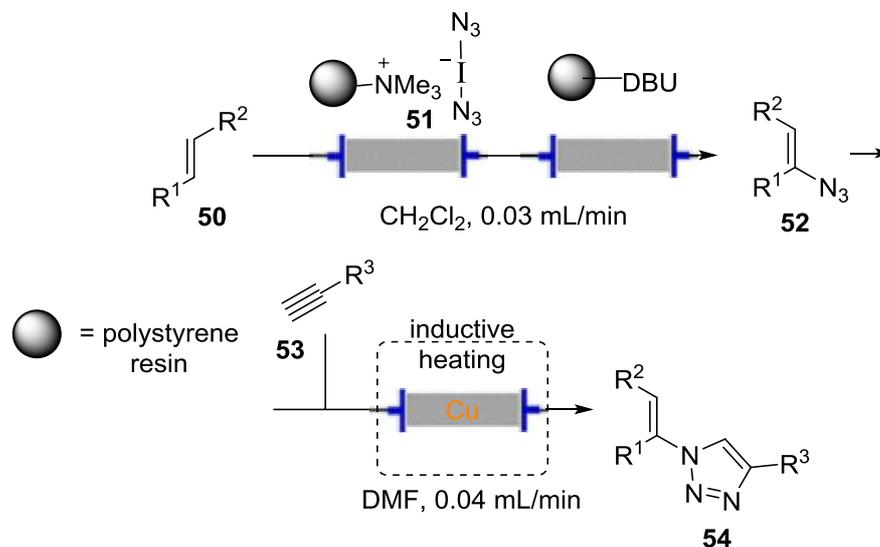


Figure 2.6: Vinyl azide synthesis by polymer supported I(I) reagent followed by triazole formation via the Huisgen click reaction catalysed by copper.

The use of a polymer supported iodine (I) reagent **51** consisting of a quaternary amine with an iodine diazide counter anion, iodine and azide was added across olefins **50**. The further elimination of HI using supported DBU allowed for the formation of vinyl azides **52** which were then cyclised with alkynes **53** in DMF under copper catalysis (Figure 2.6).

A similar system was developed by Fülöp *et al.* showing the (large scale) gram synthesis of novel 1,2,3-triazole-modified β -aminocyclohexanecarboxylic acid derivative **57** from a click reaction of **55** and **56** Figure 2.7.^[75] In addition the temperature was reduced to room temperature by the supplementing of basic and acidic co catalysts (acetic acid and DIPEA).

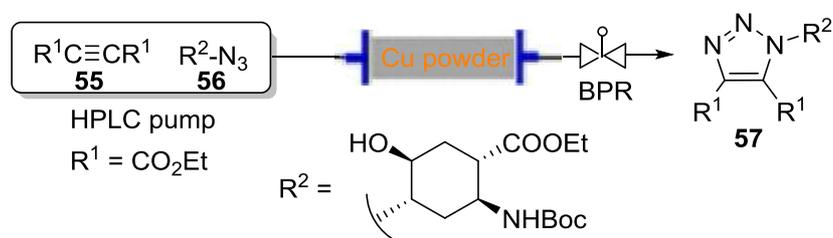


Figure 2.7: Gram scale formation of novel β -amino acid triazole via click reaction in flow.

Very recent work has shown the use of polymer supported copper nanoparticles for the catalysis of the cycloaddition of phenyl azides **58** and phenylacetylene **59** Figure 2.8.^[76]

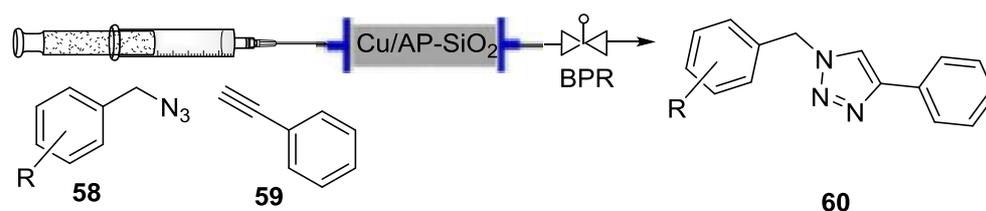


Figure 2.8: Click reaction in flow using Cu supported nanoparticles for the synthesis of triazoles.

Using flow chemistry as a method, they showed the reusability of the nanoparticle system with excellent conversions in up to 12 uses with minimal leaching of the metal.

Further uses of extreme heating not only have been shown for reactions such as the Huisgen cyclisation but also the formation of tetrazoles from azides in the presence of nitriles. The growing interest sparked from their use as bioisoteres of carboxyl groups ^[77] has led to a number of publications in flow chemistry. Kappe developed a synthesis of tetrazoles from organic nitriles and in-situ generated hydrazoic acid Figure 2.9.^[78] Conversions were excellent within a residence time of 10 minutes at temperatures ranging from 160-220 °C. They also showed the application of flow chemistry for scale up within these reaction conditions where one process allowed for 18.9 g of 5-phenyl-1*H*-tetrazole to be produced.

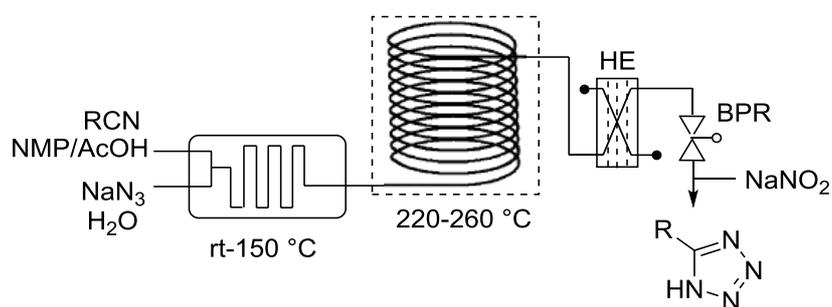


Figure 2.9: Tetrazole formation using high temperature conditions under continuous flow.

Further work within this area was published by the same authors additionally showing the decomposition of tetrazoles at extreme temperature profiles. It was shown that toxic products such as HN_3 could be produced from the decomposition and therefore demonstrates that the continuous nature of flow chemistry allows for a much safer protocol compared to batch conditions.^[79] To avoid the potential of forming such highly toxic compounds such as HN_3 , Jamison devised a similar set-up without the formation of HN_3 . Conditions were virtually identical but with the absence of a proton donor such as acetic acid. Reaction times were longer within the range of 30 min but yields of the desired products were not diminished due to the lack of acetic acid using near equimolar amounts of sodium azide. They also

demonstrated an in-line quench using sodium nitrite followed by addition of sulphuric acid to consume the residual azide ions in solution.

Thermolysis of azides has been shown to be facile within flow chemistry set-ups. The Hemetsberger-Knittel synthesis of indoles has been presented in recent years by two groups. Seeberger *et al.* demonstrated the formation of indoles **62** from azido acrylates **61** Figure 2.10.^[80]

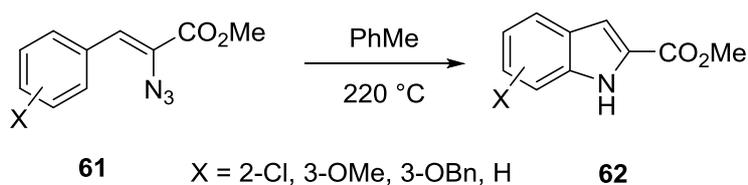


Figure 2.10: Formation of indoles from azido acrylates via the Hemetsberger-Knittel reaction in flow.

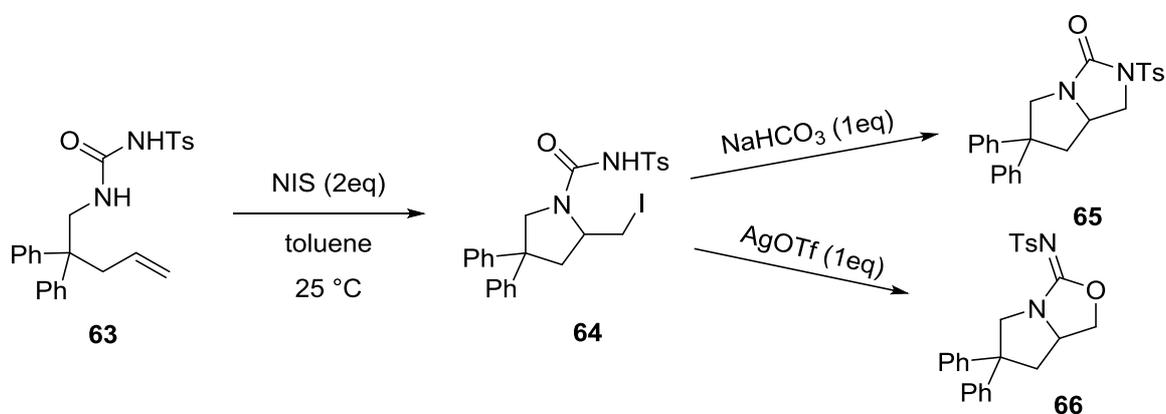
They showed that using the properties of flow chemistry to allow for solvents to be heated above their standard boiling point, high boiling solvents and sealed tubes could be avoided. Using toluene at temperatures ranging from 180-220 °C excellent yields of up to 99% could be obtained in much shorter reaction times than conventional methods.

2.1.3 Iodine reagents and their use in diamination reactions

The existence of organic hypervalent iodine was first discovered in 1886 by C. Willgerodt.^[81] He showed the synthesis of PhICl_2 from iodobenzene and chlorine gas. Huge interest has been observed over the last few decades and hypervalent iodine reagents have been used in many organic syntheses as mild and selective oxidants.^[82] Moreover hypervalent iodine reagents have been extensively in many useful synthetic protocols. Numerous bond forming reactions have been demonstrated such as carbon carbon, carbon-heteroatom and oxidative rearrangement reactions.

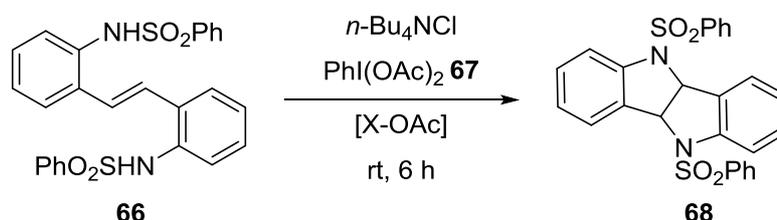
Hypervalent iodine reagents have been used largely for carbon-heteroatom bond formation and in recent years have been successful for multiple accounts of metal free diaminations.^[83] The use of iodine compared to many transitions metal catalysed reactions presents a more environmentally friendly approach. Muñiz and co-workers have been at the forefront of such a transformation after their original dual hypervalent iodine-Pd-catalysed intramolecular diamination of olefins.^[84] Later a metal free method using already exploited substrates was devised.

Widenhoefer *et al.* showed that *N*-iodosuccinimide (NIS) can be used to activate the double bond and upon attack of the urea **63**, form the intermediate of nitrogen iodine addition **64**.^[85] With addition of sodium hydrogen carbonate the iodine could then be displaced by the second nitrogen of the urea to produce **65** Scheme 2.4. Furthermore, if silver triflate was used instead of a base, displacement of the iodine could occur via the oxygen in an oxyamination reaction **66**. The latter has since been performed enantioselectively by Wirth *et al.*^[86]



Scheme 2.4 : Diamination and oxyamination of double bonds using NIS to form bicyclic compounds.

A further intramolecular addition was established by Chang *et al.* where they attained an intramolecular diamination of olefins **66** to form bisindolines **68**. This was achieved by an *in situ* generation of a halogen(I) reagent from (diacetoxyiodo)benzene (DIB) **67** and potassium iodide or *tert*-butyl ammonium chloride (Scheme 2.5).^[87] Yields were up to 95% within 6 h and the method showed a reasonable substrate scope.



Scheme 2.5: Intramolecular diamination of olefin **66** to form bisindoline **68** via iodine (I) activation.

Not only have intramolecular diaminations been demonstrated using hypervalent iodine but more recently intermolecular diamination protocols have been established. Muñiz later described that a bench-stable nitrogen containing iodine reagent **69** could be synthesised by simple ligand exchange with (diacetoxyiodo)benzene Figure 2.11.^[88]

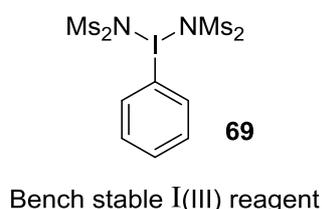
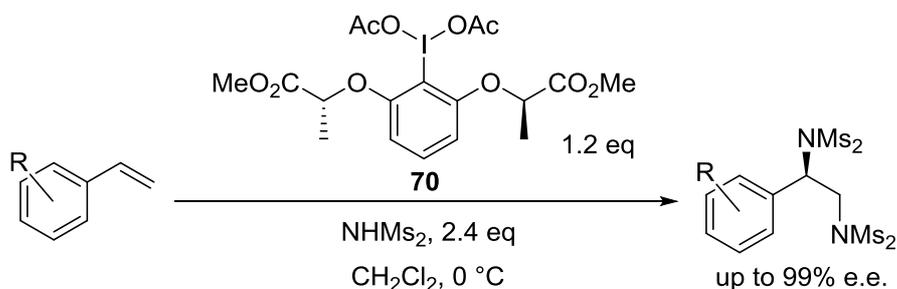


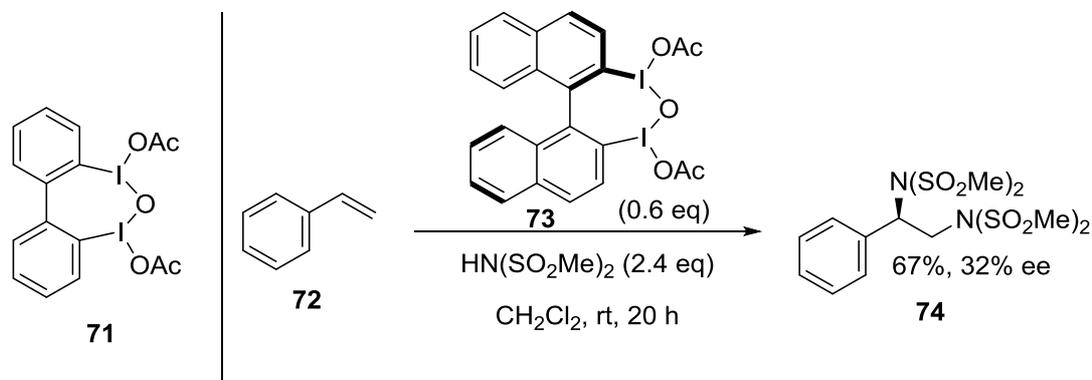
Figure 2.11: Bench stable dimesylamineiodobenzene reagent produced by Muniz *et al.*

They then demonstrated the first enantioselective diamination of styrenes Scheme 2.6. Yields were moderate to good (44%-75%) with excellent stereochemical control of up to 99% using reagent **70**. A large functional group tolerance was observed for moieties such as esters and halides, showing the mild nature of such reagents.



Scheme 2.6: Stereoselective diamination of styrenes controlled by lactate based iodine reagent.

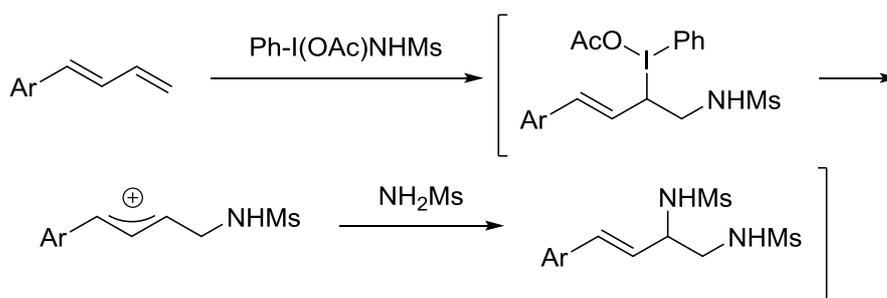
Muñiz again extended the diamination field with work using a novel dinuclear iodine (III) reagent **71**.^[89] They used this for the same reaction of intermolecular diaminations for styrene derivatives accomplishing good yields with a range of substrates.



Scheme 2.7: a) Novel dinuclear iodine reagent b) Enantioselective diamination of styrene using novel binaphthyl iodine reagent.

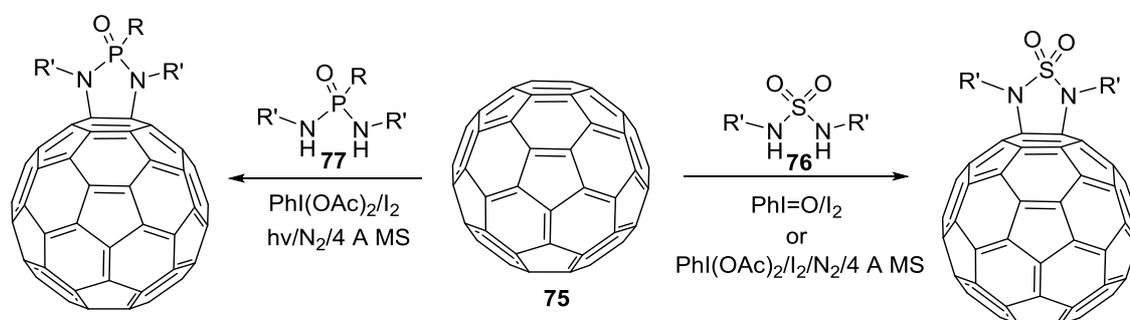
The structure of the reagent translates very well to binaphthyl type compounds (**73**) and therefore presents a novel reagent class for stereocontrol of such reactions. They demonstrated this was possible attaining **74** in 67% yield with ees of 32%. (Scheme 2.7).

Muñiz has since extended the use of (bisdimethylaminoiodo)benzene to demonstrate the regioselectivity of such reagents on reaction with conjugated dienes and trienes.^[90] They successfully showed that the terminal olefin of the conjugated alkene systems could be selectively aminated leaving the internal alkenes untouched Scheme 2.8. Yields again were very good for such transformations. When using butadiene systems, addition of the amines occurred at both terminal positions. The electrophilic addition of the iodine reagent occurred at the less hindered olefin followed by attack of the nitrogen source. Upon elimination of iodobenzene an allylic cation is formed and due to the absence of the aryl group to stabilise the addition at the internal position of the allyl cation addition at the external less hindered site occurs.



Scheme 2.8: Regioselective diamination of dienes by a hypervalent iodine (III) reagent.

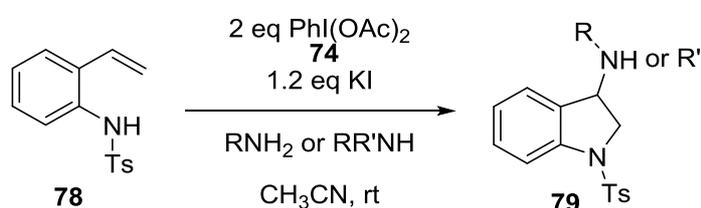
Not only have styrene systems been intermolecularly diaminated but Miao and co-workers have devised a protocol to functionalise fullerenes (**75**) by addition of sulphamides **76** and phosphoryl diamides **77** mediated by hypervalent iodine.^[91]



Scheme 2.9: Addition of sulphamides and phosphoryl diamides to fullerene using an I(III) and I₂ combination.

DIB and iodosylbenzene were used as reagents for this transformation in combination with I₂ Scheme 2.9. They also showed that when DIB **67** was used the reaction went through the formation of an aziridine. Oxidation of a benzamine intermediate to a benzimine followed by hydrolysis formed a primary amine this was then further oxidised to undergo aziridination.

Further work has moved on to describe intra/intermolecular diamination reactions where one nitrogen moiety is tethered to the molecule and a second is introduced externally. Two systems have been reported recently. Johnston *et al.* have demonstrated the formation of indoline **79** from 2-amino styrene **78** derivatives Scheme 2.10.^[92] Addition of DIB **74** in combination with potassium iodide in MeCN allowed for cyclisation onto the styrene followed by trapping with either a primary or secondary amine to form the desired products **76**. Yields were good to excellent and completed within an 18 h time frame at room temperature.



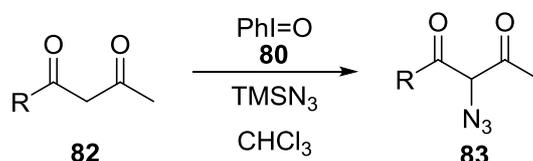
Scheme 2.10: Formation of dihydroindoles by intra/interdiamination of styrenes.

The second system was used for either oxyamination or diamination of double bonds where the choice of the iodine reagent was key to the product formed. The use of a diprotected nitrogen species bonded to the organic hypervalent iodine was the nitrogen source for this

transformation and in combination with the tethered amidine nitrogen, diamination could be performed. The addition across the double bond was achieved in dichloromethane and they attained yields of up to 85% when mesyl was used as the protecting group.

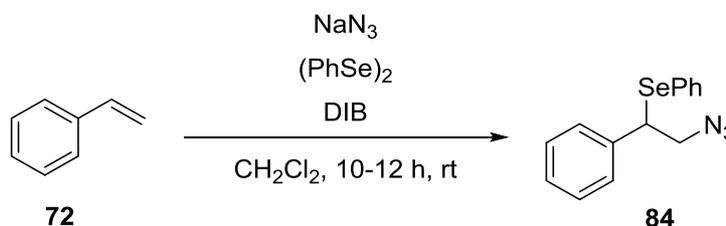
2.1.4 Hypervalent iodine compounds in combination with azides

Oxidation with azides has been commonplace within the literature with multiple methods developed to oxidatively add azides to electron rich sites. Methods range from metals such as Mn,^[93,94] Fe^[95] and Ce^[96] to iodine compounds^[97]. Hypervalent iodine has proved to be a successful method for the addition of azides to double bonds and alpha carbonyl positions and has been reported in some cases. The majority of work presented in the literature has been developed before the turn of the millennium where multiple groups have shown that iodine (III) reagents such as DIB **67**, iodosyl benzene **80**, and PIFA **81** can activate azides for reaction.^[97] Moriarty showed that activated double bonds could be converted to 1,2 diazides by the combination of iodosyl benzene and sodium azide in acetic acid. Temperatures varied depending on substrate although generally good yields were obtained. Following this a similar method was then used to add an azide to the α -position of β -dicarbonyls **82** Scheme 2.11.^[98] The solvent used was chloroform instead of acetic acid whilst also changing the azide source to TMSN₃. Reaction conditions involved stirring at room temperature for 2 h before reflux for 3 h where yields of up to 83% were observed for products such as **83**.



Scheme 2.11: Azidation of 1,3- dicarbonyls using iodine (III) reagent.

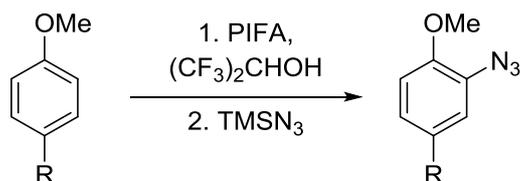
This was then followed by azido selenation of double bonds by Tingoli *et al.*^[99] They used a simple system consisting of DIB with NaN₃ in the presence of diphenyl diselenide and olefins (Scheme 2.12).



Scheme 2.12: Azido selenation of styrene using DIB, NaN₃ and diphenyl diselenide combination.

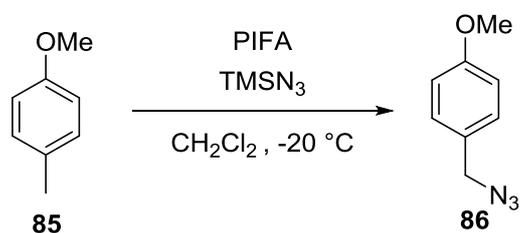
Only one regioisomer was observed **84** and yields obtained were between 62 and 83% varying between styrenyl and alkyl double bonds.

Kita also showed the capabilities for I(III) systems for the azidation of aromatics where a PIFA **81**, TMSN₃ system was used to add an azide to electron rich aromatics (Scheme 2.13). Regioselectivity was generally very good with yields of up to 85% obtained for highly electron rich aromatics.^[100]



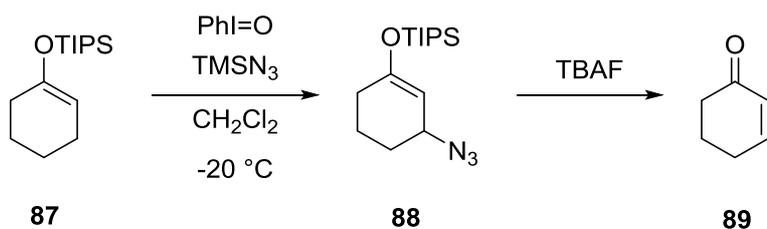
Scheme 2.13: Addition of azide moiety to electron rich aromatics using PIFA/TMSN₃ combination.

In later work it was shown that the reaction conditions could be tuned to have an alternate outcome.^[101] When using substrates such as *p*-alkylanisoles **85** the conditions reported in the previous work resulted in azidation at the aromatic site but upon switching to solvents such as CH₂Cl₂ or MeCN then azidation occurred at the alkyl chain **86** Scheme 2.14.



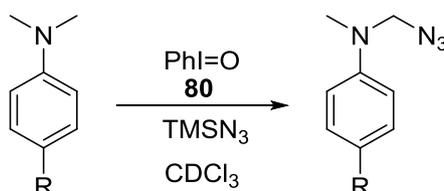
Scheme 2.14: Alkyl azidation of *p*-methylanisole by I(III) reagent PIFA.

Magnus *et al.* used the oxidative addition of azides to form α , β -unsaturated carbonyls **89** from silyl enol ethers **87** (Scheme 2.15). Using iodosylbenzene and TMSN₃ at -20 °C in CH₂Cl₂ they were able to add an azide to the β -position and upon deprotection of the silyl group using a fluoride source the product **89** was formed, with the azide being eliminated.^[102]



Scheme 2.15: Addition of azides to TIPS enol ether followed by deprotection and elimination of azide to form cyclohex-2-enone.

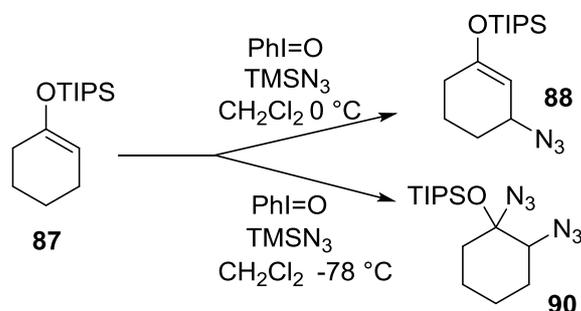
They further showed that upon addition of TEA that the reaction was essentially depressed; as the *in situ* formed iodine reagent preferentially reacted with TEA. The latter deduction led them to investigating the addition of azides to tertiary aryl amines as shown in Scheme 2.16. By using the same conditions they were able to achieve *N*-alkyl azidation of *N*-dimethylarylamines and subsequently allow for further transformations using the azide as a leaving group.^[101]



Scheme 2.16: Oxidative *N*-alkyl azidation of *N*-dimethylarylamines using iodobenzene.

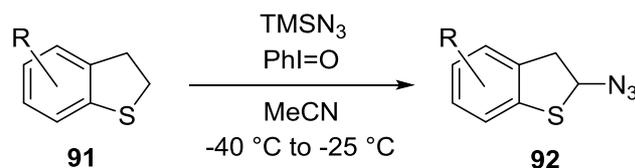
Using similar conditions to the previous reports, α -addition to amides has been accomplished by changing the temperatures to $-40\text{ }^{\circ}\text{C}$ to avoid decomposition of the reagent intermediate. Yields of up to 82 % were obtained if decomposition was not allowed to occur.^[103]

Work moved to further functionalization of silyl enol ethers where either α -diazidation or β -azidation could be performed using a combination of iodobenzene and TMSN_3 . Using temperatures of $-20\text{ }^{\circ}\text{C}$ and above resulted in β -azidation as the dominant product **88**. If temperatures were of the order of -45 to $-78\text{ }^{\circ}\text{C}$ diazidation dominated **90** as shown in Scheme 2.17.^[104] The affect of TEMPO was studied where addition of this resulted in suppression of the β -azidation pathway. Very good yields could be observed when using simple alkane enol ethers of up to 91%. The work was later expanded to a larger substrate scope showing that a vast amount of cyclic silyl enol ethers could be used as substrates. They also showed formation of triazoles was tolerable following the initial conditions in another publication.^[105]



Scheme 2.17: Iodine (III) mediated temperature dependent azidations on TIPS silyl ethers

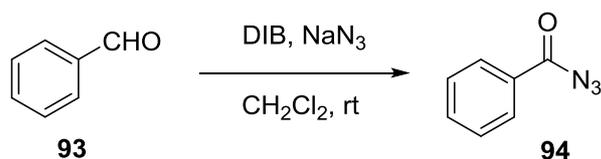
Not only has this technique been used for α -azidation of amines but similarly cyclic sulphides **91** have shown activity towards these conditions (Scheme 2.18).



Scheme 2.18: Addition of azide moiety to cyclic sulphides using TMSN₃ iodosylbenzene combination.

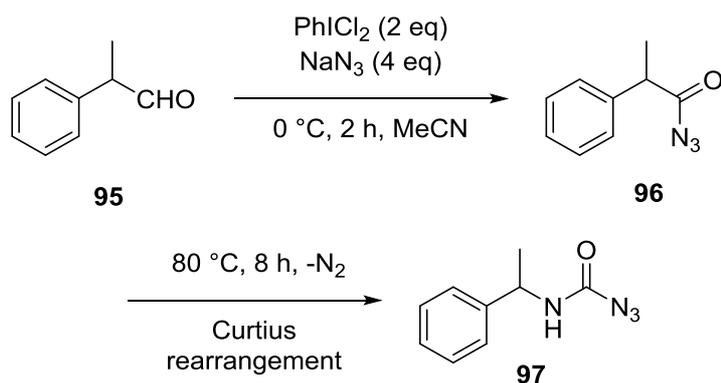
Using iodosylbenzene and TMSN₃ Hirofumi and co-workers showed that azidation could occur on a multitude of cyclic sulphides in MeCN where temperatures had to be controlled below – 25 °C to obtain yields of up to 70%.^[106]

The formation of benzoyl azides has been shown using a combination of DIB and NaN₃ by oxidative addition to aldehydes. Chen *et al.* demonstrated a mild and efficient method to produce aroyl azides **94** in yields between 43 and 92% for a variety of aldehydes (Scheme 2.19).^[107]



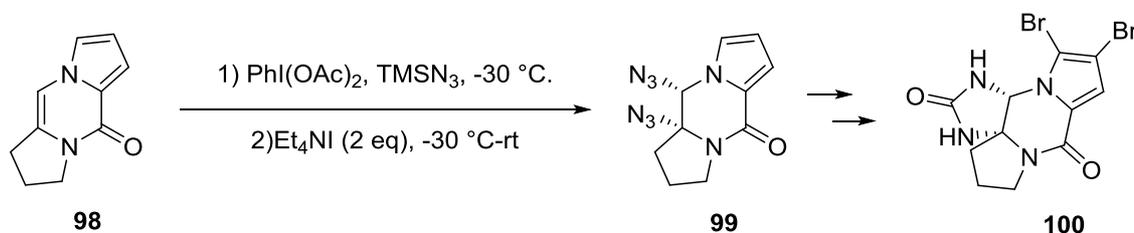
Scheme 2.19: Oxidative addition of azide to form benzoyl azides from benzaldehydes.

Many years later Zhang extended this by taking advantage of the formed aroyl azides. Using PhICl₂ in combination with NaN₃ in MeCN formation of the aroyl azide was established in 2 h at 0 °C.^[108] The authors suggested a radical based reaction, where the sodium azide is oxidised to an azide radical by the iodine reagent This in turn oxidises the aldehyde to an acyl radical which reacts with another azide radical to form an acyl azide **96**. The reaction mixture was then heated at 80 °C for 8 h whereupon a Curtius rearrangement took place followed by addition of a further equivalent of azide to form the carbamoyl azide **97**. Substrates ranged from alkyl to aromatic aldehydes with yields of up to 99% Scheme 2.20.



Scheme 2.20: Sequential formation of isocyanates followed by carbamoyl azide using (dichloriodo)benzene and sodium azide.

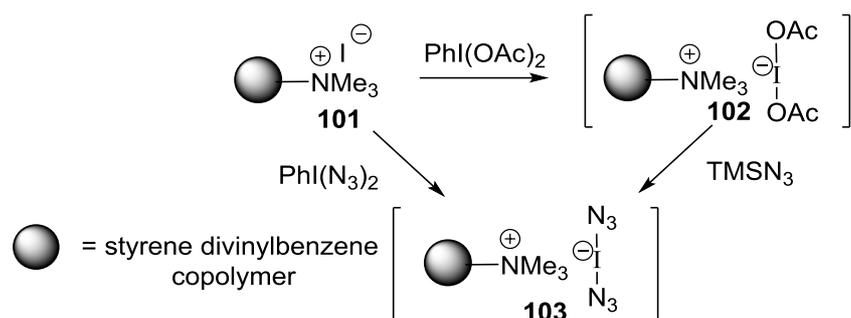
Further approaches of diazidations have been demonstrated in the synthesis of (\pm)-Dibromophakellstatin **100** Scheme 2.21.^[109]



Scheme 2.21: Key syn diazidation step en-route to the synthesis of (\pm)-Dibromophakellstatin.

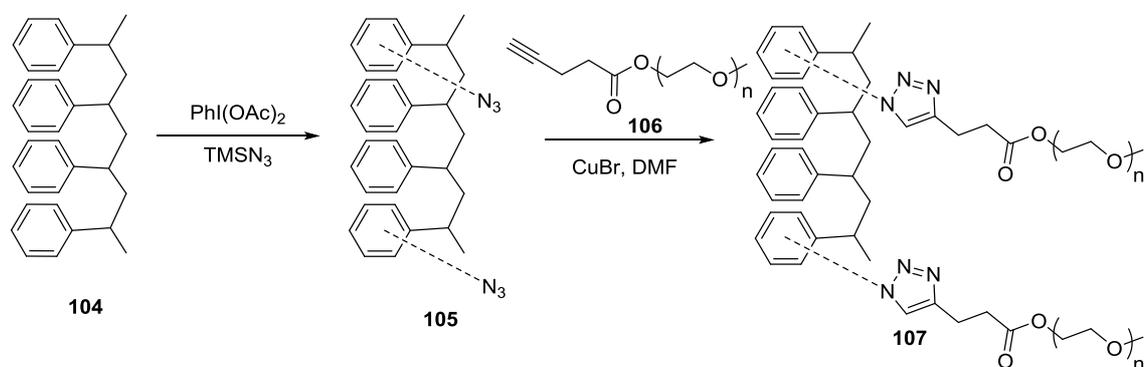
Austin showed that *syn*-addition to **98** could be controlled to some degree by *in situ* formation of the $[\text{I}(\text{N}_3)_2]^-$ reagent. This system showed favourability toward the *syn* product (41%) **99** as compared to the *anti*-diazide product (7%). This was compared against other conditions involving reagents such as IN_3 and $\text{PhI}(\text{N}_3)_2$ where the former produced solely the *syn*-product and the latter β -azidation.

Kirschning *et al* showed an alternative method using a polymer bound iodine (I) reagent **102** Scheme 2.22.^{[110],[3]} This represented a safer method as compared to traditional syntheses, where the safety concerns associated with iodine monoazide limit its use. They showed that reagent **103** could be manipulated safely for the addition of iodide and azide, and if left for a longer period of time diazidation occurred via substitution of the iodine.



Scheme 2.22: Formation of polymer supported azide iodine reagent.

Tsarevsky demonstrated that diazidation could be directly applied to polystyrene **104** using a DIB/TMSN₃ combination (Scheme 2.23).^[111] The reaction was performed on a 10 mmol scale with cooling applied by a salt-ice bath for 2-4 h before being heated to 50 °C for 2h.



Scheme 2.23: Diazidation of polystyrene using DIB/TMSN₃ combination followed by click reaction to form triazoles.

Incorporation was shown by various techniques such as IR and elemental analysis and a secondary reaction could be performed of click chemistry with **106** to form a triazole product **107**.

In recent times a bench stable azide containing hypervalent iodine reagent (Figure 2.6 **108**, **109**) have been developed by Zhdankin.^[112] This has allowed for chemistry not previously permitted by the traditional DIB/TMSN₃ type systems and allowing for increased safety as compared to heating the same iodine reagents with NaN₃. They developed a benziodoxole iodine reagent **108** of the same structural orientation as IBA where its stability allows for reactions at room temperature with the same reactivity as before.

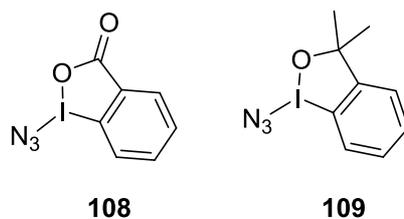
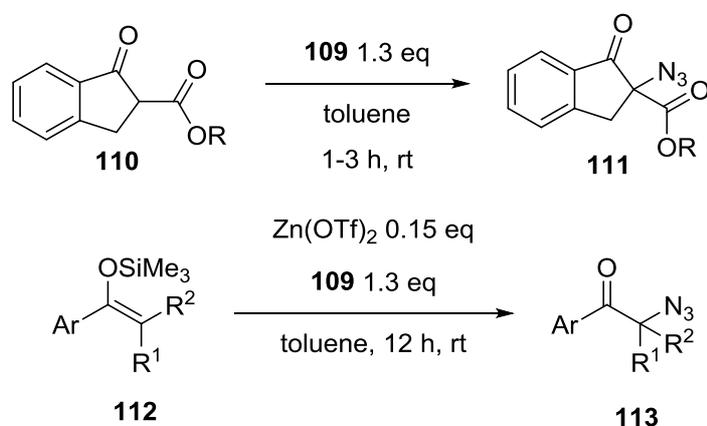


Figure 2.6: Benziodoxole azide reagents first synthesised by Zhdankin.

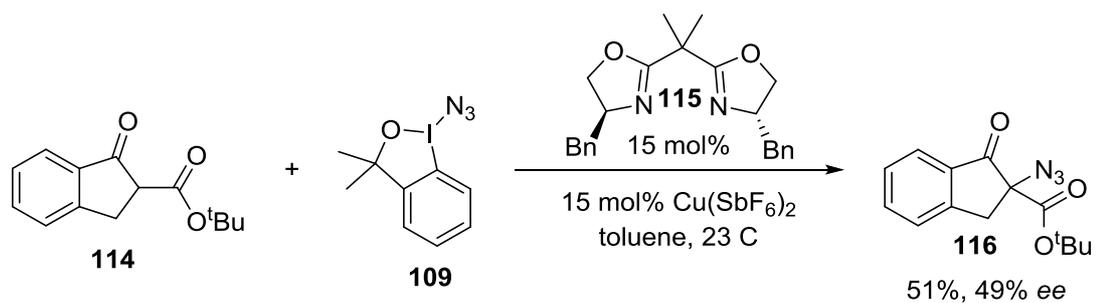
Using these new characteristics many groups have sought to take advantage of this. Waser *et al* demonstrated the addition of an azide to β -ketoesters (**110**) using the benziodoxole type derivative Scheme 2.24.



Scheme 2.24: Azidation of β -ketoesters **110** and silylenol ethers **112** by reagent **109**.

They showed that quantitative yields could be obtained for some substrates in 1-3 h at room temperature.^[113] They further compared two types of benziodoxole derivatives showing that **109** was the superior due to the higher basicity of the alkoxide formed on loss of the azide. This then extended to silyl enol ethers **112** where a Lewis acid $\text{Zn}(\text{OTf})_2$ was used in order to achieve yields of up to 82% (**113**).

In addition by using a chiral bisoxazoline ligand in combination with a Cu Lewis acid enantiomeric excess could be achieved of up to 49% e.e Scheme 2.25.

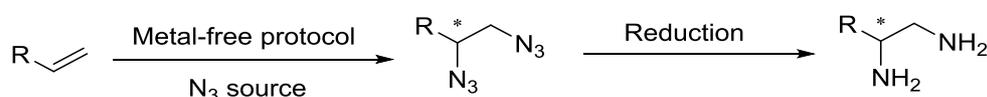


Scheme 2.25: Chiral azidation of β -ketoester **114** by Cu bisoxaloline catalysis with **119**.

Although the mechanism was not completely determined, they surmised that it was likely a nucleophilic of the enolate form of **114**. They decided from the conclusion that the use of TEMPO within the reaction did not change the yield or ee. This suggests the mechanism is not either a radical or electron transfer process. Furthermore if the Cu catalyst was not used they observed no product **116**. They therefore decided it is likely co-ordination of the Cu salt to **115** activating the ketones, followed by reductive elimination to form the desired product.

2.1.5 Aims of project

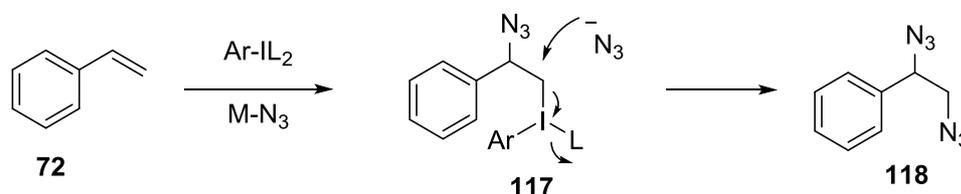
The aim of this project was to develop a stereoselective metal-free diazidation reaction of unactivated double bonds under continuous flow conditions. Although there have been numerous reports of diazidations using metal free conditions none have reported a stereoselective transformation. As well as this, very little has been reported in the area of metal free stereoselective diaminations. The reports to date use nitrogen precursors containing protecting groups such as tosyl and mesyl and although high selectivity could be achieved, removal of the protecting group prior to transformation is difficult and uses harsh conditions. The use of azides could circumvent this as reduction of azides to amines is facile with a multitude of conditions available.



Scheme 2.26: Schematic outline of transformations for the aim of this project.

Project Approach

The project started with the choice of iodine reagent for the successful ligand exchange of azide with the substituents on the hypervalent iodine. This was then used in stoichiometric amounts as a hypervalent iodine (III) reagent in the addition of azides to alkenes. In the reaction scheme, after activation of the double bond by the iodine reagent the first azide reacts at the most delta positive position to give intermediate **117**. The hypervalent iodine is then bonded to an sp³ hybridized carbon and therefore becomes an excellent leaving group, one million times better than a triflate. The displacement of the iodane by attack of a second azide then completes the protocol to form the diazide product **118** Scheme 2.27. The transformation of the azide moieties can then further lead to diamines via various facile reduction methods.



Scheme 2.27: Iodine (III) mediated diazidation of styrene.

Based on the reaction scheme described the method can then be further extended to the enantioselective synthesis of diamines from alkenes. As a new stereocentre is produced, chiral

hypervalent iodine reagents could be used to lead towards enantiomerically pure diamines. As with other metal free chiral syntheses using hypervalent iodine reagents many lactate-based chiral iodine reagents have been used of the type shown below Figure 2.12.^[114]

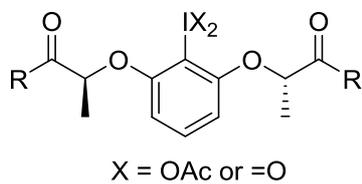


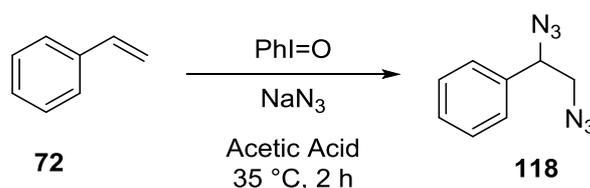
Figure 2.12 General lactate based chiral hypervalent iodine (III) reagent

This then would be converted into a continuous flow process allowing for a secondary reduction step to be coupled, converting the organo-azide to an amine. The method allows for a safe product to be isolated and therefore the reactive azide moieties never have to be dealt with.

2.2 Results and Discussions

2.2.1 Initial diazidation conditions

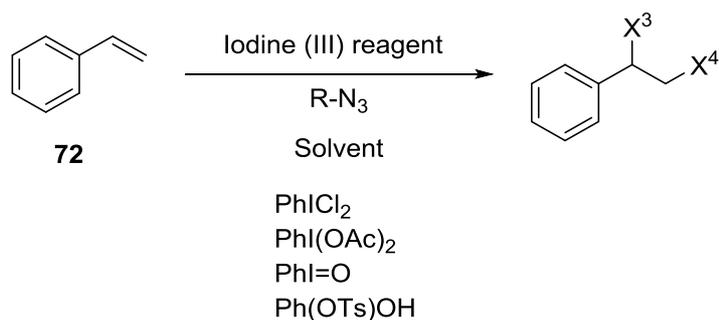
The investigation began by using previously reported procedures and modifying them for the potential use in continuous flow. As flow chemistry suffers from the problems of blocking from insoluble particulates it is imperative that precipitation does not occur. The first conditions reported by Moriarty^[97] use iodosylbenzene dissolved in acetic acid with the addition of sodium azide. This is then heated to 35 °C for 2hr to afford the diazide product **118** in 70% yield (Scheme 2.28) and gave us a point of reference to compare other methods to.



Scheme 2.28: Diazidation of styrene using iodosylbenzene , sodium azide conditions.

Although this worked well it was hard to envision an asymmetric synthesis using such a polar protic solvent as acetic acid as the sole solvent system. It was then thought best to try to find another range of conditions that also could be trialled for the enantioselective version with **118** in hand to compare to.

The first aryl hypervalent iodine reagent reported was the (dichloroiodo)benzene derivative by Willgerodt.^[81] The facile synthesis of this reagent from iodobenzene, sodium hypochlorite and hydrochloric acid was achieved in 90% yield and was used for diazidation reactions. The increased solubility of the reagent allowed for its use in an organic solvent as shown below in Table 2.1.



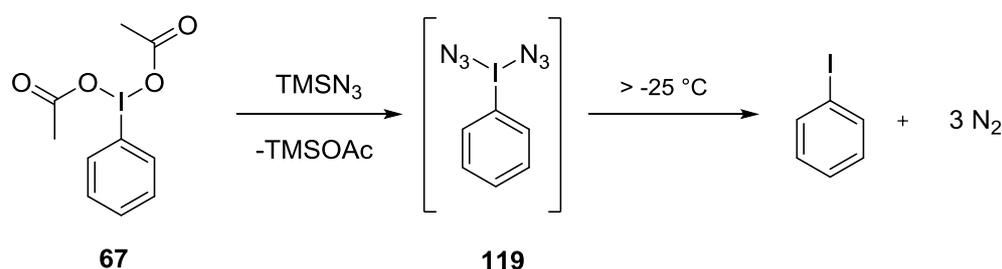
| Iodine reagent | Azide source | Solvent | Temperature (°C) | Reaction time (h) | Yield (%) |
|-----------------------|-----------------------------|--------------------------|------------------|-------------------|---|
| Iodosylbenzene | NaN_3 | AcOH | 35 | 2 | $\text{X}^3 + \text{X}^4 = \text{N}_3$ (70) |
| (Dichloroiodo)benzene | $(\text{nBu})_4\text{NN}_3$ | CH_2Cl_2 | rt | 5 | $\text{X}^3 + \text{X}^4 = \text{Cl}$ (56) |
| (Dichloroiodo)benzene | TMSN_3 | CH_2Cl_2 | rt | 5 | $\text{X}^3 + \text{X}^4 = \text{Cl}$ (34) |
| Koser's reagent | TMSN_3 | CH_2Cl_2 | rt | 1 | n.r |
| Diacetoxyiodo)benzene | TMSN_3 | CH_2Cl_2 | rt | 1 | $\text{X}^3 + \text{X}^4 = \text{N}_3$, (15) |

Table 2.1: Initial diazidation conditions of styrene in batch where: Iodine reagent (1.5 eq), azide source (2.5 eq) were used in 5 mL of solvent at the specified temperature.

As the solvent switched now to a less-polar solvent (CH_2Cl_2), the source of azide had to be reconsidered. Sodium being a very hard counter ion does not lend itself to solvation in non-polar solvents therefore tetrabutylammonium azide and trimethylsilyl azide were considered better for conversion to flow conditions. When using (dichloroiodo)benzene no product was observed even if used in combination with any of the azide sources. Either dichlorination occurred as within the case of PhICl_2 or recovery of the starting material with Koser's reagent. It was then thought that ligand exchange is not facile enough with Koser's reagent or the (dichloroiodo)benzene reagent leading to reaction directly with the styrene to furnish the undesired product or none at all. Koser's reagent delivered similar results where starting material was recovered again.

As it was thought that upon solvation of the iodosylbenzene derivative in acetic acid it is converted into DIB, conditions were moved towards systems involving this reagent. Previous reports in the area with the combination of DIB and TMSN_3 have been reported where ligand exchange is facile due to the affinity of oxygen to the TMS group. Initial trials involved dissolving DIB in methylene chloride followed by addition of the TMSN_3 reagent. Upon addition an instant colour change occurred of colourless to yellow thus implying that ligand exchange had occurred. Although almost immediately after colour change effervescence was observed.

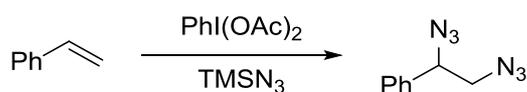
Upon addition of the styrene derivative and stirring at rt for 2h a yield of 15% was achieved but full conversion had not been reached. Although the styrene had not been completely consumed the entire hypervalent iodine reagent had been. It was therefore thought that as reported in the literature from previous uses of the combination of such reagents, decomposition of the *in situ* formed hypervalent azide reagent **119** occurred.^[103,105] Although there are varying results from within the literature of temperatures used with this reagent, with some even being used at room temperature, it was reported by Zhdankin^[115] that decomposition can occur at temperatures in excess of $-25\text{ }^{\circ}\text{C}$ with a release of nitrogen gas and iodobenzene (Scheme 2.29).



Scheme 2.29: Decomposition of formed diazidoiodobenzene reagent

This was indeed observed in many of the previous reactions where temperatures above $-30\text{ }^{\circ}\text{C}$ were used.

The formation of the reagent was then performed at $-30\text{ }^{\circ}\text{C}$ and then allowed to warm to room temperature. This improved the yield of diazidation to 67% in 6 h. Solvent conditions were screened to then ascertain the optimal solvent for the transformation.

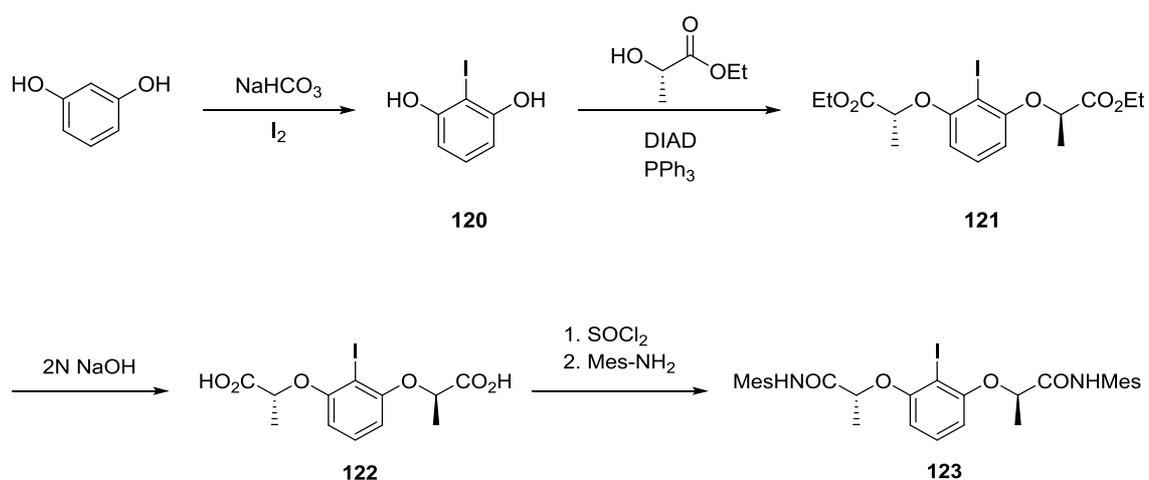


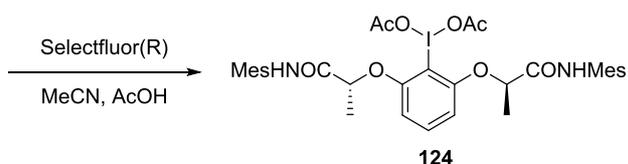
| Solvent | Temperature ($^{\circ}\text{C}$) | Reaction time (h) | Conversion (Yield) (%) |
|--------------------------|---------------------------------------|----------------------|---------------------------|
| CH_2Cl_2 | -30-RT | 6 | 90 (67) |
| CHCl_3 | -30-RT | 6 | 72 (51) |
| MeCN | -30-RT | 6 | 40 |
| THF | -30-RT | 6 | 20 |
| Diethyl Ether | -30-RT | 6 | 0 |

Table 2.2: Solvent screening of diazidation using 1eq of styrene, 1.2eq of DIB and 2.4eq of TMSN_3 .

As shown in Table 2.2, CH₂Cl₂ was shown to be the optimal solvent for the transformation where protic solvents were not used due to their risk in potentially being a secondary nucleophile in these reactions. MeCN showed the highest rate of decomposition likely due to the strong coordination ability of the nitrogen and as with other examples with iodine shown in the literature incorporation of an amide was not observed.^[116]

The work then moved on to synthesis of the chiral hypervalent iodine reagents. Lactate based hypervalent iodine species have been shown to be extremely effective for the stereoselective transformations used in many hypervalent iodine reactions and have been synthesised by Fujita and Ishihara.^[114] It was therefore thought to be a great starting point for the enantioselective transformation. The synthesis begins from the known literature procedure with the formation of 2-iodoresorcinol where addition of sodium hydrogen carbonate to resorcinol precedes the addition of iodine to give a colourless oil. This procedure gave the desired product **120** in good yield. The second step of the synthesis is a Mitsunobu reaction of the phenolic groups **120** with the alcohol of (-)-lactic acid ethyl ester in the presence of triphenylphosphine (PPh₃) and diisopropyl azodicarboxylate (DIAD) which produces the ester product **121**. This can then be used as a chiral reagent or further transformed to **123** which in some reactions has shown superior enantioselective control. Therefore this was synthesised via the known literature modification. The ester **121** was hydrolysed using aqueous sodium hydroxide solution to give the symmetrical acid **122** in almost quantitative yield. **122** was then converted into the acid chloride using thionyl chloride *in situ* followed by adding an excess of a mesityl amine.



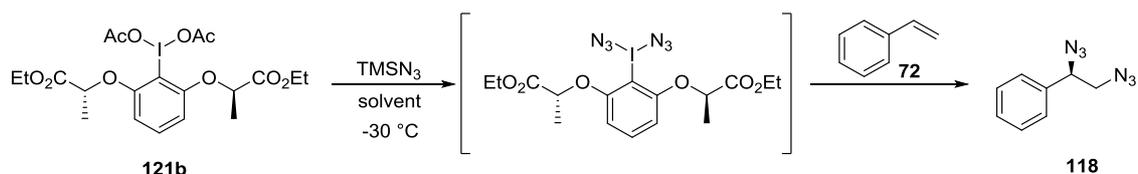


Scheme 2.30: Synthesis of chiral lactate iodine reagent **121** and amide **123**.

A range of oxidation methods are available to transform **121** and **123** into the active iodine (III) reagents such as sodium perborate, peracetic acid and Selectfluor® in the presence of acetic acid. As Selectfluor® had become a reliable reagent within our labs, this method was used to oxidise the reagent to give the product **124** (Scheme 2.30).^[117]

2.2.2 Stereoselective diazidations

The first trials of the stereoselective synthesis began by using the **121b** hypervalent reagent (1.2 eq), in dichloromethane (Scheme 2.31). With the addition of TMSN₃ (2.4 eq) to the reagent solution at -30 °C the resulting mixture was allowed to stir for 2 mins which resulted in a slight yellow tinge to the solution implying ligand exchange. Styrene (1 eq) was then added and the solution was allowed to warm to room temperature over 6 h. The yield was considerably lower with the chiral ester reagent **121** likely due to the change in the electronics of the aryl ring and consequently at the iodine centre.



Scheme 2.31: Proposed stereoselective diazidation of styrene.

Largely starting material was recovered therefore increased reaction time (12 h) was needed to reach the full conversion.

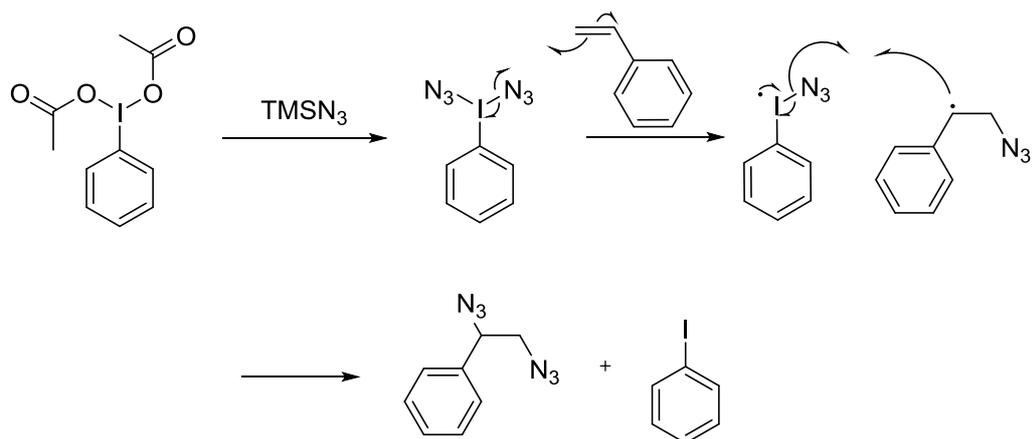
The diazide product **118** was purified by flash chromatography and then resolved by chiral HPLC on an OD-H column. Unfortunately no induction of asymmetry was observed. The conditions were then altered by changing the solvent system and the chiral reagent.

| Iodine reagent | Solvent | Temperature (°C) | Time (h) | Yield of 118 (%) | ee (%) |
|----------------|---------------------------------|------------------|----------|-------------------------|--------|
| 121b | CH ₂ Cl ₂ | -30-rt | 12 | 54 | 0 |
| 121b | CHCl ₃ | -30-rt | 12 | 50 | 0 |
| 121b | THF | -30-rt | 12 | 12 | 0 |
| 121b | Ether | -30-rt | 12 | 0 | 0 |
| 124 | CH ₂ Cl ₂ | -30-rt | 12 | 48 | 0 |
| 124 | CHCl ₃ | -30-rt | 12 | 51 | 0 |

Table 2.3: Chiral diazidation attempts of styrene 1eq using chiral lactate based reagents 1.2 eq and TMSN₃ 2.4 eq.

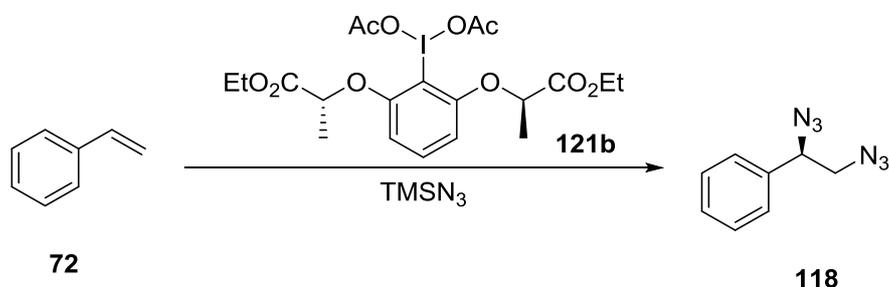
As shown in Table 2.3, several conditions were trialled. Changing the solvent system showed no difference in enantiomeric excess observed but drastically affected the yields in some cases. Moving temperatures to -78 °C and sustaining it for 4 h also did not show any change in e.e. suggesting that there is a rapid non-competitive racemic side reaction or that the sole pathway is racemic regardless of temperature. Changing the chiral reagent to the lactate amide also showed no increased activity and therefore it could be assumed that the reaction pathway is independent of the reagent in these solvents.

It was presumed that the lack of stereochemical induction was due to the mechanism of the reaction. As with some of the work published within this area,^[104] although not all, it is assumed that the reactivity of the (diazidoiodo)benzene derivative goes through a radical type mechanism. This implies that addition occurs after homolytic cleavage of the iodine azide bond forming an azide radical, which can then add to the substrate. In this case styrene is used therefore addition occurs at the least hindered terminal position. This allows for stabilisation of the alkyl radical formed upon addition to the double bond at the benzylic position. A second radical azide is then trapped at this position to form the diazide, Scheme 2.32



Scheme 2.32: Likely free radical pathway for diazidation of styrene.

Due to the results observed, it was thought that the reaction went through a radical mechanism. Therefore attempts to tune the conditions were applied. Many of the solvents used were aprotic solvents of moderate to poor polarity therefore it was supposed that if highly polar aprotic solvents were used then the reaction could be driven through an ion induced mechanism. Although previously feared as a solvent due to the nucleophilic aptitude and potential to be oxidised alcoholic type solvents were used for this reaction.



| Iodine reagent | Solvent | Temperature (°C) | Time (h) | Yield (%) | ee (%) |
|----------------|-------------------|------------------|----------|-----------|--------|
| 121b | MeOH | -30-rt | 12 | 44 | 0 |
| 121b | EtOH | -30-rt | 12 | 35 | 0 |
| 121b | ⁱ PrOH | -30-rt | 12 | 38 | 0 |

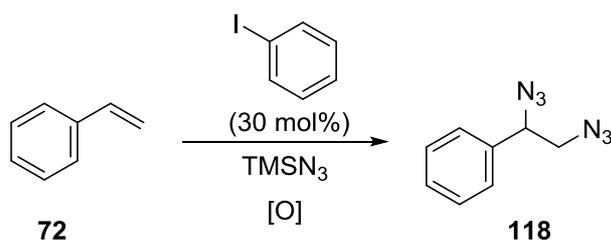
Table 2.4: Stereoselective conditions using polar protic solvents. 1 eq of styrene was used with 2.4 eq of TMSN₃ and 1.2 eq of the chiral ester reagent.

Again low temperatures were used for formation of the initial reagent before addition of styrene. Unfortunately as shown from Table 2.4 no chiral induction occurred. Switching to polar protic solvents showed no ability to suppress the radical pathway therefore this left the

conclusion that the chiral diazidation reactions could not be reagent controlled and would need to be substrate controlled.

2.2.3 Catalytic diazidations

Further conditions were attempted to catalyse the diazidation using non-stoichiometric quantities of iodine reagents (Scheme 2.33). By using iodobenzene in the presence of an oxidant the hypervalent species could be made *in-situ* and therefore perform addition of the azides to styrene. A number of oxidants were trialled to determine the best oxidant for these conditions without alternatively oxidising the double bond independently to the azide source.



Scheme 2.33: Proposed catalytic diazidation of styrenes.

TMSN₃ was chosen as the azide source for solubility and MeCN as the solvent. MeCN has shown to be a reliable solvent in many catalytic transformations using iodine therefore it was thought to be a good place to start. Sodium perborate was chosen as the oxidant to begin trials

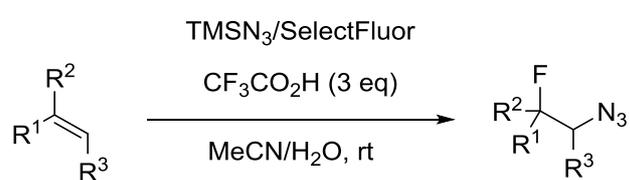
| Oxidant | Temperature (°C) | Time (h) | Result |
|--------------------------------------|------------------|----------|--------------------|
| NaBO ₃ ·4H ₂ O | rt | 4 to 16 | n.r |
| NaBO ₃ ·4H ₂ O | 70 | 4 to 16 | n.r |
| Oxone [®] | rt | 4 to 16 | n.r |
| Oxone [®] | 70 | 4 | Benzoic acid (32%) |
| mCPBA | rt | 4 to 16 | n.r |
| mCPBA | 70 | 4 | Traces of epoxide |

Table 2.5: Catalytic diazidations of styrene (1eq) using catalytic iodobenzene (0.3eq) with a co-oxidant (1.5 eq).

As Table 2.5 shows NaBO₃·4H₂O showed no ability to oxidise the iodine catalyst in the presence of TMSN₃ and therefore only starting material was recovered. When raising the temperature to 70 °C the same result was observed. Oxone presented another alternative and showed a much greater oxidative potential. Although starting material was not recovered solely a large amount of side product was obtained. The side product was determined to be benzoic acid after purification. This was thought to be due to the formation of the diol and

then oxidative cleavage in the presence of water. Repeat attempts at this did not provide a consistent method for catalytic oxidative cleavage where this has now been reported using an alternative iodine reagent in recent times.^[118] mCPBA resulted in epoxidation preferentially to the oxidation of the iodine compound at elevated temperatures with no oxidation of the azides.

Oxidants such as Selectfluor[®] were avoided as they have shown activity by itself to activate double bonds resulting in either addition of solvent, such as in acetonitrile where amidefluorination occurs or in the presence of azides, azido-fluorinations occur through radical N₃ addition as shown in Scheme 2.34.^[119]



Scheme 2.34: Azidofluorination of double bonds

As shown from Table 2.5, the attempts to form a synthetic protocol for the catalytic diazidation of styrenes using in-situ formed hypervalent iodine reagents were unsuccessful. It was shown that either the oxidant had little to no effect on either the azide source or the iodine reagent and in some cases acted independently from either the azide source or the iodine reagent, forming alternate products. Therefore it was decided that these synthetic protocols would not be continued.

2.2.4 Flow conditions

As there was no stereochemical induction when using the chiral reagents work shifted towards producing a safer protocol for diazidation by using flow chemistry to create the reactive intermediate in-line. Using low temperatures below 0 °C is costly within industry and therefore it was thought best to produce a system where cold temperatures were not needed. As the iodosylbenzene sodium azide system in acetic acid previously mentioned showed promising results in batch, and due to facile ligand exchange of the TMSN_3 with oxygen, a hypervalent iodine reagent system was devised that would not lead to the quick decomposition of the diazide iodine reagent (Scheme 2.29)

To provide a basis for the flow conditions the batch conditions were replicated as close as possible in flow. A solution of PhI=O dissolved in acetic acid was drawn into one syringe and a second solution of NaN_3 and styrene in acetic acid drawn into a second syringe were attached to a reactor coil via luer fittings; as shown in Figure 2.13.

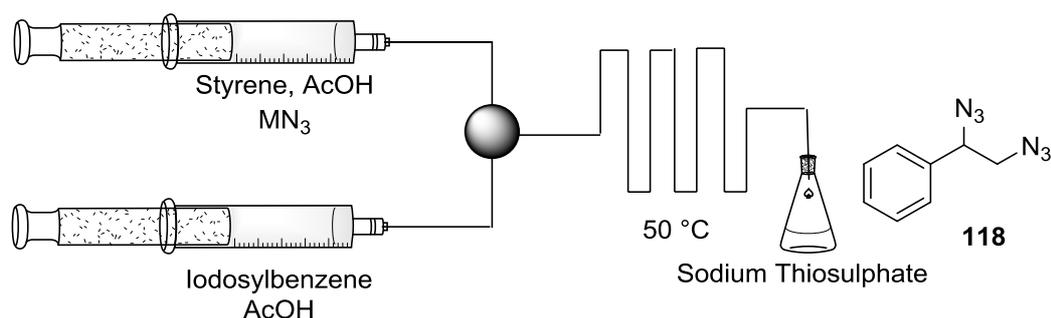
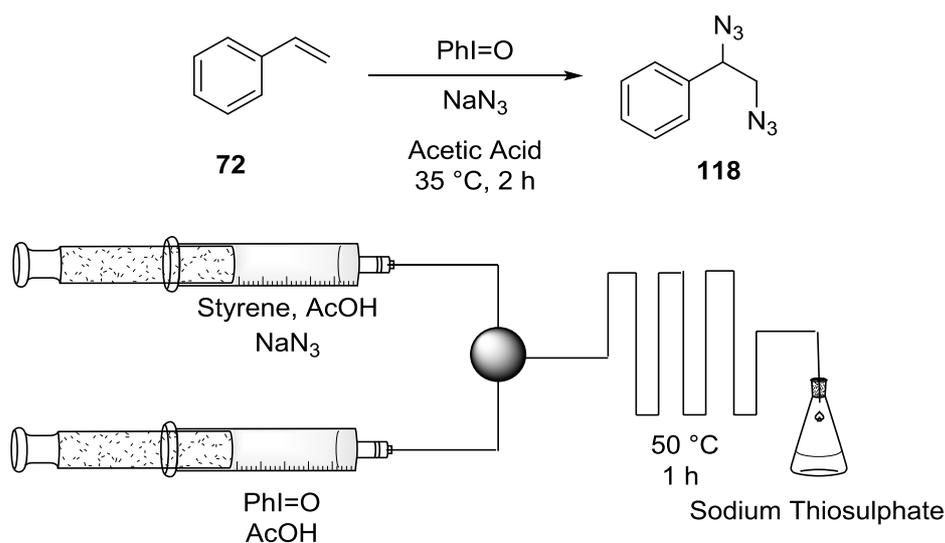


Figure 2.13: Flow set-up for diazidation of styrenes.

The solutions were then pumped to allow for a 1 h residence time within a 2 mL (0.5 mm i.d) PTFE coil and finally quenched with aqueous sodium thiosulphate to allow for an accurate residence time, avoiding further oxidation in the collection flask. Collection time for the reaction was set for 30 min. To allow for the reaction to reach equilibrium one column volume was discarded before collection; this is called reaching steady state.

The yield of **118** was good (72%) and showed comparable conversion to batch conditions (2 h) but in a shorter reaction time. Although yields were good it was thought that conditions could be improved by using more soluble iodine reagents.

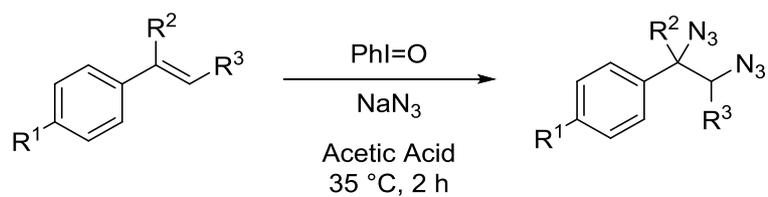


| Azide source | Iodine reagent | Yield (%) |
|----------------------------------|----------------|-----------|
| NaN ₃ | Iodosylbenzene | 72 |
| NaN ₃ | DIB | 64 |
| (Bu ₄ N) ₃ | Iodosylbenzene | - |
| (Bu ₄ N) ₃ | DIB | - |
| TMSN ₃ | Iodosylbenzene | 0 |
| TMSN ₃ | DIB | 0 |

Table 2.6: Screening of azide source (2.2eq) and iodine reagent (1.5 eq) for diazidation of styrene in flow at 50 °C for 1 h of residence time.

As seen from Table 2.6, the original conditions of iodosylbenzene in acetic acid resulted in the best yield for the diazidation of styrene. When switching to DIB slightly less yield was observed suggesting maybe the active species of the dissolution of iodosylbenzene is not DIB but an alternative hypervalent species, such as an intermediate between PhI=O and DIB. When switching to the alternate azide sources, yields suffered dramatically. Tetrabutylammonium azide gave poor yields with both iodine sources, whereas using TMSN₃ gave no product within the reaction time. This was to be expected as with easy formation of the (diazidoiodo)benzene, decomposition occurs at elevated temperatures. By using the Na⁺ counter ion formation of the hypervalent azide species is slower and therefore addition to the double bond can be achieved before decomposition.

As the iodosylbenzene reagent dissolved in acetic acid with NaN₃ seemed to be the optimum conditions for this transformation a substrate scope was chosen to test the versatility of the conditions.



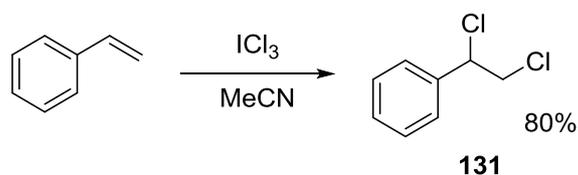
| Olefin | Product | Yield (%) |
|--------------------------|----------------|-----------------------------|
| styrene | 118 | 72 |
| 1-indene | 125 | 64 (d.r = 1.1) |
| α -methyl styrene | 126 | Starting material recovered |
| <i>p</i> -bromostyrene | 127 | 64 |
| <i>p</i> -methylstyrene | 128 | 72 |
| <i>p</i> -methoxystyrene | 129 | 76 |
| cinnamyl alcohol | 130 | 61 (d.r = 1.1) |

Table 2.7: Substrate scope of diazidation in continuous flow: styrene (1eq), Iodosylbenzene (1.5 eq), NaN₃ (2.5 eq), 1 h residence time at 50 °C

As shown throughout Table 2.7 the scope all of the yields are generally within the same range. This could imply that the reaction is a free radical process where the effect of the substituent does not affect the yield in a detrimental manner. Although yields were generally lower with

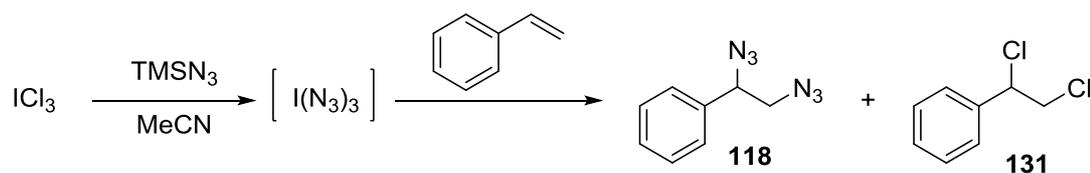
125 and **130** this does not support that. Furthermore, that no product is observed for **126** α -methylstyrene this would also suggest no radical mechanism is present.

A further effort using the reagent ICl_3 for the diazidation of styrene was attempted. Reaction conditions started in batch, using ICl_3 in MeCN with styrene to better understand the addition of these reagents (Scheme 2.35).



Scheme 2.35: Dichloronation of styrene by ICl_3 in batch.

The reaction mixture was kept under an argon atmosphere using dry MeCN as to not hydrolyse the iodine reagent. This then led to the addition of chlorine across the double bond (**115**) in a reaction time of 30 minutes. It was then hoped with ligand exchange using TMSN_3 the diazidation of styrene could occur in a rapid and clean manner (Scheme 2.36).



Scheme 2.36: Proposed diazidation of styrene using ICl_3 TMSN_3 combination.

Due to the suspected formation of iodine triazide, reaction under batch conditions was determined too dangerous and therefore moving directly to flow would allow for a much safer option. Dissolving iodine trichloride in solution in one syringe and TMSN_3 in another the reagent could be pre-formed in one coil at $-10\text{ }^\circ\text{C}$ before being added to the styrene and subsequently warmed to room temperature in a secondary coil Figure 2.14.

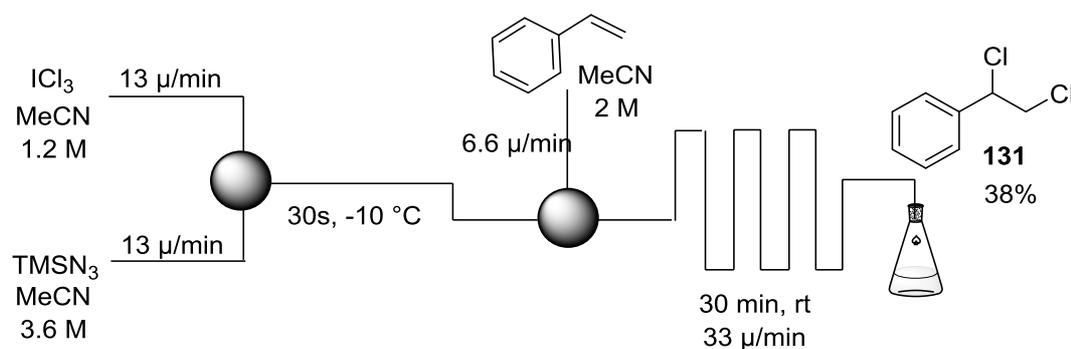
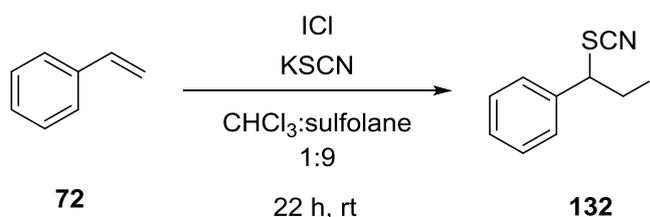


Figure 2.14: Flow system for $\text{I}(\text{N}_3)_3$ reaction with styrene (1 eq) ICl_3 (1.2 eq) and TMSN_3 (3.6 eq)

Ligand exchange was apparent upon mixing of the iodine reagent and the azide source where a deep red colour emerged. This was then allowed to continue to meet the styrene and again an instant colour change occurred fading to a very light yellow colour before returning to a deep red indicating the presence of iodine. Upon analysis by TLC and NMR a number of products were observable. Clearly the dichloride species **131** had been produced as a major product but no formation of the diazide species was observed, thus either ligand exchange was not as facile as thought or decomposition of the iodine azide reagent had occurred at $-10\text{ }^{\circ}\text{C}$.

2.2.5 Azido thiocyanation.

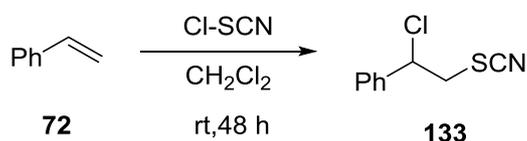
As the addition of azides was shown to be achievable to styrene derivatives, other additions were sought to form mixed product species. A few attempts at this have been reported in the literature; with reagents such as TEMPO,^[120] hydroxyphthalimide,^[121] CN⁻,^[122] iodide,^[123] fluoride^[119] and selenide.^[99] No reports, to our knowledge, had shown the addition of the thiocyanate group in tandem with azido moieties. Thiocyanates have shown a great aptitude for addition to unsaturated systems in conjunction with many oxidants, as well as, hypervalent iodine compounds.^[124] The first reported work of addition of thiocyanates to olefins was in 1925 by Söderbäck where iodine and thiocyanate were added across double bonds. It was not until 1976 that this area was further explored. Woodgate showed that iodine(I) compounds could be used to allow for addition of thiocyanates to alkenes (Scheme 2.37).^[125]



Scheme 2.37 Anti-Markovnikov iodothiocyantation of styrene using ICl and KSCN combination.

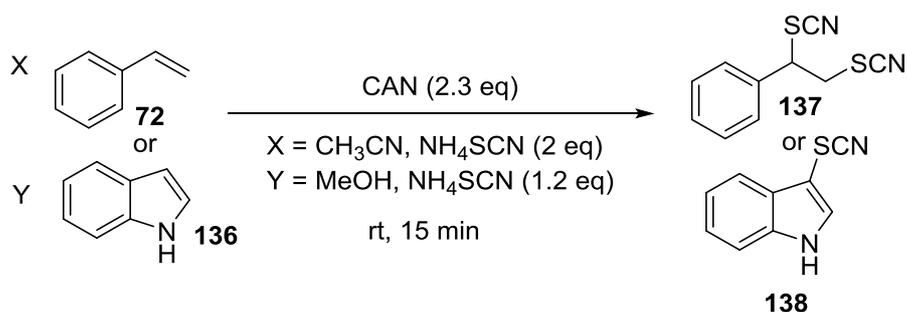
It was further shown that molecular iodine is similarly capable in performing this transformation and led to the Markovnikov product **132**, although in a much longer reaction time of 48 h.

Later work by Wakselman showed that the addition of thiocyanates could equally be accomplished using chlorine(I), and thereby the addition of chloride and thiocyanate was shown across various alkenes (Scheme 2.38).^[126]



Scheme 2.38: Markovnikov addition of Cl and SCN using Cl^(I) reagent.

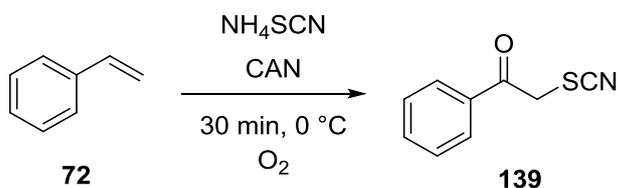
With the previous work using iodine, the addition was Markovnikov in nature. This was not shown using chlorine and the reaction proceeded through an anti-Markovnikov addition to give **133**, likely suggesting a change in mechanism. This was not explored in their work.



Scheme 2.40 CAN-mediated dithiocyanation of styrene and thiocyanation of indole.

Furthermore, this method could be extended to monothiocyanation of indole **138** using similar reaction parameters in a later publication.^[129]

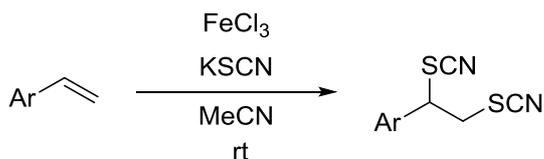
Since then the same group used CAN to allow for oxidative addition of alkenes to form functionalized acetophenones.^[130] Using the previous conditions in combination with molecular oxygen the acetophenone **139** could be synthesised. Upon terminal addition of thiocyanate radical, molecular oxygen could then be added to the benzylic position as shown in Scheme 2.41.



Scheme 2.41: Formation of 1-phenyl-2-thiocyanatoethanone from styrene by CAN, NH₄SCN, O₂ mixture.

Yields were up to 65%, although when changing the nucleophilic source to NaN₃ yields of 95% could be obtained. This work was extended more recently by Zou *et al.* where they showed that CAN was not essential for the product formation.^[131] With only using O₂, the product **139** could be formed in 79% yield, although at 25 °C and in an 8 h reaction time.

Other metal salts such as ferric chloride (FeCl₃) have been used for the dithiocyanation of styrenes (Scheme 2.42).^[132]



Scheme 2.42: Iron(III) chloride catalysed dithiocyanation of styrene.

Good yields of up to 91% were achieved for a number of functionalised styrenes with varying reaction times of 2-15 h, at rt in MeCN. They further compared a number of metal halides to FeCl₃, showing that FeCl₃ was the only metal salt capable of promoting this reaction.

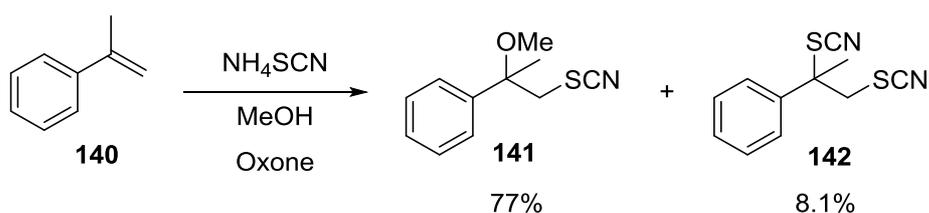
Even common inorganic salts have the aptitude to allow for oxidative addition to olefins. Sodium perborate was also shown to be a useful oxidant for the dithiocyanation of styrene (Scheme 2.43).^[133]



Scheme 2.43: Dithiocyanation of styrene using sodium perborate as the oxidant.

A yield of 92% (**137**) was obtained in 15 min of reaction time at rt. Moreover, addition could also be achieved to the para position of aromatic ring substrates such as aniline and phenol; and to the 3 position on indole. Electron poor substrates such as nitrobenzene did not undergo such an addition.

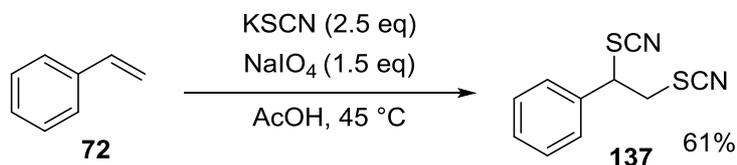
Wu and co-workers showed that Oxone was a suitable reagent for oxidative addition of thiocyanates to α -methyl styrene **140**.^[134] Unlike previous methods where dithiocyanation occurred as the major product in the presence of an oxidant, a mixed species was obtained. As the solvent in this case was methanol, this was incorporated into the product at the benzylic position **141**, though a small amount of dithiocyanation (**142**) occurred (Scheme 2.44).



Scheme 2.44: Anti-Markovnikov methoxy thiocyanation of α -methylstyrene by Oxone, NH₄SCN combination in methanol.

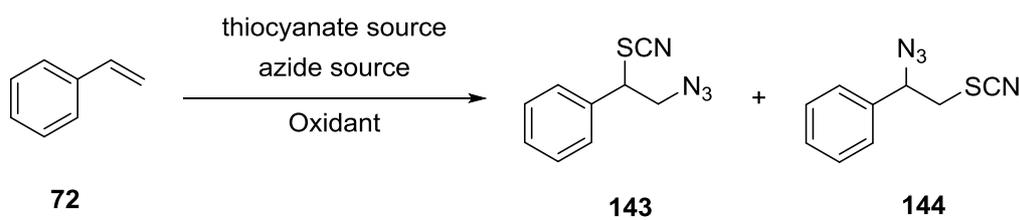
2.2.6 Results

Using simple conditions of sodium periodate and KSCN in acetic acid resulted in dithiocyanation in good yield for styrene (61%) as shown in Scheme 2.45.



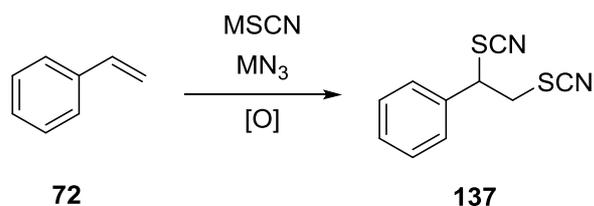
Scheme 2.45: Dithiocyanation of styrene using KSCN and NaIO₄ combination.

This is in concurrence with similar conditions from the literature.^[124] The next step was to introduce the azide moiety to the mixture (Scheme 2.46). By adding 1 equiv of sodium azide the reaction was performed again under the same conditions. Unfortunately the mixed species was not found and the dithiocyanate product **132** was attained along with starting material.



Scheme 2.46: Proposed oxidative azido thiocyanation of styrene.

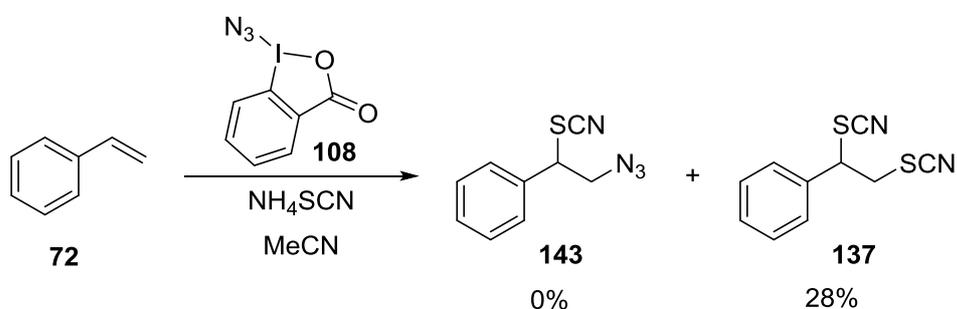
The work moved on to screening oxidants and SCN sources shown below.



| Oxidant | MSCN source | Result /Yield(%) |
|-------------------|---------------------|------------------|
| NaIO ₄ | KSCN | 137 /27% |
| NaIO ₄ | NH ₄ SCN | 137 /34% |
| DIB | KSCN | 137 /22% |
| PHIO | KSCN | 137 /17% |
| 108 | NH ₄ SCN | 137 /28% |

Table 2.8: Azido thiocyanation conditions using styrene (1eq), oxidant (1.5 eq), NaN₃ (1 eq^a, 2 eq^b) and SCN source (1 eq) in AcOH at 45 °C for 1 h in batch.

As shown in Table 2.8 .changing the SCN^- source to NH_4SCN from KSCN was also ineffective at allowing addition of the azide moiety. It was thought best then to move to a species with the azide moiety directly bonded to the iodine reagent to allow for formation of the azide radical preferentially and thus trap the thiocyanate (Scheme 2.47).



Scheme 2.47: Azido thiocyanation of styrene using azido benziodoxole reagent.

When using azide benziodoxole type reagent **108** it was apparent that formation of thiocyanogen was much more facile than what had been believed. Instant colour change indicated the oxidant likely had reacted with the SCN^- source. Upon observation of the crude mixture the styrene had not been consumed entirely although a new compound was observable. After purification it was determined to be the dithiocyanation **137** product attained from previous experiments. This therefore clarified that the formation of thiocyanogen followed by its addition to the double bond is much more facile than that of azide radical formation under mild oxidation conditions even when using a preformed azide containing reagent.

2.3 Concluding remarks and Future work

The project aim was to produce a rapid and more facile enantioselective formation of diamines using a metal-free protocol. The use of hypervalent iodine species has been shown to be a useful method for the addition of nitrogen containing moieties to double bonds but largely containing difficult groups to cleave after incorporation. Azides are easily converted to amines and therefore this project set out to for chiral 1,2-diazide compounds that could then be converted to the corresponding diamines. Although formation of the 1,2 diazides were shown to be achievable, the induction of chirality was not achieved even after successive methods were used. The reaction mechanism was assumed to go through a radical pathway and thus any notion to controlling the enantioselective outcome by reagent control was highly unlikely. Future work would therefore likely consist of substrate controlled additions where similar cases have been shown with other radical reactions. Using systems like enones in combination with a chiral amines such as L-proline the substrate can be made chiral and activate the double bond preferentially which could therefore lead to the addition of radicals in a controlled manner.

Furthermore, the radical nature of the reaction was attempted to be used for the mixed addition of further functionalities noted for undergoing radical addition. By using the azide radical to add to a styrene derivative and form a benzylic radical it was hoped that a thiocyanate could be trapped in this position. Although oxidation and addition of SCN proved to be successful the control of them was difficult where their formation was much more facile than that of the azide radical. This led to dithiocyanation of the styrene derivative with no addition of the azide moiety. Further work would consist of using the SCN benzyloxole derivative to induce terminal addition of a SCN which then in turn could allow for incorporation of an azide into the benzylic position.

3.1 Introduction to nitroaldol reactions

3.1.1 Nitromethane: A highly energetic chemical

Nitromethane has been shown to have extensive energetic properties and been used as a fuel and explosive for over decades.^[135] Its explosive properties were first reported in 1958 in a rail tanker accident; although not considered a dangerous compound at the time, the events on this day caused a reinvestigation into the properties of the chemical. Though insensitive by itself, upon mixture with oxidants, amines or microbeads, detonation can be triggered readily.^[136] This obviously poses a risk when it is being used in chemical synthesis. It has been shown that as little as 3% of an amine in MeNO₂ can cause detonation within a confined space. As many bases tend to be amines, and nitromethane can be used in a multitude of condensation reactions, it could pose a serious risk factor upon scale up. To gain some perspective, it is also worth noting that chemical mixtures such as ammonium nitrate/nitromethane have been used as improvised explosives, most notably in a bombing in Oklahoma in 1995.^[137]

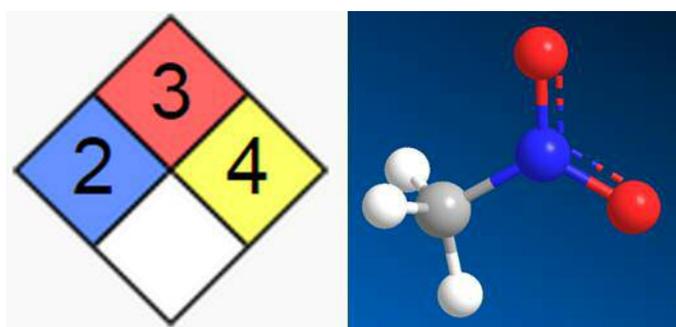


Figure 3.1: Safety informatics for nitromethane.

The majority of synthetic conditions do not use elevated temperatures as a part of their reaction parameters, instead favouring room temperature or below. Although, if time becomes more important than the cost of reagent, accelerating the reaction would be in the best interest, saving on other overhead costs. Heating is an obvious choice when moving to systems where time is of importance. As stated nitromethane has shown explosive properties in combination with a number of initiators and could therefore be considered dangerous when applied to large scale synthesis. The use of large scale batch reactors present a huge risk when using reaction conditions that are exothermic and/or are explosive, due to the higher chance

of adiabatic conditions being met resulting in thermal runaway. If large volumes of explosive reactants are in high concentrations potentially disastrous consequences can be observed where thermal runaway can lead to uncontrolled explosions.

In brief, nitromethane is a highly energetic compound utilised in organic synthesis under a limited set of reaction conditions. Therefore scale-up for these reactions remains a challenge particularly in high concentrations.

3.1.2 Synthesis of compounds containing nitro groups.

The synthesis of nitro-containing compounds is diverse, and multiple methods have been developed for the formation of aromatic and aliphatic nitro compounds. Aromatics can be simply nitrated using HNO_3 or similar reagent combinations, whereas haloalkanes are transformed via reaction with silver nitrite. Alkenes have shown reactivity via radical addition, using ceric ammonium nitrate (CAN).^[138] Preparation from ketones via oximes has also been achieved using oxidising agents such as $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ ^[139]. Additionally it is possible to oxidise azides to nitro compounds using $\text{HOF} \cdot \text{CH}_3\text{CN}$ ^[140] (Figure 3.2).

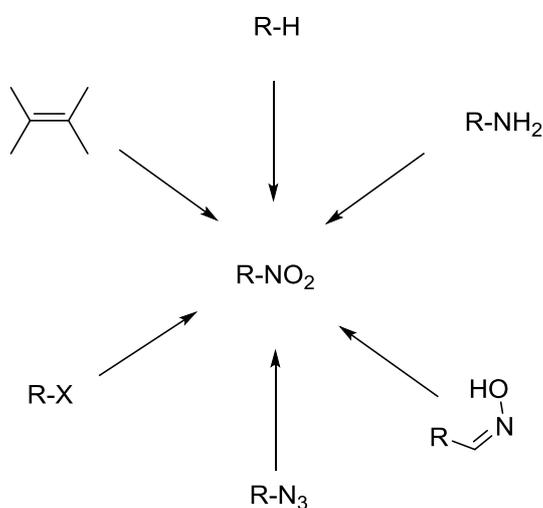
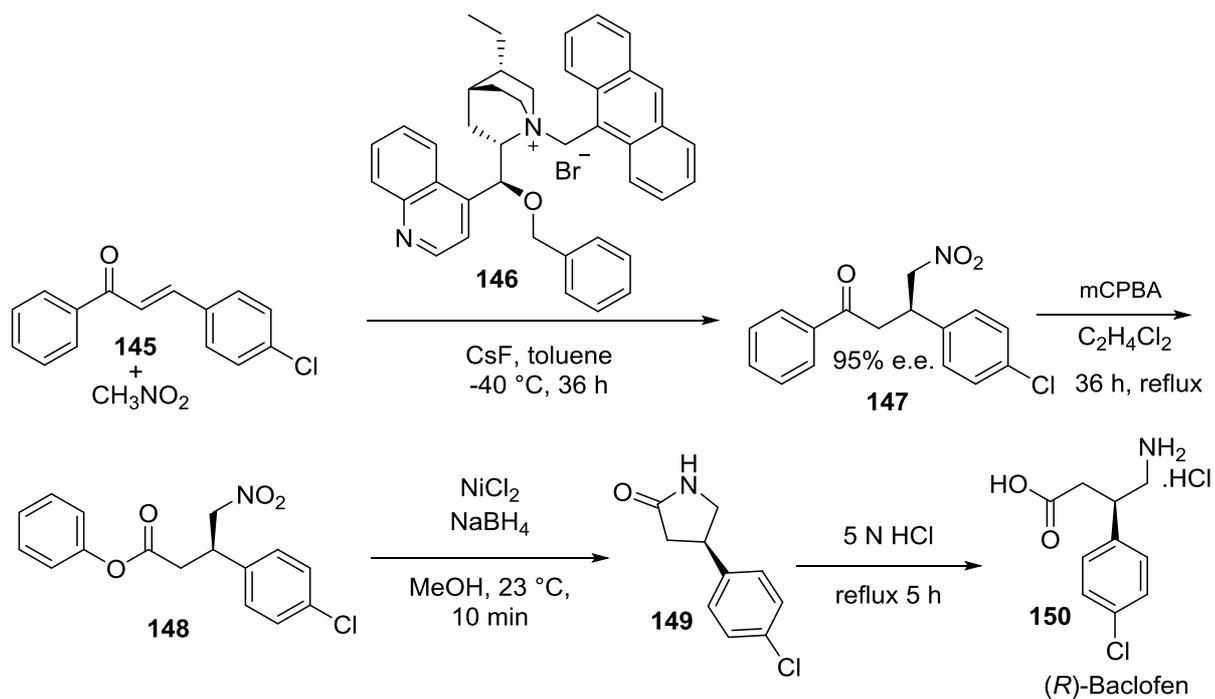


Figure 3.2: Synthesis of nitro group containing compounds.

Additional methods of synthesising nitroalkanes can be result from condensation type reactions. The Henry reaction has been widely studied for the introduction of a nitro group to carbonyls via a condensation. The Henry addition product can then undergo further elimination to form nitroolefins. The double bond of the nitroolefin can be selectively reduced using sodium borohydride^[141] or further transformed via a Michael addition. Furthermore, nitro compounds can then be used as a nucleophile and can allow introduction of chirality, as many enantioselective methods have been presented as exemplified below in the synthesis of (*R*)-Baclofen **150** (Scheme 3.1).^[142]



Scheme 3.1: Enantioselective Michael addition of nitromethane to an α,β -unsaturated enone using chiral quaternary ammonium salts.

Corey demonstrated the diverse nature of the nitro group, using the Michael addition of nitromethane as a key step in the synthesis of a simple natural product.^[142] Not only was it useful for the initial introduction of functionality (**145** to **148**) but it could then be transformed under reductive conditions (**149**) leading to key steps in the formation of the desired product: (*R*)-Baclofen **150**.

3.1.3 The Nitroaldol Reaction

Carbon-carbon bond formation is at the core of organic synthesis. The Henry reaction, or the nitro-aldol reaction, is a reaction between nitroalkanes and carbonyl compounds to produce nitro alcohols, which was discovered in 1895.^[143,144] The reaction has gained a considerable amount of attention in recent years. Classically, the nitroaldol reaction is promoted by the presence of a base in an organic solvent, and conducted at room temperature. The most common bases and solvents used for this reaction are metal hydroxides, carbonates, bicarbonates and alkoxides in water or ethanol. Many reviews have been written on the nitroaldol reactions under batch conditions^[145–147] but only a few publications have been presented using continuous flow technologies.^[148–150]

The earliest publication by Asefa *et al.* showed a fixed bed glass reactor filled with a silica supported primary amine catalyst for the conversion of aldehydes to nitro alcohols (Figure 3.3).^[148]

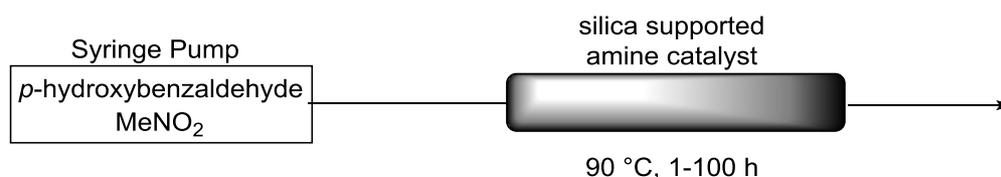


Figure 3.3: First Henry reaction in flow using a silica supported amine catalyst.

They compared the effect of retention time within the reactor against the selectivity of the nitroaldol product showing that if left longer they appeared to have less selectivity towards the nitro aldol product. (1 h 97:3. 100 h 90:10). They also showed that this did not hugely affect the conversion of the reaction observing an 85% conversion at 100 h and a lower 75% at 1 h.

A second publication showed a homogeneous flow method using a fluorine containing hemiacetals instead of aldehydes (Figure 3.4).^[149]

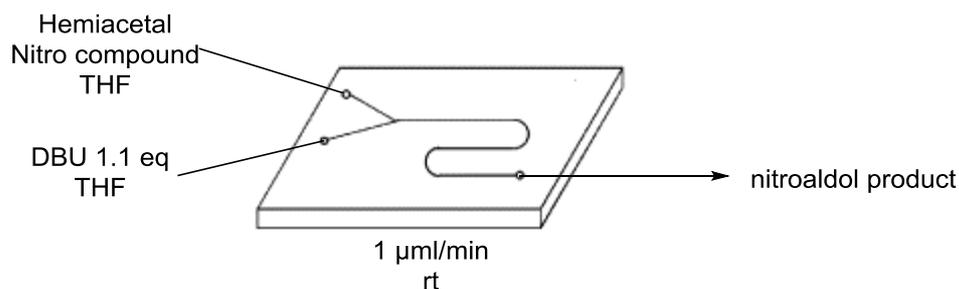


Figure 3.4: Continuous flow Henry reaction of fluorine containing hemiacetals using DBU in a glass chip microreactor

Using DBU (1.1 eq) in THF and flowing through a glass chip reactor they were able to form the fluorine containing nitroalcohols in reasonable yields of 40-80%. Furthermore, they compared their yields to batch reactions which were shown to be higher in all cases although they did not state the g/min comparison.

The first and only enantioselective Henry reaction in flow was reported by Shibasaki and co-workers (Figure 3.5).^[150]

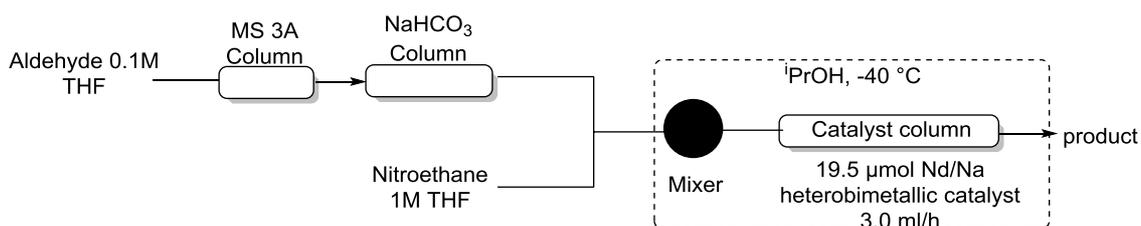


Figure 3.5: Enantioselective synthesis of nitroalcohols using a heterobimetallic catalyst column under continuous flow conditions.

They showed that it was possible to form enantiopure nitroalcohols in continuous flow. Using a fixed bed reactor and a heterobimetallic Nd/Na catalyst they were able to achieve enantiomeric excesses of up to 92% within 2 h. Furthermore, if left continuously they were able to achieve 10g of product in around 30 h.

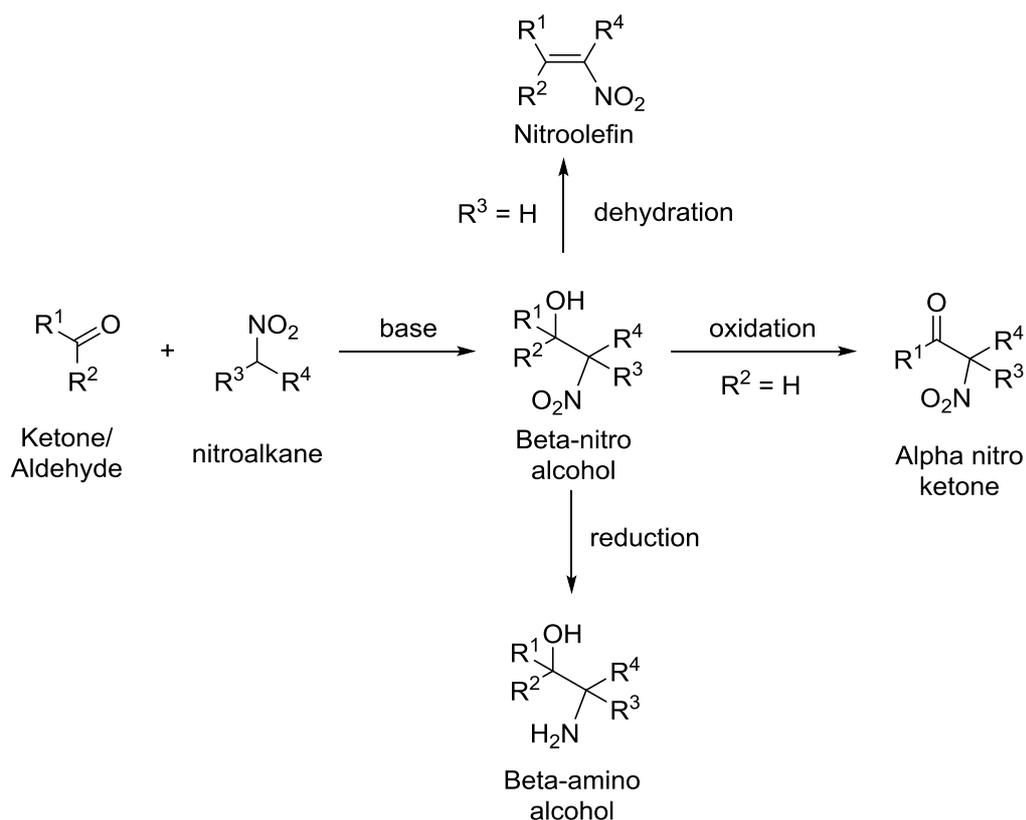
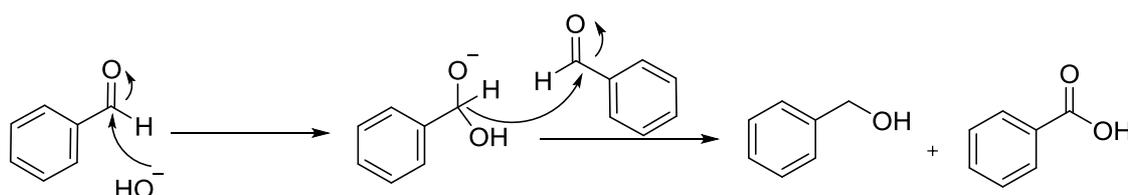


Figure 3.6: Scheme depicting the versatility of nitro alcohols.

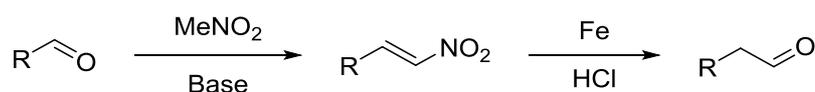
As the nitroaldol reaction is performed under basic or Lewis acidic reaction conditions, there is the potential for a multitude of side reactions depending on the electrophile used. For instance, if an aldehyde is used, there is the potential for the Cannizzaro reaction to occur as shown in Scheme 3.2.



Scheme 3.2: Cannizzaro reaction of benzaldehyde.

The Cannizzaro reaction is common when bases such as NaOH and other hydroxide salts are used. If a ketone is used, side reactions such as the cross aldol condensation can occur where mixed products are obtained, and thus conditions must be suitably controlled to limit this. Furthermore there is also a chance for the β -nitro alcohol formed to undergo an additional transformation by elimination of the hydroxyl group forming nitro olefins. It is therefore paramount to control the basicity of the reaction medium as well as the time frame for reaction. Due to the detrimental effects of these conditions, nitroaldol reactions are usually

left for considerably long reaction times, as long as 72 h, and are performed at low temperatures to avoid them. Although these side products are unwanted it does show the versatility of such products due to the apparent ease of transformation. Having multiple functionalities can then allow for these further transformations shown in Figure 3.6. The addition of a nitro group can also enable the installation of a carbonyl moiety (Scheme 3.3) and has been used in carbohydrate chemistry for many years (Nef reaction). This in combination with the nitroaldol reaction extends the carbon chain while also installing an additional carbonyl. This can be considered a homologation sequence.

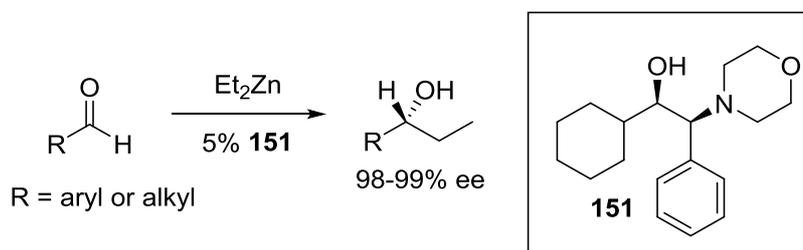


Scheme 3.3: Further transformations shown sequential to the nitroaldol reaction.

Nitroolefins have been shown to be very useful substrates for Michael additions, β -amino alcohols have been extremely useful in asymmetric catalysis (as catalyst themselves or in ligand synthesis) and α -Nitro ketones are extremely useful within the synthesis of heterocycles. This is due to having the distinct properties of both an electrophile, at the carbonyl, and nucleophilic properties α to two activating groups, the carbonyl and the nitro moieties.

The versatility of the β -nitro alcohol does not just lend itself to a large variety of chemical transformations, but upon a simple reduction to amino alcohols, can then be used as chiral auxiliaries for stereochemical induction.^[151,152]

For example Nugent showed that β -amino alcohols could be used as ligands (**151**) for the asymmetric addition of alkyl zinc reagents. Scheme 3.4.



Scheme 3.4: Synthesis of chiral secondary alcohols via a reduction and addition reaction using β -amino alcohols and Zn reagents.

A range of aldehydes were used ranging from benzaldehydes to hexanal. Yields were generally excellent, up to 98%, and with ees of up to 99%. This was all achieved in a reaction time of 3 h at room temperature.

3.1.4 Utilization of the nitro group

The nitro group has shown a great impact in many fields of chemistry due to its characteristics. The strong electron withdrawing nature allows for the properties of compounds to be changed dramatically; either making them readily more acidic, like within the nitroaldol, adding the ability to be a Michael acceptor (**153**) in addition reactions and causing the reagent to be more Lewis acidic, such as in urea H bond **152** (Figure 3.7).^[153]

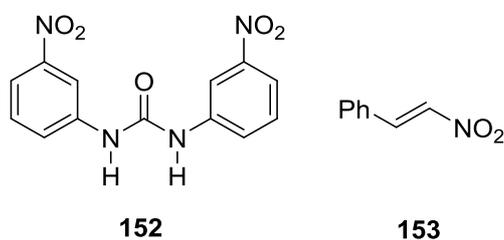


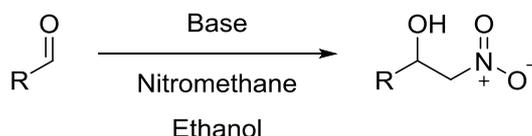
Figure 3.7: Using the electron deficiency of the nitro group left as a Lewis acid catalyst and right as a Michael acceptor.

Not only can it affect surrounding moieties, but the variety of transformations that the nitro group is able to undergo allows for a synthetic diversity. Reduction can generate a number of functional groups such as amines, hydroxylamines,^[154] oximes^[155] and although difficult to achieve complete reduction to hydrocarbons.^[156] Hydrolysis can, as in the Nef reaction,^[157] lead to carbonyl containing compounds such as ketones and aldehydes.

3.2 Results and Discussion

3.2.1 Initial Flow Conditions

The project described herein began with finding conditions that would be applicable under continuous flow. Solvents and concentrations had to be carefully chosen to avoid precipitation as clogging can be a huge factor in flow chemistry. Initial conditions began by using a common base used in condensation reactions, triethylamine (NEt₃) and a polar solvent was chosen to stabilise the formation of charged intermediates. Conditions such as these are common in many organic syntheses of a similar type (Scheme 3.5). Methods in batch conditions have been well established for decades therefore moving straight to flow was thought to be the most efficient route.



Scheme 3.5: General Henry reaction conditions for flow.

The flow system started by using a syringe containing NEt₃ (10 mol%) dissolved in ethanol (0.5 M) with a second syringe containing 4-nitrobenzaldehyde **154** dissolved in ethanol containing 10 eq of nitromethane (1 M) (Figure 3.8).

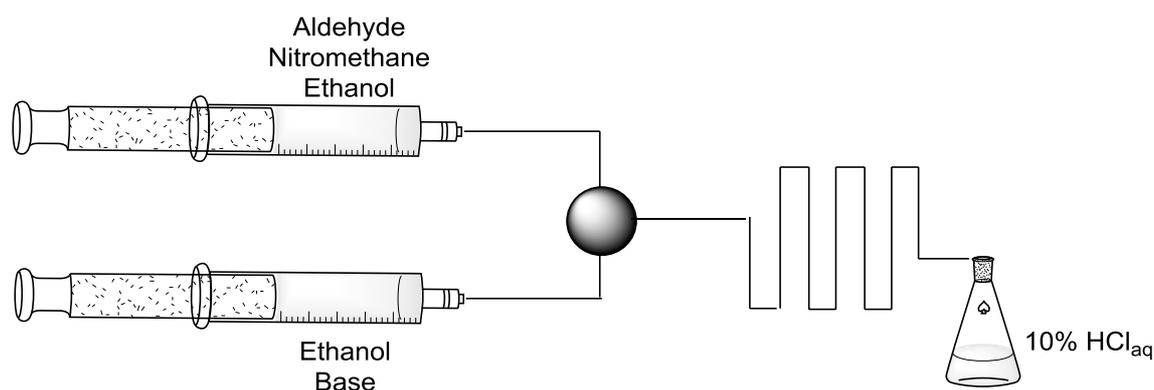


Figure 3.8: Schematic of initial flow set-up for the nitro aldol reaction.

The reaction was then performed using a PTFE coil (1 ml, 0.5 mm i.d.) with a Comet mixer^[158] attached for increased mixing properties. Residence time within the coil was 30 min at room temperature. Upon quenching with 10% aqueous hydrochloric acid the product was isolated. The quench solution was tested to ascertain if it could catalyse the reaction solely. This was

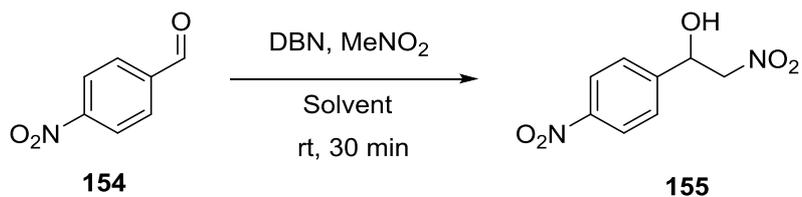
done by adding the reactants of the reaction to a solution of 1M HCl and leaving to stir for 12 h. Upon TLC and NMR analysis no conversion of the starting material was observed.. After initial reaction conditions using NEt_3 were established the base was then varied to find the optimal reagent.(Table 3.1).



| Base | Yield 155 (%) |
|----------------|-------------------------|
| NEt_3 | 51 |
| Hüings Base | 21 |
| DBU | 75 |
| DABCO | 24 |
| DMAP | 23 |
| Proton Sponge | 27 |
| Butylamine | Traces |
| DBN | 92 |
| TBD | 90 |
| KOH | 81 |

Table 3.1 Screening bases for the catalysis of the nitro aldol reaction using 4-nitrobenzaldehyde 1eq, nitromethane 10 eq and base 0.5 eq in ethanol at RT and 30 mins residence time.

As shown in Table 3.1, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) proved to be the best base for this transformation under the designed conditions as well as similar bases such as 1,8-diazabicycloundec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) leading to yields in the range of 75-92%. As expected due to the lower basicity of triethylamine (NEt_3) and others, yields were considerably lower when these were employed. The project then moved on to solvent screening to find the optimal solvent for this reaction (Table 3.2).



| Solvent | Yield 155 (%) |
|---|-------------------------|
| Ethanol | 92 |
| Methanol | 91 |
| Acetonitrile | 86 |
| Toluene | 20 |
| THF | 58 |
| CH ₂ Cl ₂ | 22 |
| Chloroform | 18 |
| Ether | 41 |
| Isopropanol | 82 |
| ^t Butanol/ CH ₂ Cl ₂ | 80 |

Table 3.2: All conditions used 4-nitrobenzaldehyde, nitromethane and DBN in solvent at room temperature for 30 min of residence time.

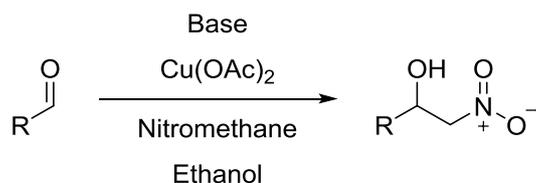
From Table 3.2 the optimal solvent system was shown to be ethanol likely due to the highly polar nature of the solvent stabilising charged intermediates. Methanol showed comparable yields, as did acetonitrile due to also being able to stabilise the intermediates well.. Ethanol was therefore chosen as a less toxic choice of the two alcohols. As the conditions of ethanol using DBN had been set, it was thought that substrate scope could now be developed. A variety of aryl aldehydes were tested under the established conditions.



| Substrate | Product | Yield (%) |
|----------------------|----------------|-----------|
| 4-nitrobenzaldehyde | 155 | 92 |
| 4-fluorobenzaldehyde | 156 | 70 |
| 4-chlorobenzaldehyde | 157 | 65 |
| 4-bromobenzaldehyde | 158 | 63 |
| 4-tolylaldehyde | 159 | 40 |
| 4-anisaldehyde | 160 | 12 |

Table 3.3: Substrate scope using nitromethane and DBN in ethanol at rt for 30 min of residence time.

Yields (Table 3.3) for the more electron poor aldehydes are good to excellent although with substrates containing electron donating substituents yields dropped dramatically. Modifications to this method were investigated in order to increase the yields when using electron rich substrates. It was hoped that by adding metal salts as a Lewis acid catalyst and increasing the temperature this could be achieved.



Scheme 3.4: Base and Copper (II) co-catalysis of the nitroaldol reaction.

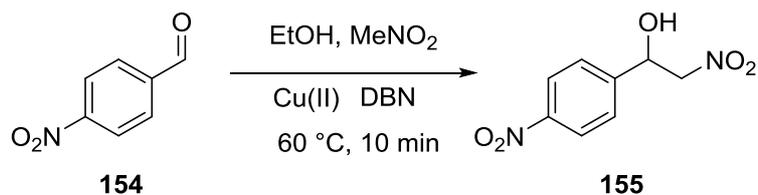
Simple copper (II) salts have been shown to catalyse the nitroaldol reaction without the addition of a base.^[159] Although reaction times are long it was thought that, in co-catalysis with a base, reaction yields could be enhanced further (Scheme 3.6). This would also then lead to an obvious way to add enantioselectivity to the system by adding a chiral ligand to the reaction mixture in further studies.



| Substrate | Conversion by NMR (%) |
|-----------------|-----------------------|
| 4-anisaldehyde | 61 |
| 4-tolylaldehyde | 74 |

Table 3.4: Effect of Cu(OAc)₂ (10 mol%) on the rate of reaction using DBN and nitromethane in ethanol at RT for 30 min residence time.

As shown from Table 3.4 the use of metal salts increased the yields of the electron rich substrates. By adding copper acetate to the syringe containing DBN coordination was apparent, the solution changed from a light blue to a deep blue solution. Running these conditions as before, (with the addition of Cu to the base syringe) led to an increase of up to 60% conversion in some cases. It is likely that the copper salt is therefore acting as a Lewis acid, activating the carbonyl for attack by the nitromethane.

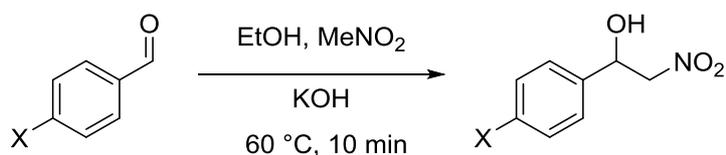


| Metal salt | Yield (%) |
|----------------------|-----------|
| Copper (II) Acetate | 92 |
| Copper (II) Sulphate | 91 |
| Copper (I) Bromide | 89 |

Table 3.5: Effect of varying metal salt(10 mol%) for established nitro aldol conditions with DBN.

As shown from Table 3.5 changing the counter ion on the copper salt did not affect the conversion of the product in comparison to each other. Other metals such as nickel and cobalt became insoluble upon addition of DBN and were therefore not applicable for continuous flow.

Although DBN is reasonably more expensive than other bases, it shows a great selectivity for the Henry reaction showing no further elimination to the nitrostyrene. The problem of further elimination of the nitro alcohol to the nitro olefin other bases cause, is not apparent. Other cheaper bases such as KOH did perform to a good degree showing excellent yields comparable to DBN. The vastly lower price of such a base can also allow for scale up being much more applicable. And as it is an inorganic base an aqueous separation can be used which is more facile compared to chromatography needed to separate many organic bases. As well as with the conditions used in combination with copper salts a secondary set of conditions using KOH were devised. Using ethanol as the solvent and heating to 60 °C allowed for almost full conversion in a residence time of 10 min.



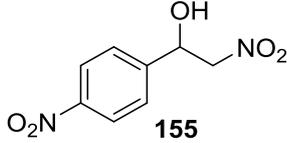
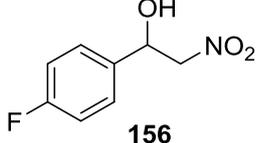
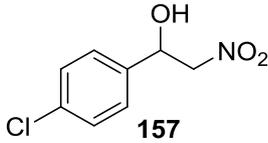
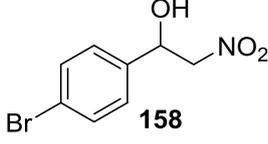
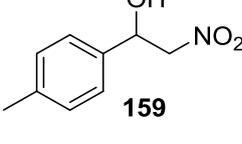
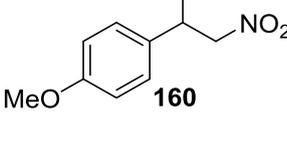
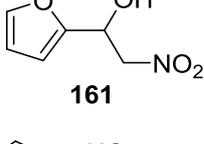
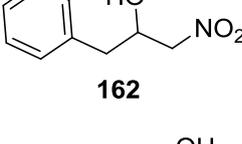
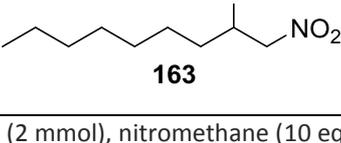
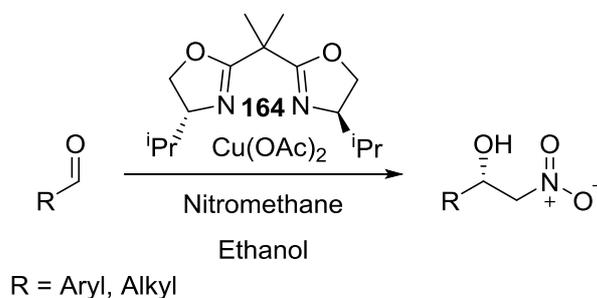
| Substrate | Product | Yield (%) |
|----------------------|--|-----------|
| 4-nitrobenzaldehyde |  155 | 81 |
| 4-fluorobenzaldehyde |  156 | 76 |
| 4-chlorobenzaldehyde |  157 | 72 |
| 4-bromobenzaldehyde |  158 | 72 |
| 4-tolylaldehyde |  159 | 60 |
| 4-anisaldehyde |  160 | 10 |
| furfuraldehyde |  161 | 45 |
| phenacetaldehyde |  162 | 62 |
| octanal |  163 | 42 |

Table 3.6: Substrate scope in flow of aldehydes (2 mmol), nitromethane (10 eq) using KOH (0.3 eq) in ethanol overall 1M solutions. 10 min residence time at 60 °C.

As shown from Table 3.6, yields were generally very good for all aldehydes. As expected the conversion of electron rich substrates was much lower than that of the electron poor substrates. Furfuraldehyde, octanal and phenylacetaldehyde also showed good yields within the reaction time.

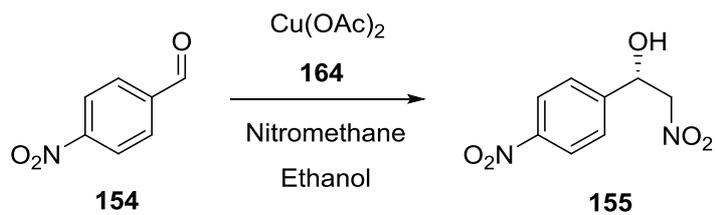
3.2.2 Chiral synthesis

After the establishment of flow conditions, the stereoselective version of the Henry reaction was investigated. Although asymmetric reactions are sometimes associated with long reaction times and low temperatures recent work in flow chemistry, specifically by Seeberger *et al.*,^[160] has shown that it does not have to be the case, and induction can be achieved at elevated temperatures in short residence times. Two different chemical techniques were devised for the formation of the chiral nitroalcohols, copper(II) catalysis and phase transfer catalysis. As copper showed applicability towards Lewis acid catalysis, batch conditions from literature were adapted for continuous flow. A report by Evans *et al.* in 2003 showed a very similar system to the one already shown in flow in the previous section.^[159] The use of $\text{Cu}(\text{OAc})_2$ in alcoholic solvents using bisoxazoline ligands showed brilliant control of stereochemical induction of up to 94% enantiomeric excess (Scheme 3.7).



Scheme 3.5: Evans conditions for stereoselective nitroaldol reactions.

The bisoxazoline ligand 2,2-bis((4S)-(-)-4-isopropylloxazoline)propane **164** was purchased to attempt these transformations. Initial conditions were attempted in batch to get a feel for the chemistry using the reported procedure, where, although yields were good, the reported enantiomeric excess could not be matched. This is likely because the ligand had racemised over time from storage within our group. Furthermore, at this stage the use of this system seemed unlikely due to the longer reaction times.



| Time (h) | Yield (%) | e.e (%) |
|-------------|--------------|------------|
| 4 | 20 | 11(S) |
| 12 | 72 | 14(S) |

Table 3.7: Batch conditions using Evans conditions where literature e.e.'s were typically around 90%. 1M solution of 4-nitrobenzaldehyde in ethanol, nitromethane 10 eq, **164** 10 mol% at rt.

While initial assessments suggested that the reaction times may be too long for continuous flow, it was hoped that the increased mass transfer properties of continuous flow may allow for an overall increase in reaction rate.

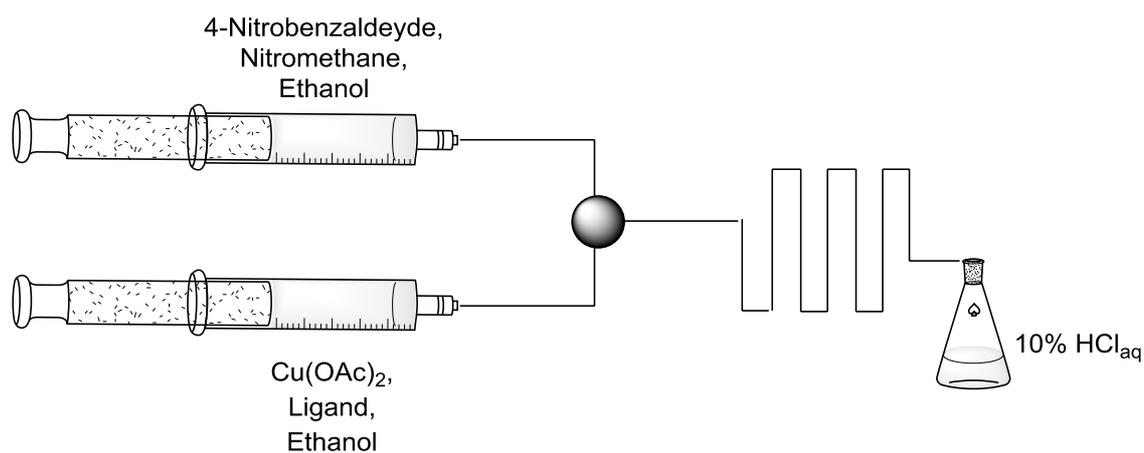
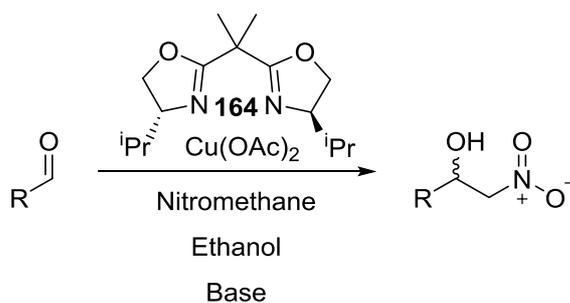


Figure 3.8: Flow set-up for the stereoselective nitro aldol reaction.

Replicating the batch conditions in flow (Figure 3.8) led to the same low yields although realistically the residence time was far too long (12 h). Even when using 4-nitrobenzaldehyde reaction times were in the order of hours. This would therefore be a huge problem when moving to systems that are not electron deficient. Heating the reaction did not allow for a large increase in rate and furthermore no asymmetry was observed at 70 °C within a residence time of 1 h.



Scheme 3.6: Adapted Evans conditions for increased rate of reaction.

To accelerate the reaction it was thought that the addition of a base would allow for co-catalysis and increase the reaction rate (Scheme 3.8). A few bases were screened within the system, such as DBU, NEt_3 and Hünig's base, where the latter was thought to be ideal due to its hindered nature. Although the products were obtained in higher yields, there was no stereochemical control. This was thought to be due to the background reaction where the base was solely catalysing the reaction with the ligand system taking little or no part. These results lead to the decision to attempt another method of chiral induction.

In tandem chiral phase transfer catalysis (CPTC) was attempted in flow, this sought to utilise the inherent surface to volume ratio increase when switching from batch to flow conditions. As PTC relies on the interaction between organic and aqueous phases, flow chemistry seemed to be ideal as segmented flow can occur. Not only does the occurrence of segmented flow formed within tubing create a much larger surface relationship, but internal vortex mixing can also occur. It was suggested that the catalyst would shuttle the inorganic base, in this case the hydroxide ion, between the segments at a rate that would drastically enhance the overall reaction rate (Figure 3.9).

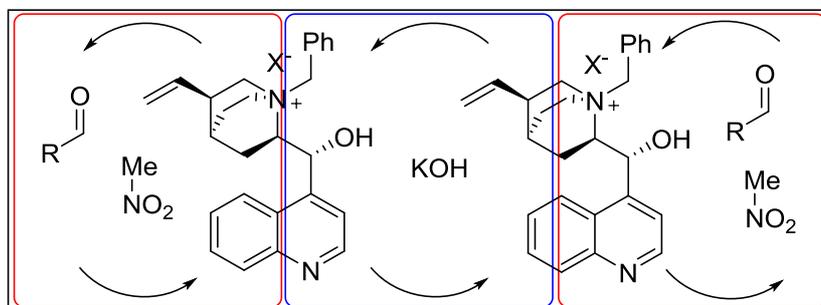


Figure 3.9: Depiction of designed segmented flow CPTC nitro aldol reaction (Organic phase, Aqueous phase) Arrows depict vortex mixing within segments created by interaction with the tubing wall.

Again initial attempts were trialled in batch using the solvent system of aldehyde, nitromethane and CPTC, dissolved in toluene, before an aqueous KOH solution was added. After the reaction had been vigorously stirred for maximum interaction between the two phases, formation of the nitro alcohol became apparent via TLC monitoring. A yield of 75% was obtained in 16 h. An enantiomeric excess of 9% was obtained showing the potential of these method for the reaction. Before optimisation of the e.e., it was thought best to see if this reaction conditions used in batch were accessible in continuous flow, due to the observation of large precipitates upon addition of the KOH solution to the organic phase. By using the same system, the reagents and catalyst dissolved in toluene in one syringe and the aqueous KOH in a second, upon mixing, using the same concentrations as within batch, precipitation of what appeared to be the PTC occurred. This led to clogging of the reactor channels and therefore a reduction in concentration was needed. When using a lower concentration of the organic phase, precipitation was still observed, but not enough to cause blocking within the channels and therefore a residence time of 1 h could be obtained. From analysis by chiral HPLC a racemate was observed and showed that the precipitation of the PTC was a large problem, likely due to the lack of interaction with the substrate. It was therefore thought that the KOH within solution would likely be catalysing the reaction independently to the PTC at the surface of the segments aided by the vortex mixing. Modifications to the solvent system by adding CH_2Cl_2 did not aid solvation. Due to this drawback, the decision was made to move on from this and focus more on a multi-step synthesis of amino alcohols within flow.

3.2.3 Multi-steps

3.2.3.1 In-line reductions

The nitro group can be reduced by numerous methods such as: zinc, nickel, tin or iron metal with Brønsted acids; Pd/C with $H_{2(g)}$; nickel and cobalt salts in combination with sodium borohydride and samarium diiodide to name but a few. In recent times there has been a growth in the area of reductions in continuous flow. This has been made popular by the commercially available H-Cube which has allowed for the introduction of H_2 gas easily within flow systems under pressure.^[161] Many of the conditions stated are heterogeneous conditions. Consequently flow methods had to be adapted for such chemistry and numerous reports of this have begun to emerge over the last decade. Multiple heterogeneous reports have also been reported using a variety of metal catalysts and have been reviewed well in the last few years.^{[162][163]} This introduction will focus on other methods not considered in these reviews. Further methodology has been developed in the last few years using systems that do not rely on transition metal based catalysis.

Seeberger *et al.* demonstrated a system consisting of sodium borohydride packed into a cartridge (Figure 3.10).^[164]

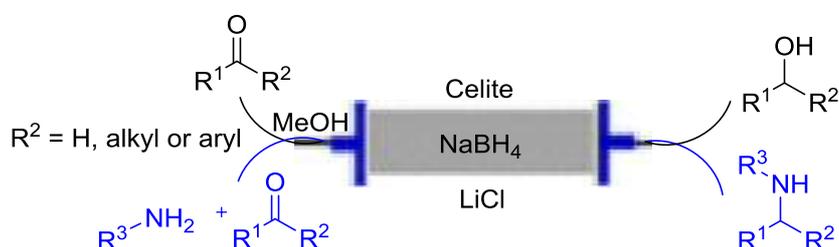
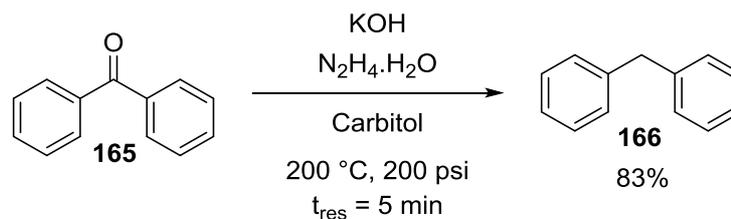


Figure 3.10: Reduction of aldehydes and ketones by a cartridge based $NaBH_4$ flow system.

They showed that a number of different functional groups could be reduced efficiently, from aldehydes and ketones to reductive aminations. Yields ranged from 74-99% for simple carbonyl reductions in a residence time of 5.6 min where gram quantities were used. Although still highly successful, yields of the reductive aminations were lower. Yields of up to 80% were obtained in a residence time of 7 min with a variety of carbonyls and amines.

In a work by Jensen and co-workers a Wolff-Kishner reduction of carbonyl compounds using a specially designed microreactor was reported.^[165] Due to the harsh conditions used in the Wolff-Kishner reaction, numerous reactor materials could be deemed insufficient. A robust silicon carbide reactor was designed for this purpose.



Scheme 3.7: Wolff-Kishner reduction of benzophenone in a silicon carbide microreactor.

A variety of carbonyl compounds, including benzophenone **165** (Scheme 3.9), were shown to be completely reduced to the saturated alkyl group (**166**) in yields of up to 96%, where as compared to batch conditions, reaction times were reduced by 2 orders of magnitude.

In a report by Alcázar *et al.* a simple economical system was developed for the reduction of nitrile compounds to aldehydes using DIBAL-H (Diisobutylaluminium hydride)^[166] (Figure 3.11).

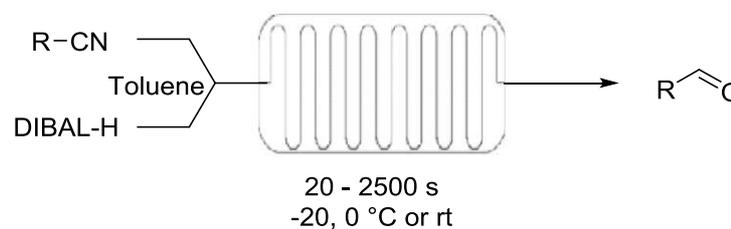


Figure 3.11: Reduction of nitriles to aldehydes by DIBAL-H in continuous flow.

It was shown that a number of alkyl, aryl and hetaryl-nitriles could be efficiently and selectively reduced to the corresponding aldehydes in yields of up to 88%. Temperatures and residence times varied depending on substrate where electron neutral and electron rich groups were reduced in 20 s at 0 °C. Strong electron-withdrawing groups, such as the nitro group required longer residence times and additional amount of reducing agent. Heterocycles such as the pyridyl analogues were also reduced, at room temperature.

A similar method was developed by Jamison *et al.* where they used DIBAL-H for the selective reduction of esters to aldehydes (Figure 3.12).^[167] A PFA reactor coil connected with T-pieces was used for mixing and a further addition of methanol to quench the reaction.

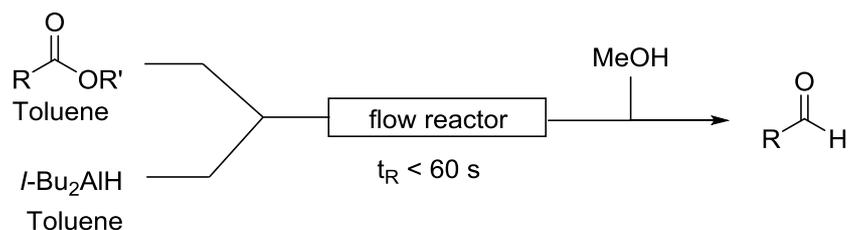


Figure 3.12: Continuous flow set-up for the rapid reduction of esters to aldehydes using aluminium hydrides.

Temperatures used were generally considerably lower for this methods ranging from $-78\text{ }^{\circ}\text{C}$, for substrates prone to over reduction, to $-40\text{ }^{\circ}\text{C}$ for the general method. Reaction times varied but overall were below 60 s obtaining yields by GC > 95%.

A third method using aluminium halides was demonstrated by Alcazar and co-workers.^[168] They showed the reduction of esters to aldehydes in a continuous flow reactor, finding that LDBBA (diisobutyl-tert-butoxyaluminum) was the most efficient reducing agent. The set-up involved the Vapourtec R2 and R4 modules for cooling the reaction to low temperatures. Furthermore they used a column containing sodium sulfate for an in-line work-up (Figure 3.13).

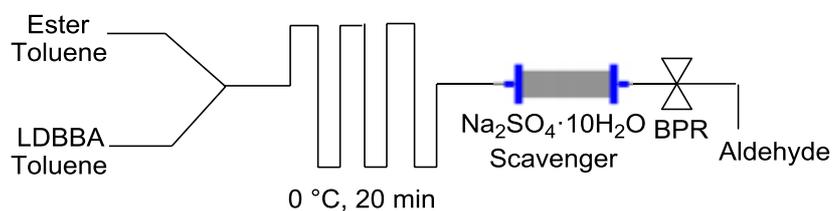


Figure 3.13: Selective reduction of esters to aldehydes in continuous flow.

Using low temperatures such as -70 to $-20\text{ }^{\circ}\text{C}$ using DIBAL showed poor conversions and complete over reduction to the alcohol. This led them to the use of LDBBA and raising the temperature to $0\text{ }^{\circ}\text{C}$. This in turn allowed for much higher conversions and selectivity with yields for some substrates as high as 97%.

An alternate method to hydride reductions of carbonyls in flow was produced by Ley.^[169] It was shown that a cartridge of hydrous zirconia could be employed for the disproportionation of substrate aldehydes or ketones with the IPA solvent (Figure 3.14). This would then produce the corresponding primary or secondary alcohol and acetone, making this a recyclable process.

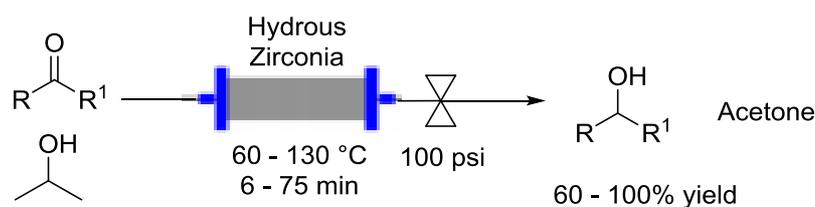


Figure 3.14: Reduction of aldehydes and ketones to alcohols in continuous flow using hydrous zirconia.

Reaction times and temperatures varied where aldehydes generally needed shorter reaction times and lower temperatures to ketones, with good to excellent yields obtained for a number of substituted carbonyls.

Jamison has contributed to reductions in flow chemistry by demonstrating an *in situ* formation of diazene from a combination of *N,O*-bistrifluoroacetylhydroxylamine **153** and hydroxylamine in a microreactor (Figure 3.15).^[170] The formed diazene was then used to reduce olefins to alkanes.

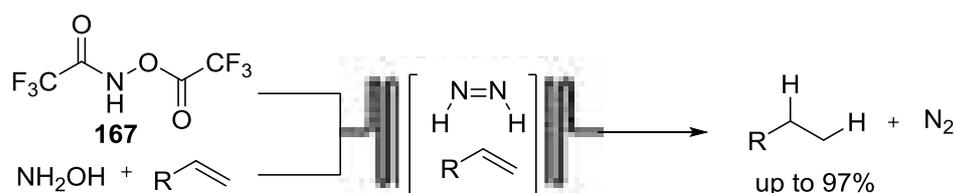


Figure 3.15 *In situ* formation of diimide from **167** and NH_2OH for the reduction of olefins in flow.

A simple PFA coil connecting the inlets via a T-piece was used where the reagent streams were fed in via syringe pumps. The reagent streams were passed through the reactor coil for 20 min at 100 °C for monosubstituted alkenes and 140 °C for disubstituted alkenes. Yields of up to 97% were achieved and functional groups such as amides, esters and nitro groups could be tolerated.

A similar method was developed by Kappe *et al.* who used oxygen gas in combination with hydrazine to form diazene *in situ* (Figure 3.16).^[171] Once the reagent mixture and gas were mixed a segmented flow occurred and the oxygen oxidises the hydrazine to diimine. This then allows a second stream to be introduced containing the substrate which with disproportionation forms the diimide to reduce to the alkane.

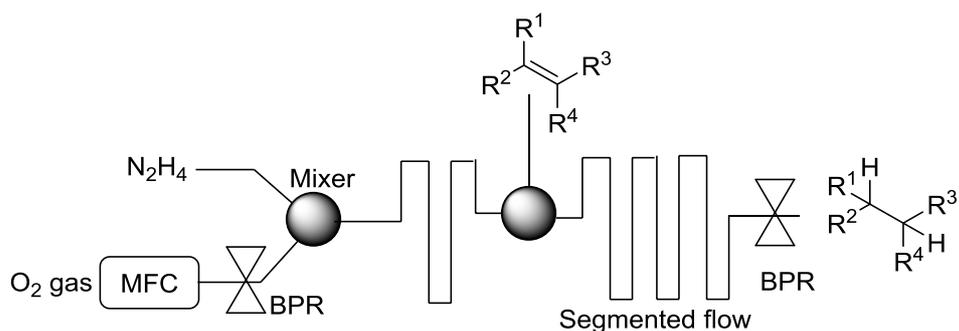


Figure 3.16: Oxidation of hydrazine to diimide followed by reduction of olefins to alkanes in flow.

Conversions were fully completed in 10 min of residence time at 100 °C with yields ranging from 58 to 99%. Functional groups such as nitro groups, esters and silyl protection all were tolerated in excellent yields showing the high selectivity of this method.

Not only have racemic reductions been employed but Luisi *et al.* described a CBS reduction of ketones to the corresponding chiral alcohol.^[172] Using borane and the Corey, Bakshi and Shibata (CBS) oxazaborolidine **169** in the green 2-MeTHF solvent they were able to efficiently reduce ketones (Figure 3.17).

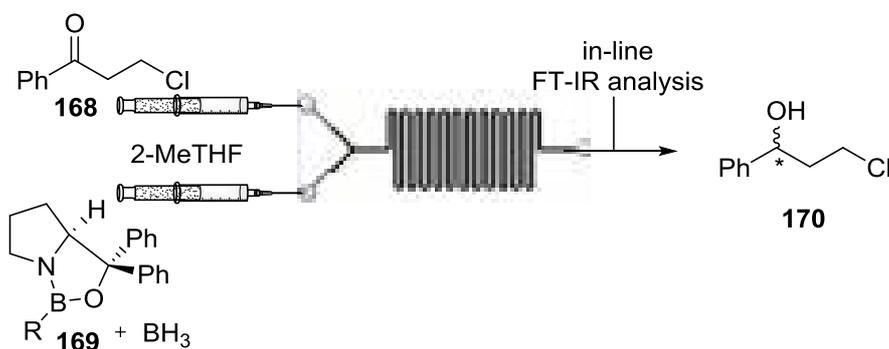


Figure 3.17: Chiral reduction of 3-chloro-1-phenylpropan-1-one by CBS oxazaborolidine monitored by in-line FT-IR in continuous flow.

The system consisted of a Syrris Asia flow reactor and monitoring the eluent flow by FT-IR they were able to determine the optimal conditions. With these conditions in hand of 8 mol% catalyst **169** at 0 °C and 1.5 eq of BH₃ they could achieve yields of up to 97% and an e.e. of up to 92% for various substrates.^[172]

Another method using transfer hydrogenation was shown by Ley *et al.*^[173] They developed a simple flow reactor system to reduce carbonyls to alcohols using a transition metal free process. They used alkali metal salts in *i*PrOH at elevated temperatures to mimic the use of microwave reactors (Figure 3.18).

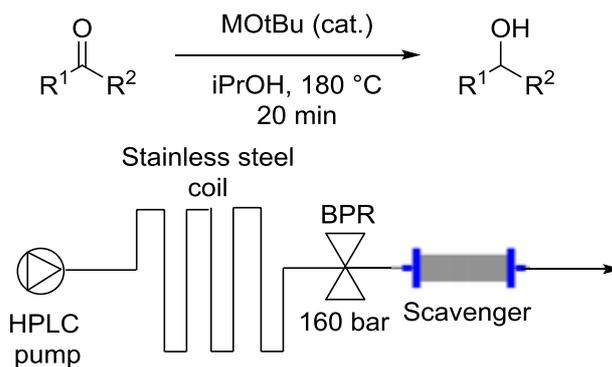


Figure 3.18: Carbonyl reduction at elevated temperature and pressure in a stainless steel flow reactor.

By using a stainless steel reactor and a BPR temperatures of 180 °C could be achieved even using alcoholic solvents. The efficient heating therefore allowed conversions of up to 99% in reaction times between 20 and 30 min. The Li salt of the alkali bases showed superiority over the Na or K salts. Additionally they used a cartridge containing tosyl-hydrazine to scavenge the residual ketone.

3.2.3.2 Transfer hydrogenations

Although there are multiple methods using inorganic reagents for the reduction of functional groups produced in flow without the use of hydrogen gas, these methods can have their drawbacks. Countless articles employing Pd/C with H₂ have shown that this combination is highly effective but most importantly very mild. Using H₂ gas though can also have its drawbacks, especially with the storage fear when working on large scale syntheses and the cost when using generators. Other such methods such as transfer hydrogenations have shown that the mild reducing nature of transition metal catalysis can be used with an alternative hydrogen source.

The concept of turning this process into a continuous flow method was first initiated in 1988 by Means *et al.* A simple method using a glass column filled with glass wool and Pd black (15.6 eq) was used. A solution of an olefin dissolved in formic acid was then allowed to pass through the column using only gravity.^[174]

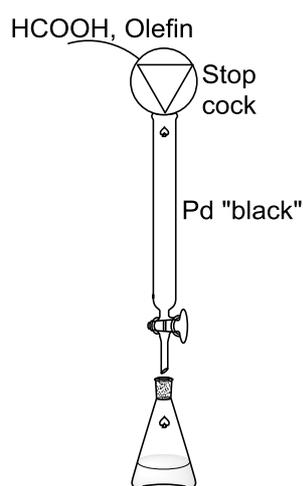


Figure 3.19: Transfer hydrogenation of olefins by formic acid and Pd black in a gravity flow column system.

As shown in Figure 3.19, a stop cock was used to control the flow rate of the column where they observed a rate of 0.1 mol/min conversion. Yields of 90% were attained for a few olefinic substrates furthermore showing that the column could be reused.

A method developed by Ley *et al.* showed an efficient system for the reduction of carbonyls in a micro flow device (MFD).^[175] The authors created tubing in which they coated the inside with a thin layer of Pd catalyst (Figure 3.20).

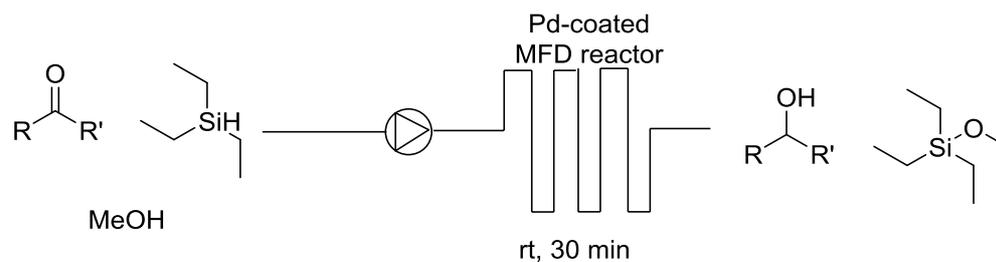


Figure 3.20: Pd-coated micro flow device (MFD) fabricated for the reduction of carbonyls in flow.

Using triethylsilane as the hydride source in methanol, carbonyl compounds could be successfully reduced to the corresponding alcohol in 95% yield at rt in 30 min. They further showed that a variety of functional groups such as acetylenes, imines, olefins and nitro compounds could also be reduced with this method.

Another method using a very similar approach was developed by Suzuki and Javaid. They again used a Pd coated tubing to catalyse the reduction of p-nitrophenol **171** (Figure 3.21).^[176] The Pd coating consisted of a co-plating of Pd and Ag and developed a method to allow for a more porous coating. This in-turn gave a larger surface area and more catalytic sites.

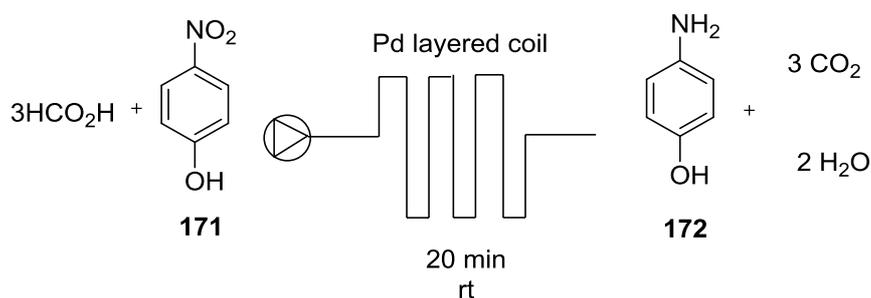


Figure 3.21: Reduction of 4-nitrophenol in Pd-layered flow reactor and formic acid.

Using formic acid as the hydrogen source was studied under varying conditions to find the most efficient process. They showed that a residence time of 20 min was needed to reach full conversion and that at a pH of 2 the highest conversion was achieved of 99.2%.

Reductive amination has also shown to be highly efficient in continuous flow. Poppe and co-workers used the ThalesNano system to convert ketones to amines under Pd catalysis (Figure 3.22).^[177]

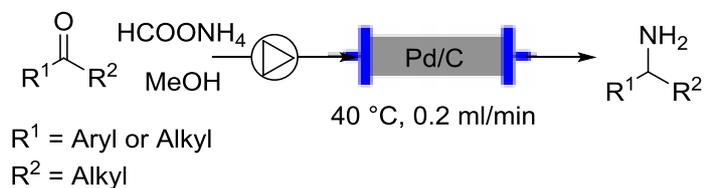


Figure 3.22: Reductive amination of carbonyls to aliphatic amines via a Pd/C cartridge based flow system.

With a cartridge filled with 10% Pd/C and ammonium formate dissolved in methanol a reduction of the *in situ* formed imines was possible in good yields (41-68%). The same column was used continuously for 56 h where no deactivation of the catalyst was observed.

A method using sodium formate and a column packed with glass beads and Pd/C for the reductive formation of cyclohexylamines from phenols and amines was developed by Vaccaro (Figure 3.23).^[178]

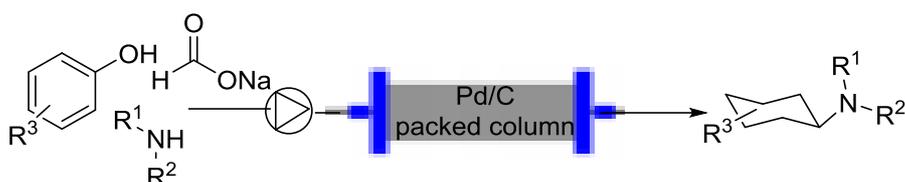
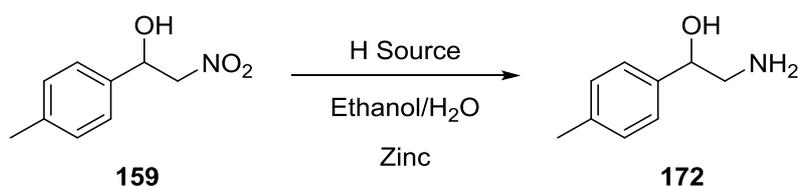


Figure 3.23: Synthesis of cyclohexylamines by reduction of phenol and subsequent reductive amination by Pd/C and sodium formate in a cartridge flow reactor.

The substrates were premixed with the sodium formate in water and passed through the column at 60 °C. Yields of up to 92% were obtained with TON and TOF values of 32.7 and 5.45 h⁻¹ respectively.

Many of the conditions stated are heterogeneous. Consequently flow methods had to be adapted for such chemistry. The first method chosen, mainly because of its cost effectiveness when thinking towards larger scale synthesis, was zinc metal with Brønsted acids. Initial conditions were optimised in batch using 2-nitro-1-(*p*-tolyl)ethanol as the substrate in ethanol. The substrate was changed from *p*-nitrobenzaldehyde to *p*-tolualdehyde and the nitro aldol product formed from the reaction with nitromethane was used to optimise the first step as it prevents the competing reduction of the aromatic and aliphatic nitro groups. Zinc was added followed by the source of hydrogen. Variation of the conditions is shown in Table 3.8.



| H source | Catalyst | Temperature (°C) | Time (h) | Yield (%) |
|---------------------|----------|---------------------|-------------|--------------|
| HCl | Zinc | rt | 1 | 78 |
| HCOONH ₄ | Zinc | rt | 1 | 80 |
| NH ₄ Cl | Zinc | rt | 1 | 80 |
| HCOONH ₄ | Zinc | 40 | 0.5 | 84 |
| NH ₄ Cl | Zinc | 40 | 0.5 | 82 |
| AcOH | Iron | 40 | 0.5 | 60 |
| HCl | Tin | 40 | 0.5 | 45 |

Table 3.8: Batch reductions of 2-nitro-1-(*p*-tolyl)ethanol using transition metals (10 eq) in ethanol 0.2 M.

As shown in Table 3.8, yields were generally very good under all conditions and changing the hydrogen source had little effect on the yields observed. Temperatures were varied and reaction times were reduced to 30 min when heating to 40 °C.

When moving to flow the zinc had to be introduced via a different method due to its insolubility in all solvents. It was determined that the best method was to use a cartridge based system packing an Omnifit® column. This would then be attached to a T-piece, where two syringes were loaded with the reagents. The first syringe was loaded with the 2-nitro-1-(*p*-tolyl)ethanol in ethanol and the second with the hydrogen source in ethanol/H₂O. The figure below shows a schematic set-up (Figure 3.24).

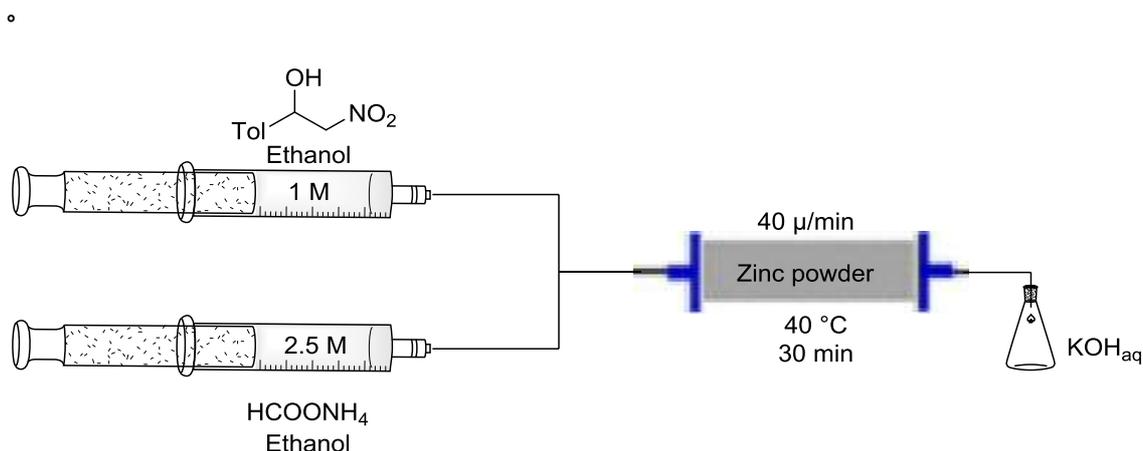
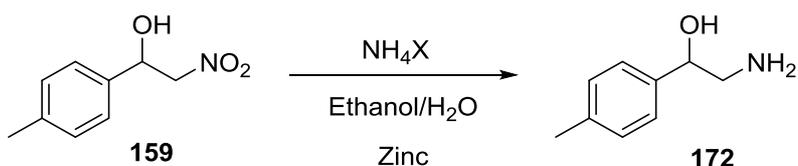


Figure 3.24: Flow set-up for reductions of nitro groups using zinc (Xs) and ammonium formate (5eq) and 2-Nitro-1-*p*-tolylethanol 2 mmol. In a 1 M concentration of **144** in ethanol.

Once the system had been set up the conditions were replicated as close as possible to that of the batch conditions. Flow rates were chosen as so that the residence time was kept to 30 minutes heating to 40 °C.



| H source | Temperature (°C) | Residence time (h) | Yield (%) |
|---------------------|---------------------|-----------------------|--------------|
| NH ₄ Cl | 40 | 0.5 | 78 |
| HCOONH ₄ | 40 | 0.5 | 83 |

Table 3.9: Initial flow reduction conditions of 2-nitro-1-(*p*-tolyl)ethanol 2 mmol using zinc in excess at a 1 M concentration.

Yields were comparable to that of batch conditions where the amino alcohols were obtained in very good yields as shown in Table 3.9. Although the zinc was now in a much greater excess than that of batch conditions, there were no problems in isolating the product and the column could then be reused up to 3 times.

The next stage was then to move onto the two step synthesis. Using the previously optimised racemic conditions in ethanol and KOH the nitro aldol reaction was then coupled via a T-piece mixer to the second step. The acidic hydrogen source was introduced via a second in-let just prior to the column where excess ammonium formate was used to quench the base from the first reaction (Figure 3.25).

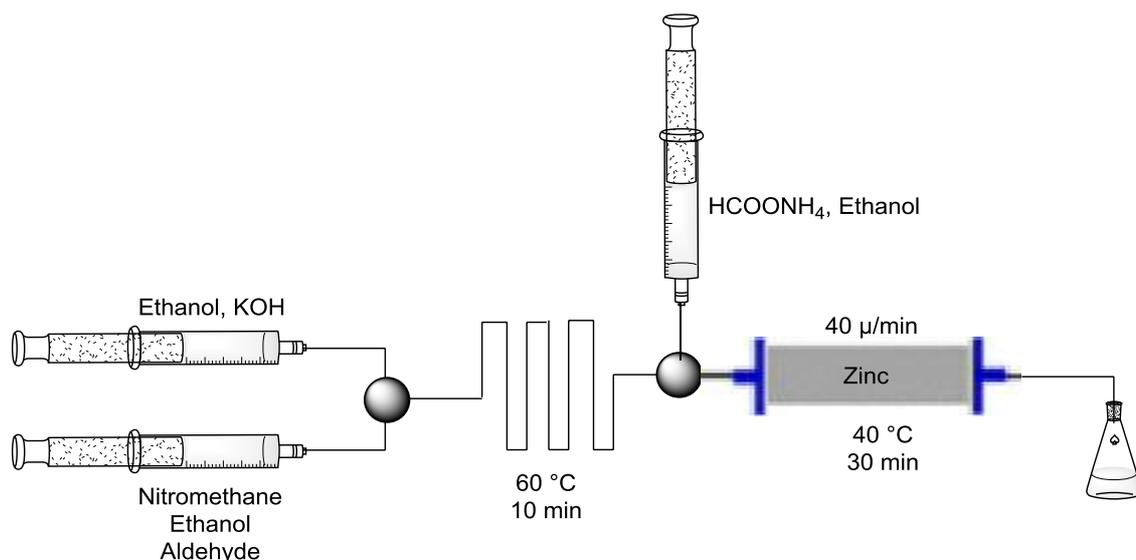
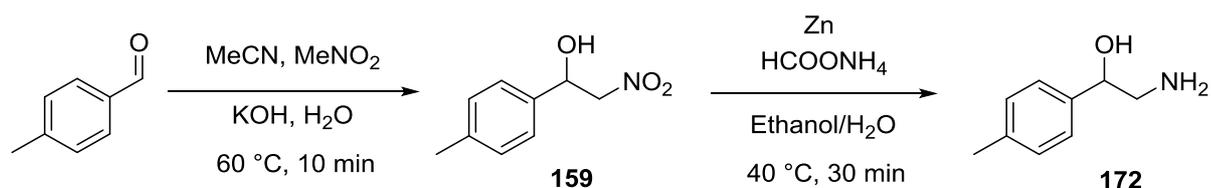


Figure 3.25: Multistep set up for synthesis of amino alcohols in continuous flow.

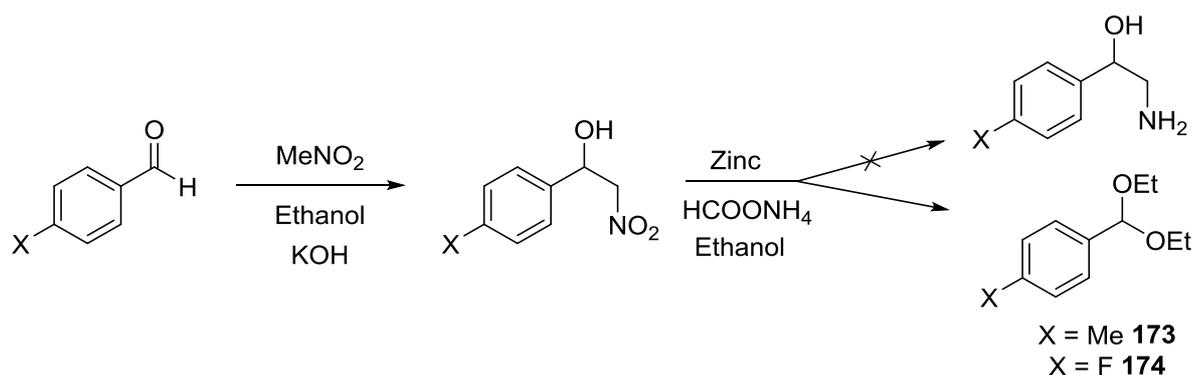
Conditions were then investigated as shown in Table 3.10



| H source | Temperature (°C) | Residence time (h) | Result (yield) |
|---------------------|---------------------|-----------------------|------------------|
| NH ₄ Cl | 40 | 0.5 | 173 |
| HCOONH ₄ | 40 | 0.5 | 173 (11%) |
| HCOONH ₄ | rt | 1 | 173 |

Table 3.10: Multi step nitro aldol to reduction conditions using 4-fluoroaldehyde (1eq), nitromethane (10 eq) and KOH (0.3 eq) in ethanol. Reduction conditions using zinc metal and H source (5 eq)

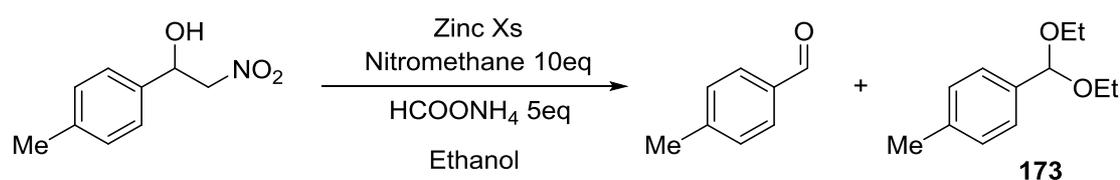
Unfortunately when connecting the two steps together the amino alcohol (**172**) was not obtained. Instead a previously unattained side product was the major product of this two-step reaction. After general analysis the product was identified to be 1-(diethoxymethyl)-4-toluene **173**, (Scheme 3.10).



Scheme 3.10: 2-step flow synthesis of amino alcohols where reduction of nitro group fails and condensation after retro-Henry reaction forms side product **173**.

As the yield of the side product was reasonably low and conversion from *p*-tolualdehyde to 2-nitro-1-(*p*-tolyl)ethan-1-ol was not 100%, it was thought that the unreacted aldehyde was forming this side product. Further investigation was then needed to determine the problem with the coupled conditions. Firstly the starting aldehyde was changed to *p*-fluoroaldehyde as the conversion to the nitro aldol product was almost 100%. Although this was the case, the acetal side product **174** was observed in 23% yield.

The only difference that could be perceived by looking at the general scheme of the reactions was the addition of KOH and nitromethane. By going back to a one step flow set-up for the reduction and adding nitromethane to the syringe containing the substrate, it could be determined if the nitromethane had a negative effect on the reductive conditions (Scheme 3.11, Figure 3.26).



Scheme 3.11: Reduction attempt of nitroalcohol **159** in flow resulting in side product **173**.

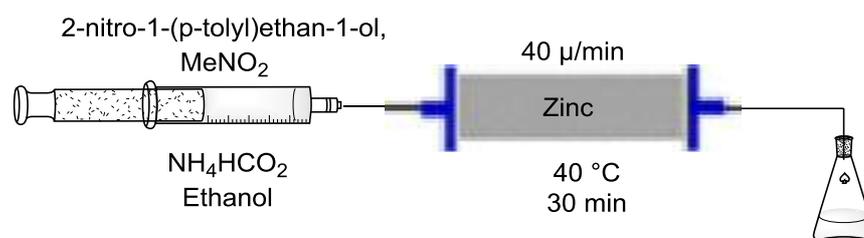
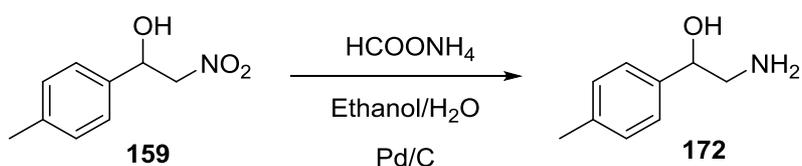


Figure 3.26: Flow set-up to test effect of nitromethane on the reduction of nitroalcohols in flow.

This again resulted in the aforementioned acetal **173** where the retro Henry takes place followed by addition of ethanol. It was thought that this was due to still being under conditions where proton transfer can easily take place, and, in combination with the reductive conditions, the nitromethane was preferentially reduced to methylamine. This could then, with the zinc or zinc salt formed, cause the retro-Henry reaction, the latter catalysed by Lewis acid co-ordination followed by the addition of ethanol. As the zinc was in quite a high excess to allow for reusability of the column, this could have led to the problems occurring.

Secondary conditions were trialled where a more mild approach was taken using Pd/C and ammonium salts.^[174] There has been relatively high success in flow using Pd/C reductions in-line most notably using the Thales nano H-cube.^[179] This uses a column derived system with the introduction of hydrogen gas to reduce the desired functional group. As we did not have the ability to introduce hydrogen gas in a device like the H-cube, ammonium formate was employed as an alternate source.

Initial conditions in batch worked well (Table 3.11) which therefore led to screening to reduce reaction time.



| H source | Catalyst | Temperature (°C) | Reaction time (h) | Yield (%) |
|----------------------------------|----------|---------------------|----------------------|--------------|
| HCOONH ₄ ₂ | Pd/C | RT | 2 | 90 |
| HCOONH ₄ | Pd/C | 40 | 0.5 | 85 |

Table 3.11: Initial batch reduction conditions using Pd/C 10 mol% and NH₄HCO₂(5eq) for the reduction of 2-nitro-1-(p-tolyl)ethan-1-ol 0.5M in Ethanol/H₂O (10/1).

As shown in Table 3.11 the reductive conditions worked well with yields of up to 90% under batch conditions. To move the conditions to flow, Celite had to be used as an inert bonding material to allow for catalytic quantities to be loaded and still allowing enough volume for the residence time. 150 mg of Pd/C was mixed with 1.2 g of celite and ground together until homogeneous. This was then loaded into the column and packed to avoid air pockets.

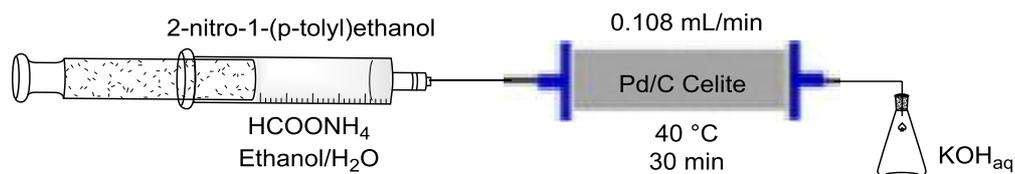
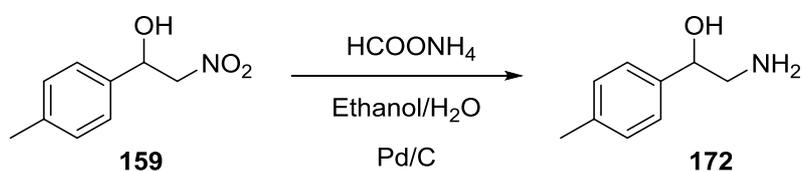


Figure 3.27: Flow system for reductions using Pd/C and NH_4HCO_2 .

The next step was to use the system set-up above (Figure 3.27) and replicate the conditions in batch for the reduction of the nitro group. The reaction was performed in the same manner, allowing for a residence time of 30 min.



| H source | Catalyst | Temperature (°C) | Residence time (h) | Yield (%) |
|---------------------|----------|---------------------|-----------------------|--------------|
| HCOONH ₄ | Pd/C | rt | 0.5 | 60 |
| HCOONH ₄ | Pd/C | 40 | 0.5 | 85 |

Table 3.12: **159** in ethanol (1 M) with reductive conditions using HCOONH_4 (2.5 eq) and 10 mol% Pd/C mixed with celite. (150 mg Pd/C in 1.2 g of celite).

The results in Table 3.12 showed that the use of celite had no effect on the reduction of the nitro group and very good yields were obtained. The success of the results in Table 3.12 led to the combined two-step process, analogous to the zinc system Figure 3.28.

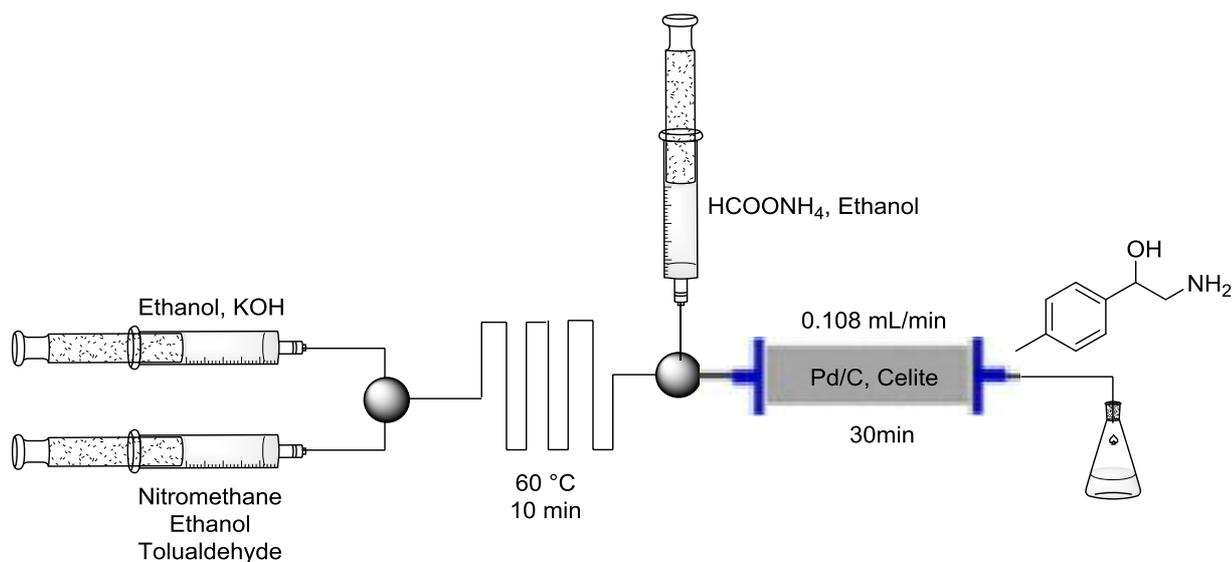
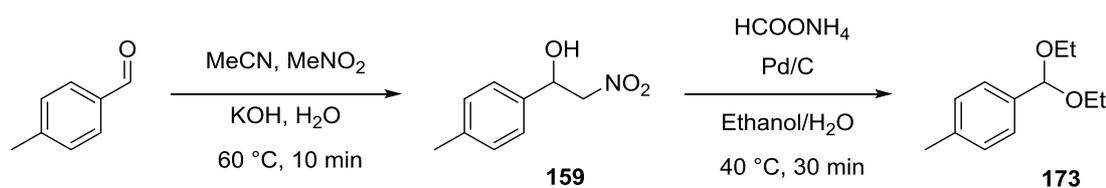


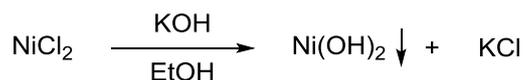
Figure 3.28: Set-up for reduction of nitroalcohols using Pd/C and ammonium formate in continuous flow.



| Temperature 2 nd coil (°C) | Residence time 1 st coil (min) | Residence time 2 nd coil (min) | Result |
|--|--|--|------------|
| RT | 10 | 30 | 173 |
| 40 | 10 | 30 | 173 |

Table 3.13: Two-step protocol for formation of amino alcohols using 4-tolylaldehyde 1 eq, nitromethane 5eq in ethanol (1 M) coupled to reductive conditions using HCOONH₄ 2.5 eq (1M) and 10 mol% Pd/C.

It was observed, again, that the amino alcohol was not formed and the side product (**173**) was obtained. This indicated that the formation of the side product was independent from the zinc and likely due to the presence of nitromethane. This could be due to the ease in reducing the nitromethane as opposed to the nitroalcohol as well as the excess equivalents. Therefore either due to the formation of methylamine by reduction of nitromethane or a background reaction involving the ammonium salt causes the retro-Henry followed by condensation with ethanol. Further techniques, such as sodium borohydride in combination with NiCl₂ and other Lewis acid metals were shown to be incompatible with the initial conditions from the Henry reaction. Reactions NiCl₂ led to formation of Ni(OH)₂ which in turn precipitated from solution due to their extremely insoluble nature shown in Scheme 3.12.



Scheme 3.12 Formation of insoluble nickel hydroxide on reaction of KOH and nickel chloride.

Although these conditions could have been used if the base was switched to an organic example such as DBN, due to the problems associated with the previous methods of reduction, it was thought the same problems would occur regardless of reduction technique. Therefore the two-step reduction was abandoned.

To test the generality of this method it was thought that other nitro group containing substrates could be tested Figure 3.29. The previous work showed reductions of aliphatic nitro compounds; therefore a number of aromatic nitro compounds were used for substrates within this methodology.

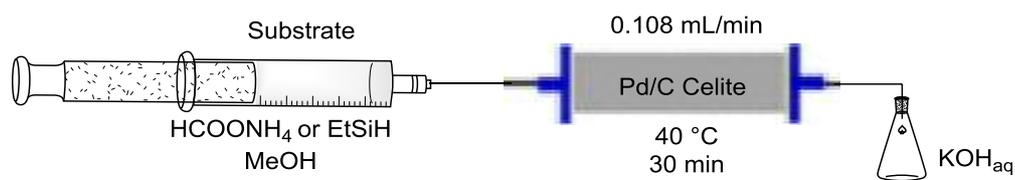
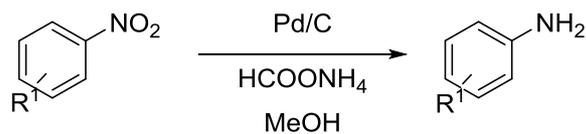


Figure 3.29: Set-up for the general reduction method using Pd/C and ammonium formate in continuous flow.

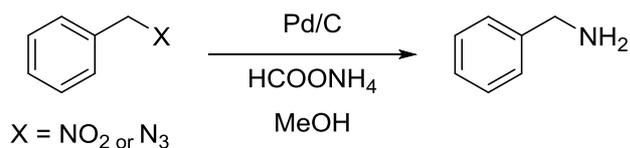


| Substrate | Product | Yield (%) |
|-----------------|-----------------|-----------|
| 174a | 174b | 90 |
| 175a | 175b | 98 |
| 176a | 176b | 78 |

Table 3.14: Methanol (1 M) coupled to reductive conditions using HCOONH₄ 2.5 eq (1M) and 10 mol% Pd/C in continuous flow. (Figure 3.29)

Yields were shown to be generally very good; 2-nitrobenzoic acid was efficiently reduced to anthranilic acid **174b** in 90% yield whereas 3-nitrostyrene **175a** was reduced in 98%. To our surprise though, the nitro group and the double bond were both reduced within the reaction time in the reactor. Furthermore, to test the longevity of the cartridge system in continuous flow, the reagent solution was allowed to pass through the column for 10 h using the exact same equipment in Figure 3.29 and just increasing the volume of the starting reservoir. This led to the collection of 10 mmol of product. Although there was a drop in yield it shows that the system can be run for larger scale reactions with only a small drop off.

It was also shown that simple phenylnitromethane **177a** could be reduced in very good yields and, to show the application towards azides, phenylazidomethane **178a** was reduced in excellent yield within the system.



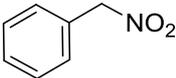
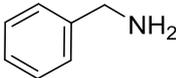
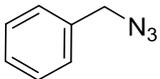
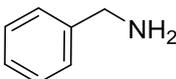
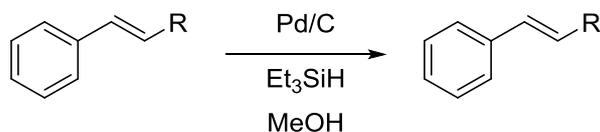
| Substrate | Product | Yield (%) |
|--|---|-----------|
|  177a |  177b | 90 |
|  178a |  177b | 98 |

Table 3.15: ethanol (1 M) coupled to reductive conditions using HCOONH₄ .5 eq (1M) and 10 mol% Pd/C in continuous flow. (Figure 3.29)

Inspired by the reduction of the double bond of 3-nitrosyrene, the work proceeded with testing some double bonds under the reaction parameters.



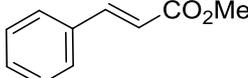
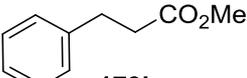
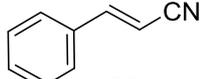
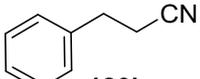
| Substrate | Product | Hydrogen source | Yield (%) |
|--|---|---------------------|-----------|
|  179a |  179b | HCOONH ₄ | 42 |
| 179a | 179b | Et ₃ SiH | 97 |
|  180a |  180b | Et ₃ SiH | 80 |

Table 3.16: ethanol (1 M) coupled to reductive conditions using HCOONH₄.5 eq (1M) and 10 mol% Pd/C in continuous flow. (Figure 3.29)

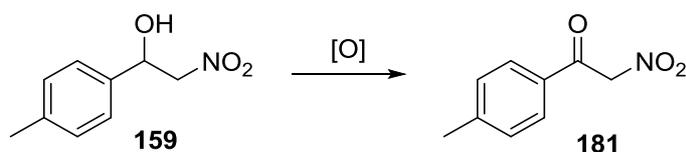
Cinnamic acid methyl ester was investigated with the same conditions although it showed poor conversion with a yield of only 42%. As this was the case it was decided to heat the reaction to 60 °C but this showed no increase in yield. A change in hydrogen source could

affect the outcome as shown in previous works.^[180] Using Et₃SiH, the conversion to the saturated compound **179b** was complete obtaining a yield of 97%. Moreover, the ester functionality was left untouched. Moving to cinnamitrile results were similar where a yield of 80% was obtained for **180b**. Again the functionality was left intact as the cyano group was not also reduced.

3.2.3.3 Oxidation conditions

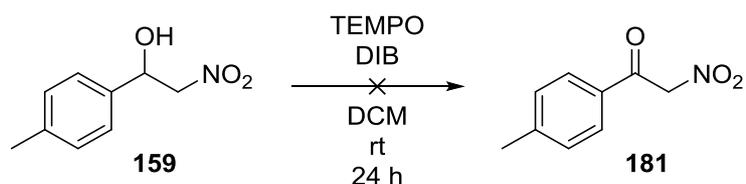
In addition to the reduction conditions an oxidation reaction could also be performed in-line to form α -nitroketones. α -Nitro ketones have been of great interest in recent times as they are very useful synthetic intermediates. This is due to the functionality contained within this structure. They contain a carbonyl which allows not only for them to exist as an electrophilic source, but also the addition of a nitro group α to this carbonyl drastically increases acidity of neighbouring protons, allowing for ease in enolate formation and thus making electrophilic addition facile. Although these properties have been known for years they have not been utilised heavily due to their difficulty in formation. Typically conditions used to make these compounds rely on long reaction times, therefore it was hoped that a rapid procedure could be developed to allow for greater synthetic applications.

Initial conditions were selected using a procedure recently developed in our lab. ^[181] These conditions consisted of TEMPO in combination with $\text{PhI}(\text{OAc})_2$ in dichloromethane. TEMPO has shown a great aptitude for oxidations of various alcohols in a relatively clean and benign manner, and was thought to be an ideal oxidant for this transformation.



| Oxidant | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|--|---------------------------------|---------------------|-------------|----------------|
| DIB 1.5 eq 10 mol% TEMPO | CH ₂ Cl ₂ | rt | 24 | 0 |
| DIB 1.5 eq 10 mol% TEMPO | CH ₂ Cl ₂ | 40 | 24 | 0 |
| DIB 1.5 eq 10 mol% TEMPO | MeCN | 80 | 24 | 0 |
| NaIO ₄ 1.5 eq 10mol% TEMPO | MeCN | 80 | 24 | 0 |
| IBX 1.5 eq | DMSO | rt | 2 | - ^a |
| IBX 1.5 eq | MeCN | rt | 2 | 70 |
| IBX 1.5 eq | CH ₂ Cl ₂ | rt | 2 | 54 |
| DMP 1.5eq | CH ₂ Cl ₂ | rt | 2 | 76 |

Table 3.17: Oxidation conditions for the oxidation of 2-nitro-1-(p-tolyl)ethanol 1 eq in batch a = was unisolatable due to enolate form being trapped in DMSO within the aqueous layer of extraction.

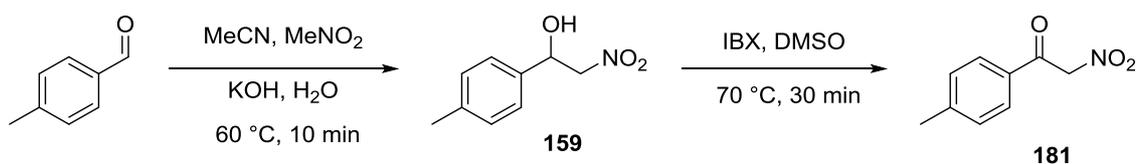


Scheme 3.13: Oxidation conditions using TEMPO and DIB.

Using these conditions in batch led to no conversion of the nitro alcohol **159** to the ketone **181** at room temperature within 30 min (Scheme 3.13). Even after leaving the reaction overnight, no product was observed. As the substrate is difficult to oxidise, due to the strong electron withdrawing effect from the nitro group, heating was deemed best to allow for increased conversion. Heating the reaction to reflux in CH_2Cl_2 and following by TLC did not indicate any conversion of the starting material. Switching the solvent to acetonitrile to allow for higher temperature ($80\text{ }^\circ\text{C}$) also did not result in formation of the product and therefore these conditions were moved on from. Further using sodium periodate as a co-oxidant no conversion to the ketone was observed, as shown in Table 3.17

Iodine(V) reagents, such as IBX and DMP were then investigated in different solvents. Results were promising with IBX under batch conditions as the nitroketone was obtained in good yield when using solvents such as CH_2Cl_2 and MeCN. The best conversions were obtained in DMSO, and it was used to move forward with. When using DMSO a further problem occurred. As the product contained a nitro group α to the ketone, this made the α -position very acidic. Therefore the product was very easily enolized and was determined to be trapped in the DMSO within the aqueous phase. This therefore made yields difficult to ascertain.

As the previous conditions used ethanol, the solvent of the first step for the oxidation was changed to acetonitrile and water, as a potential oxidation of the solvent could then be avoided.



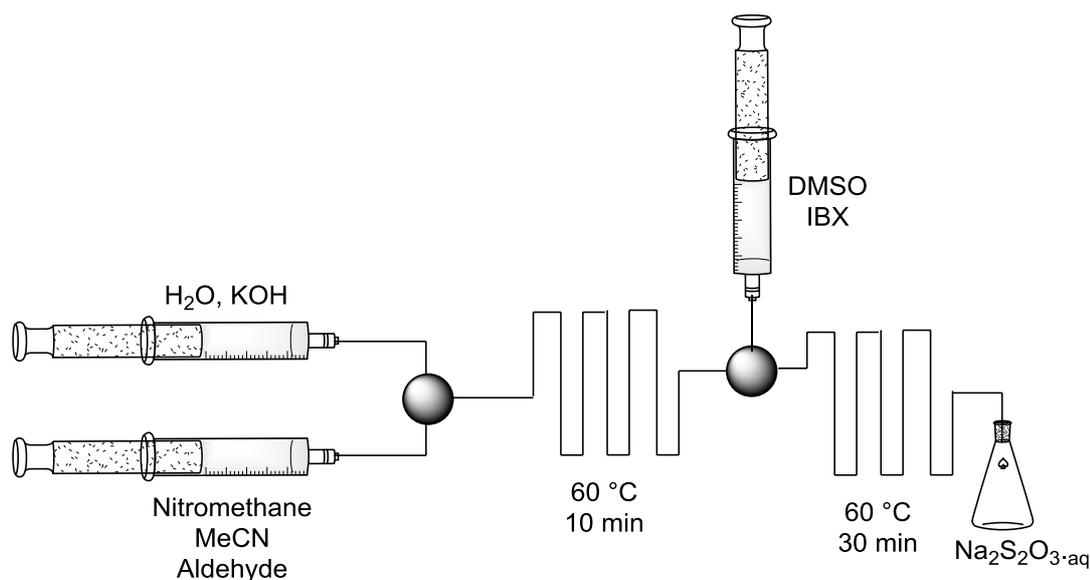


Figure 3.30: Two step nitro aldol followed by oxidation set-up.

Coupling the nitroaldol and oxidation in flow (Figure 3.30) utilising MeCN and DMSO caused precipitation, this resulted in the reactor tubing blocking readily; even after the addition of sonication to the system. The precipitation problem was overcome by a decrease in the concentration of the overall reaction solution. This though led to a large reduction in conversion of the nitroalcohol to the ketone where only traces were observed by NMR. By adding stoichiometric amounts of trifluoroacetic acid (TFA), the IBX reagent could easily be solubilised in considerably less DMSO utilising TFA as a co-solvent. Although initial solvation of the iodine(V) reagent was successful, again clogging occurred after a short time. Increasing the residence time further did not result in a large increase in conversion therefore it was thought best to modify the IBX type reagent to allow for greater solubility.

Multiple modifications have been presented in the literature to solve the insolubility factor of IBX **182**, ranging from simple ligand exchange on the iodine centre, to modifications on the aryl ring (Figure 3.31). Dess Martin periodinane **186** (DMP), is the most commonly known modification due to the ease of formation, the addition of acetates to the iodine core results in a slightly more soluble reagent which can then be dissolved in CH_2Cl_2 . To avoid the problem of precipitation DMP was taken into consideration, however this problem could not be resolved. This led to the conclusion that the problem does not lie directly in the initial solubility but also on the reduced form. Upon reduction of the I(V) species, to the I(III) species the insoluble 1-hydroxy-1,2-benziodoxol-3(1H)-one (IBA) derivative is formed, causing clogging within the channels. Modifications to the reagent at the aryl positions were thought to be a more reliable option. Recently many modifications have been demonstrated in the attempts to allow for

greater solubility in organic solvents, and thus allow for increased reaction scope. For example: tetra fluorolIBX **188**, methyl **183**, dimethyl **184**, tetramethylIBX **185** and methoxy methyl IBX **187**.

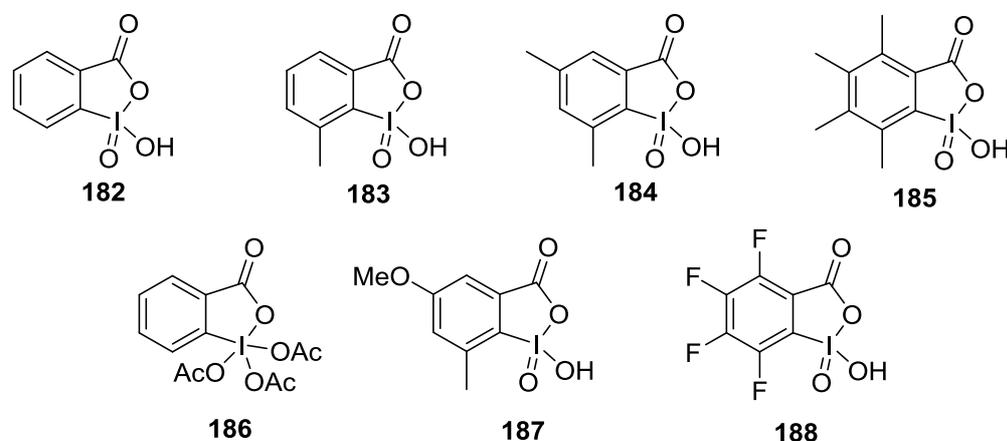
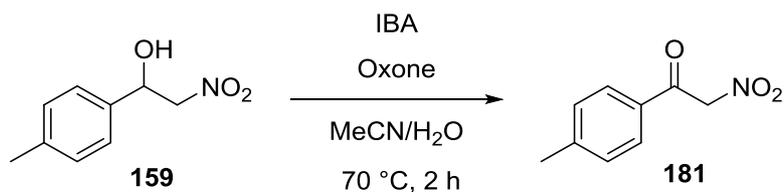


Figure 3.31: IBX and its derivatives synthesised for greater solubility and reactivity.

These have all shown greater reactivity as compared to simple IBX. A common characteristic between these compounds (excluding DMP **186**) is the substituent in the ortho position. This is due to the change in conformation around the iodine centre. The sterics of the ortho substituent create a twist of the iodooxilane ring. This twist is beneficial in breaking up the polymeric type bond between the individual molecules.^[182]

The first selection began with the synthesis of the tetrafluoro derivative **188**, first reported by Wirth *et al* in 2007.^[183] Using the reagent from within stock of our lab, FIBX **188** was used under batch conditions in THF. Oxidation was complete within 1 h 30 min under reflux. This then led to trials under mixed solvent conditions to establish if precipitation could be an issue under flow conditions. Adding MeNO₂ and MeCN drastically reduced the solubility of the reagent leading for a search for a more soluble IBX derivative.

The next derivative synthesised was the tetramethylIBX **185**.^[182] Again this has been shown to allow for a greater rate of reaction and increased solubility. Although superior in reagent ability, synthesis of this reagent is time consuming and laborious consisting of 5 steps before oxidation. Under batch conditions the oxidation went smoothly where 68% yield was obtained in 30 mins. Moving the conditions to flow resulted in again the precipitation of the I(III) reagent after reduction from the I(V) species. The decision was made to move away from IBX type derivatives in solution phase.



Scheme 3.14: Oxidation of nitro alcohols using in-situ formation of IBX.

As the IBX type reagents showed that their solubility was low in organic solvent their applicability in solution phase flow chemistry is very limited. However its lack of solubility could be used to its advantage. By using a solvent mixture that allows for minimal solubility and packing a column with the I(III) reagent the more active I(V) species could be created *in situ*. As IBX is believed to be explosive, most notably in its impure form, this provides a safer alternative to other methods and saves on spectator material such as in SIBX (stabilised IBX).^[184] Conditions in batch when using IBA (1-Hydroxy-1,2-benziodoxol-3(1H)-one) in MeCN mixed with water gave promising results and conversion to the product was complete in 2 h in 70% yield.

As results showed they were efficient under batch conditions, a flow system was devised to replicate this, making the IBA reusable (Figure 3.32)

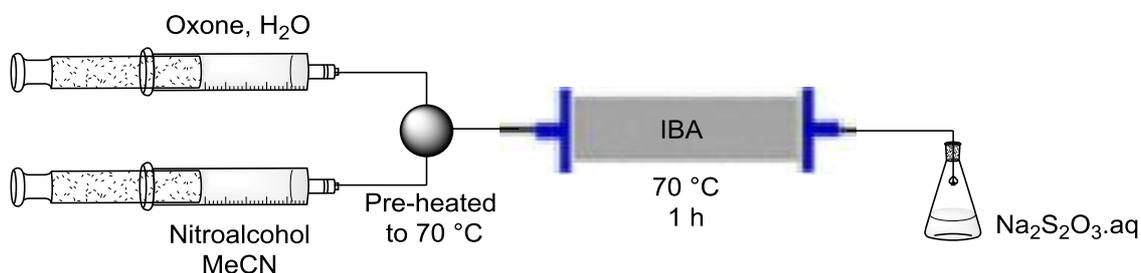
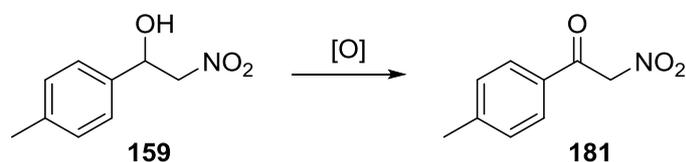


Figure 3.32: Flow system for in-situ formation of IBX and oxidation of nitro alcohols.

The system created worked by packing a column with IBA and sand, using the sand to reduce the pressure in the column due to the very fine particle size of IBA. A co-oxidant (Oxone) was introduced from one inlet and the alcohol from another where they mixed at a T-piece before entry to the column. Initial conditions resulted in clogging due to the solvent mixtures. Oxone being virtually insoluble in most solvents, except water, caused large precipitation upon mixing at room temperature with the acetonitrile stream. Heating to 70 °C prior to mixing and at the mixing zone led to less precipitation and therefore elution could be achieved through the coil. Although a residence volume could be obtained the concentration had been drastically reduced as compared to the batch procedure. This unfortunately led to decreased conversions as compared to the batch procedures and as residence time could not be realistically

increased, it was thought that modifications were needed to the system to allow for increased concentration.

As iodine reagents proved to be difficult to solubilise other techniques were taken into consideration. This is shown in Table 3.18.

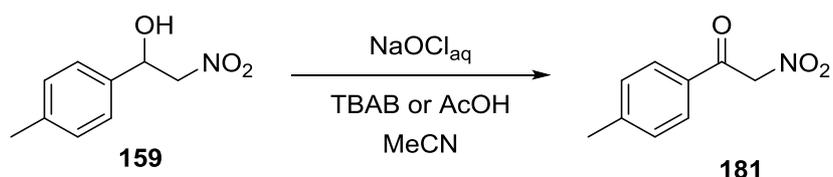


| Oxidant | Solvent | Temperature (°C) | Time (h) | Result |
|---|------------|---------------------|------------------------|--------|
| CAN, TEMPO | MeCN | 80 | Overnight | N.R |
| CAN (3.5 eq), NaBrO ₃ (0.35eq) | MeCN | 80 | 1.5-6 | N.R |
| NBS (1.5 eq) ^[185] | DME 10% aq | rt | Overnight ^b | N.R |

Table 3.18: Oxidation conditions trialled for in-line oxidations of 2-nitro-1-(p-tolyl)ethan-1-ol in batch.

Conditions with TEMPO were attempted using a previously reported procedure by Lu.^[186] They showed the oxidation of alcohols with the combination of CAN and TEMPO. Using this procedure for the oxidation of the nitroalcohols in MeCN did not yield the desired ketone at room temperature or upon reflux. Further conditions using NaBrO₃ in combination with CAN resulted in no formation of the ketone with only starting materials observed by TLC.^[187]

Jamison *et al.* showed that using a strong oxidant like NaOCl, in combination with TBAB could form a segmented flow process which is able to oxidise alcohols as quickly as in 10 min.^[188] As these conditions were already developed in flow the reaction conditions were trialled directly into flow. Using the exact conditions as in the report the reaction was run at rt for a residence time of 10 min. Upon interaction of the oxidant with the TBAB it was apparent that Br₂ had been formed and the reaction was quenched into sodium thiosulphate (Figure 3.33).



| Oxidant | Solvent | Temperature (°C) | Time (h) | Result |
|---|-------------|---------------------|-------------|--------------|
| NaOCl (2 eq), TBAB (7.5 mol%) | MeCN (0.8M) | rt | 10 mins | tolualdehyde |
| NaOCl (2eq), AcOH (xeq), TBAB (7.5 mol%) | MeCN (0.8M) | rt | 0.5 | N.R |

Table 3.16: Flow oxidation conditions for the oxidation of 2-nitro-1-(p-tolyl)ethan-1-ol

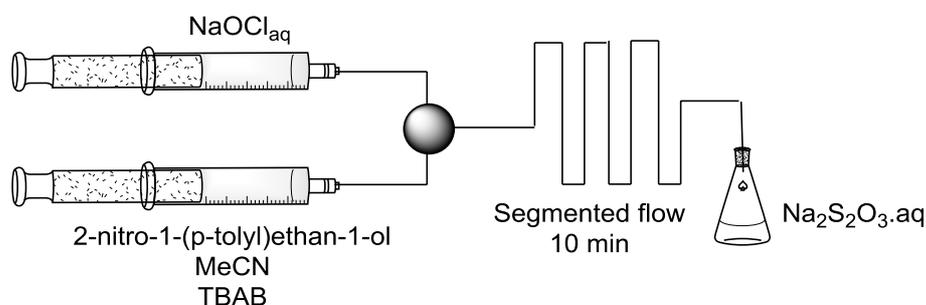
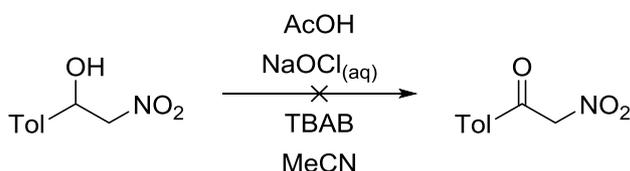


Figure 3.33: Set-up for flow oxidation of 2-nitro-1-(p-tolyl)ethan-1-ol adapted from Jamison *et al.*

Unfortunately these conditions did not show oxidation to the corresponding ketone but a retro Henry reaction occurred, isolating tolualdehyde. This was probably due to the high pH of the bleach solution (pH 12). To combat this, the mixture was buffered to around pH 7 by addition of AcOH as in the traditional oxidation technique. This was considered ideal for flow chemistry as the formed hypochlorous acid could not easily escape from the closed system.

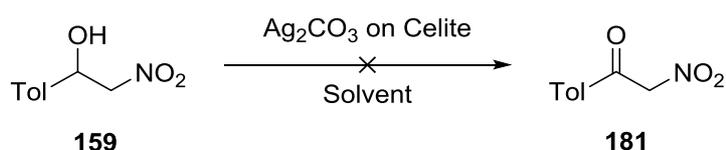


Scheme 3.15: Adjusted oxidation condition for the oxidation of 2-nitro-1-(p-tolyl)ethan-1-ol in flow using AcOH to buffer the pH to 7.

Although the retro-Henry reaction was not achieved, the oxidation to the ketone was unsuccessful and the nitro alcohol was recovered even after increasing the residence time to 30 min (Scheme 3.15). This is in concurrence with a study of hypobromous acid (HOBr)

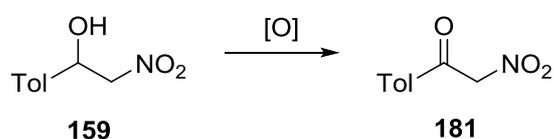
reaction rates in comparison to Br₂ oxidation rates. It was shown that with decreasing pH, and larger concentrations of HOBr, that the rate of oxidation decreased.^[189] This would therefore explain the loss of oxidative activity when buffering the solution with AcOH.

As conditions that subject the substrate to strongly basic media seemed to allow for a retro Henry reaction, some milder conditions were trialled. Fetizon's reagent has been shown to be extensively used as mild oxidant in many organic syntheses in the literature^[190], and looked to be the ideal reagent for these substrates for two reasons: Its mild nature and the composition of the formed reagent. As the silver oxidant is deposited onto Celite it would be packed into a cartridge, where separation would be facile upon collection of the product. Initial batch conditions in acetonitrile led to no oxidation of the substrate, and small amounts of the aldehyde were observed using NMR. As it is still slightly basic and within a polar solvent the aldehyde was observed, therefore moving to a less polar solvent e.g. toluene would avoid this. Unfortunately the oxidation was also not observed and starting material was recovered. Fetizon's proved to be too mild an oxidant to achieve the desired product (Scheme 3.16).



Scheme 3.16 Oxidation of alcohols using Fetizon's reagent.

Using this concept of a solid phase oxidant that could be easily abstracted from the reaction mixture, a further supported oxidant was trialled. MnO₂ has seen a small renaissance in recent times due to its strong oxidative ability, where groups such as the Ley group have looked to use the insoluble nature of the oxidant to allow for cartridge based methods.^{[191][192][193]} They have shown the applicability of MnO₂ for a number of applications for instance the oxidation of hydrazides to diazo compounds. On initial trials using MnO₂ under batch conditions oxidation was not observed. No product was obtained and the nitro alcohol was recovered in each case. A recent paper by Lee^[194] showed that the combination of KMnO₄ and MnO₂ was an effective combination to oxidise alcohol substrates in solid phase milling as well as heterogeneous conditions. Tests in batch did not yield the product, again starting material was recovered.



| Oxidant | Solvent | Temperature (°C) | Time (h) | Result |
|--|---------|---------------------|-------------|--------|
| MnO ₂ | MeCN | 70 | 2 | N.R |
| MnO ₂ (17 eq)/KMnO ₄ (3eq) | MeCN | 80 | 5 | N.R |

Table 3.19: Oxidation of 2-nitro-1-(p-tolyl)ethan-1-ol in batch

Although initially avoided due to the insoluble side products formed and strongly acidic conditions, chromium based reagents were trialled in an attempt to oxidise the product. As these reagents are considered very toxic, keeping these reagents in a closed system could be beneficial, if a technique could be used to capture the side product. This makes the extraction of product and therefore the work-up easier. Batch methods have involved using alumina to trap the sticky chrome by-product and it was envisioned that a cartridge of Al₂O₃ could be placed in-line to capture the chromium before the elution of the product, preventing contamination of the product mixture with a toxic side product (Figure 3.34).

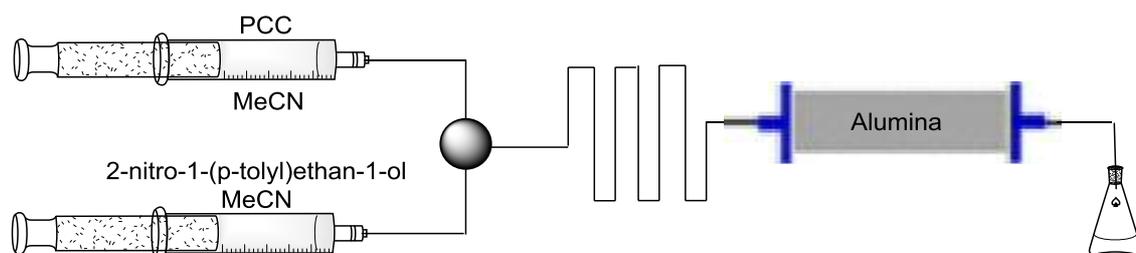
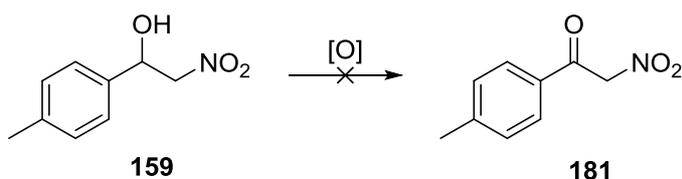


Figure 3.34: Proposed set up for continuous flow chromium based oxidation with alumina to trap reduced chrome polymers.



| Oxidant | Solvent | Temperature (°C) | Time (h) | Result |
|--|---------------------------------|---------------------|-------------|--------------|
| PCC | CH ₂ Cl ₂ | rt | overnight | N.R |
| PCC | MeCN | rt | overnight | N.R |
| PCC | MeCN | reflux | 2 | N.R |
| PCC | DMF | 80 | 2 | tolualdehyde |
| CrO ₃ | CH ₂ Cl ₂ | 40 | 3 | N.R |
| Na ₂ Cr ₂ O ₇ | MeOH/H ₂ O | 0-rt | 2 | N.R |

Table 3.20: Oxidation of 2-nitro-1-(p-tolyl)ethan-1-ol using chromium based reagents under batch conditions

Initial batch conditions of PCC on alumina in CH_2Cl_2 failed to oxidise the alcohol to the ketone (Table 3.20). Moving to MeCN and further heating to reflux also showed no oxidation. Switching to DMF, which has been used to hugely increase the oxidative potential of the PCC reagent, did not yield any ketone. As within the highly basic media of the bleach oxidation conditions the retro-Henry product was observed. The combination of an acidic reagent with a highly polar solvent allowed for formation of the aldehyde. Reports from Castle^[195] showed that using sodium dichromate resulted in oxidation of similar compounds, via a sequential addition of the oxidant with the nitro alcohol was followed by addition of 8 M sulphuric acid in aqueous batch conditions. They reported that nitro alcohols from the condensation of nitroethane with aldehydes could be oxidised to the corresponding ketones in very good yields using this method. When trialling these conditions in batch it quickly became apparent that the concentration of these conditions was far too high. Within the flask there was a very thick slurry of inorganic salts. This would therefore not be ideal for continuous flow unless concentrations were lowered. Even when using these conditions in batch no appreciable conversion was observed, and further testing the conditions at reduced concentrations in flow yielded no formation of the ketone.

As a two-step in-line oxidation of nitro alcohols to nitro ketones was unsuccessful the system was modified to a semi-batch process. The first step was then run in continuous flow as in the previous methods with KOH in MeCN. This was then allowed to drop directly into a flask which contained a stirred solution of DMP in MeCN. Once addition had been completed the overall mixture was allowed to stir for a further 30 min to yield the ketone **181** in a 52% overall yield over two steps (Figure 3.35)

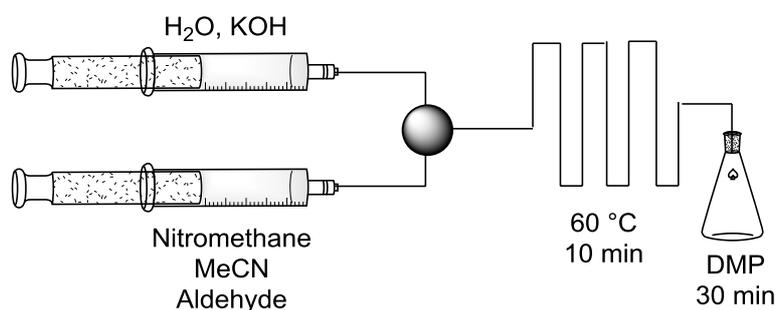
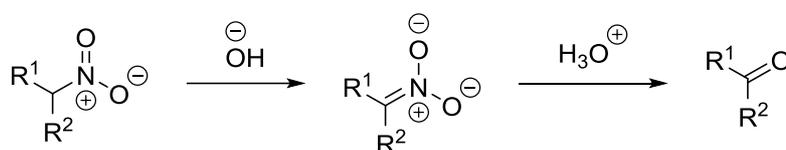


Figure 3.35: Semi batch process for the Henry reaction followed by oxidation.

3.2.3.4 Nef reaction for a 2 step homologation

One further reaction of interest associated with nitro group containing compounds is the Nef reaction. This reaction is usually considered a hindrance to formation of the nitro alcohol, due to their susceptibility to undergo the Nef reaction through nitro aldol conditions^[196](Scheme 3.16). The Nef reaction requires either the presence of a base/acid with water or an oxidant to convert the nitro group to a carbonyl.^[197] This being said many conditions have been demonstrated in batch but only one has been developed in continuous flow.^[198]



Scheme 3.16 Hydrolysis of nitro compounds to ketone (Nef reaction).

Ley *et al.* showed that primary and secondary nitroalkanes could be smoothly oxidised to aldehydes and ketones, respectively (Figure 3.36).^[198] Using a number of bases, where KOH was shown to be the most efficient, they could form the desired products in yields of up to 95% for aldehydes and 92% for ketones. Efficiency was high where only one equivalent of KMnO_4 was needed to achieve the desired result. Furthermore, the insoluble MnO_2 byproduct could easily be dealt with using sonication. The sonication therefore prevented blocking and the MnO_2 could further be isolated for future use.

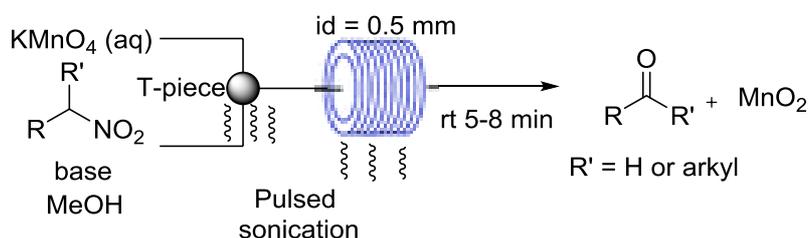


Figure 3.36: Nef reaction of nitroalkanes in continuous flow catalysed by KMnO_4 .

As mentioned for the first process only 1 eq of KMnO_4 was used, although if 2 eq are used in combination with primary nitroalkanes oxidation to the carboxylic acid occurs (Figure 3.37).

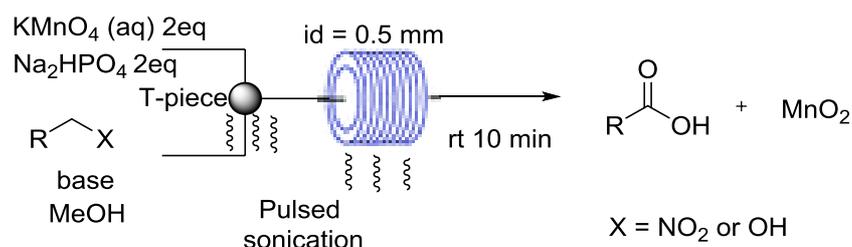
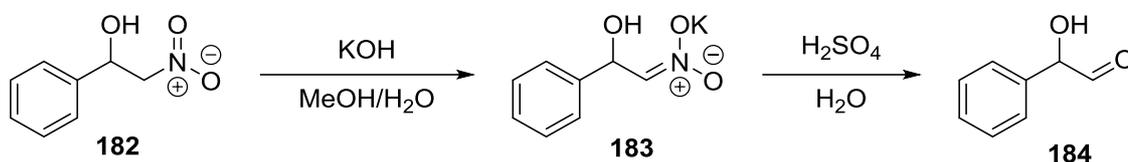


Figure 3.37: Oxidation of nitroalkanes, aldehydes and alcohols to carboxylic acids in continuous flow catalysed by KMnO_4 .

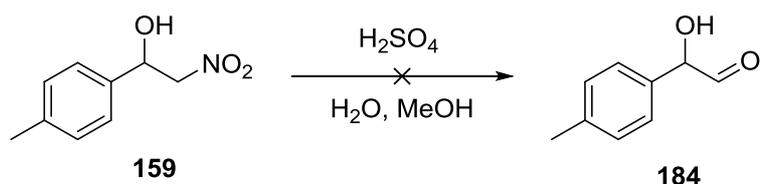
They demonstrated that the same system could be used to oxidise primary nitroalkanes, aldehydes and primary alcohols with the addition of sodium phosphate. Yields were again excellent of up to 97%, 98% and 87% for the respective starting materials.

Although under the conditions reported in the sections 3.1 no Nef product was observed, the Nef reaction could be an interesting addition to the system, as a type of 2-step reaction previously used for synthesis of some carbohydrates.^[157] Following Noland's initial conditions of the nitro aldol, the reaction was followed by a hydrolysis using aqueous H_2SO_4 . Noland's method was then investigated for use within this work (Scheme 3.17). Due to the exothermic nature of adding an acid to a base, flow conditions would benefit the addition of the sequential reactions allowing efficient cooling.



Scheme 3.17 Proposed Nef reaction to form 2-hydroxy-2-phenylacetaldehydes.

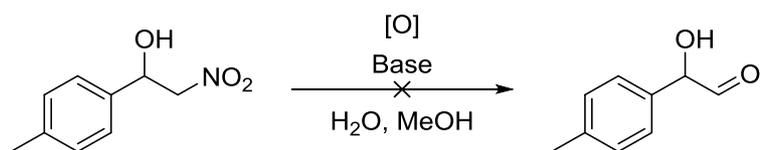
Following the nitro aldol conditions in section 3.2.1 a second T-piece was added to the flow system and a stream of aqueous H_2SO_4 was allowed to meet the produced nitro alcohol. The flow rate of the microreactor method was adjusted to have a residence time of 60 min. Upon collection of the reaction mixture the desired product was not observed and the nitro alcohol from the first step was obtained. This led to a variation of the conditions as shown in Table 3.21.



| Time (h) | Results |
|-------------|-----------------|
| 1 | 159 100% |
| 3 | 159 100% |

Table 3.21: Nef condition using H₂SO₄ in MeOH/Water (1:1) at 0→RT.

The hydrolysis step of the Nef reaction is not only limited to acidic and basic conditions but reports have been shown using oxidants. Oxone[®][199] has been shown to achieve this as well as KMnO₄[198] in aqueous solutions. Ley *et al.* recently presented the latter in flow. [198] They showed that using KOH in combination with KMnO₄ it was possible to convert nitro groups to carbonyls and therefore that this could be used in combination with the nitro aldol reaction. Initial conditions began and by using the intermediate nitro alcohol in methanol with 30 mol% of KOH in water. After adding the KMnO₄ and stirring for 1 h the reaction showed no change by TLC although it was highly apparent that the KMnO₄ had been largely converted into the brown coloured MnO₂. Leaving the reaction for a further 2 h did not yield any change to the reaction.



| Oxidant | Base | Solvents | Result |
|--------------------------|--------------|------------|--------------|
| KMnO ₄ (1 eq) | KOH (0.3 eq) | Water/MeOH | S.M |
| KMnO ₄ (1eq) | KOH (1 eq) | Water/MeOH | tolualdehyde |
| Oxone (2eq) | NaOMe (1 eq) | Water/MeOH | S.M |

Table 3.22: Nef reaction conditions at RT for 1 h in Batch.

By using 1 equivalent of KOH and leaving for 1 h formation of a new compound was observable by TLC. After leaving for 4 h it was apparent that no nitroalcohol was in solution and that a new product had taken its place. Crude NMR showed this, where a retro-Henry reaction had occurred, yet again showing the formation of the tolualdehyde showing the sensitivity of these compounds to pH changes.

4.1 Introduction to Koch carbonylations

4.1.1 Carbon Monoxide

Carbon monoxide is a colourless, tasteless and odourless gas that is highly toxic to humans in concentrations exceeding 35 parts per million (ppm). Its toxicity may have even been noted as early as 384-322 B.C. when Aristotle described how coal fumes lead to a heavy head and death in some instances.^[200] It is thought that CO poisoning may contribute to 50% of poisonings in industrial countries as of 2002 and causes a large number of deaths in Europe and North America yearly.^[201] The cause of this toxicity is that highly reactive nature of CO towards haemoglobin having a 200-250 times higher affinity than oxygen. High concentrations of CO in the blood stream lead to hindrance of oxygen absorption onto the haemoglobin producing the highly stable carboxyhaemoglobin (COHb).^[202] This therefore severely reduces its ability to transport oxygen around the body.^[203]

Industrially CO is produced via many methods. Some of the more common methods are the Boudouard reaction^[204] where air is passed through coke at high temperature. Initially a gas mixture of nitrogen and carbon dioxide is produced but over time with the excess carbon the system equilibrates to CO. At temperature above 800 °C CO is predominantly formed. A second and highly researched field is the water-gas shift where steam is passed over carbon in equilibrium to form CO and H₂ gases. This is commonly used in industry to form synthesis gas (syngas) for many of the applications in industry (Figure 4.1).

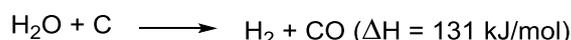


Figure 4.1: Energy of formation of CO from coke and the formation of syngas.

The methods stated above are the methods used in industrial applications, although there is another method used mainly in laboratories. Dehydrating formic acid in the presence of a strong acid leads to the formation of CO gas and this has been shown extensively in the Koch-Haaf carbonylation method.

The use of CO as a reagent, although being a very attractive and extremely efficient C1 unit for the introduction of carbon-carbon bonds, has limited scope on an industrial scale due to the very high level of toxicity. Many methods have been devised to contain the reagent within

sealed reactors, which need to be under pressure and thus on large scale batch conditions is not such an attractive system. In situ formation of CO gas from H₂SO₄ and HCOOH mixtures would therefore be considered an undesirable system due to their hazardous nature. The latter if combined with a technique of continuous flow offers a highly attractive assembly for the use of carbon monoxide in organic synthesis.

The nature of CO allows it to be used as a nucleophilic C1 source in organic synthesis. The bonding of carbon to oxygen via a triple bond, where the oxygen donates one of its lone pairs to facilitate this third bond, creates a strong dipole across this molecule. The oxygen is therefore δ -positive and the carbon δ -negative. This allows for the reactivity of this molecule through the carbon. Although CO is a very poor nucleophile.

CO has also shown a strong affinity to neutral donor bonding to metals and has been used to purify metals industrially in the Mond process.^[205,206] It is a fairly weak Lewis base and therefore prefers to bind to metals that are in a lower oxidation state as this allows for backbonding to the carbonyl ligand stabilising such an interaction. This process can also be used to make important carbonyl complexes such as iron pentacarbonyl which has many uses in chemistry.^[207]

4.1.2 Carbonylations

Carbonylation reactions have been shown in recent times to be powerful carbon-carbon and carbon-hetero atom bond forming protocols within chemical synthesis. To date many different systems have been devised to produce numerous carbonyl-containing compounds such as ureas, carbamates, oxamates, oxamides, α -keto amides, ketones and esters (Figure 4.2).^[208] The main advantage associated with carbonylation reactions is that it is generally a very economical method for the synthesis of carbonyl containing products, which introduces an additional carbon. Moreover, this reaction allows for the introduction of the simplest C1 source, carbon monoxide (CO), which is a relatively cheap, readily available source.^[209]

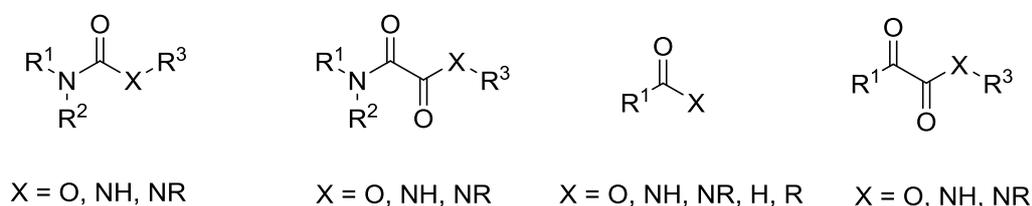


Figure 4.2: Various functionalities containing carbonyls that can be synthesised using carbonylations.

Two well established industrial techniques make use of CO gas, these are the Monsanto^[210] and the Cativa^[211] process. They have been used in industry from the late 1960s and late 1990s respectively, although the first reported industrial process was from BASF in 1965 featuring a high pressure system using a cobalt catalyst.^[212–214] These processes involve the carbonylation of methanol to acetic acid using transition metal catalysis, where the Monsanto process uses rhodium and the Cativa uses iridium. The general cycle of these transformations consist of conversion of MeOH to MeI by hydrogen iodide followed by an oxidative insertion of MeI into the metal [M] **186**. Ligand exchange of the iodide with CO then occurs via a migratory insertion **187** proceeding to form the acyl group bonded to the metal **188**. This is then reductively eliminated assisted by the iodide to form acetyl iodide and regenerating the metal catalyst **185** (Figure 4.3).

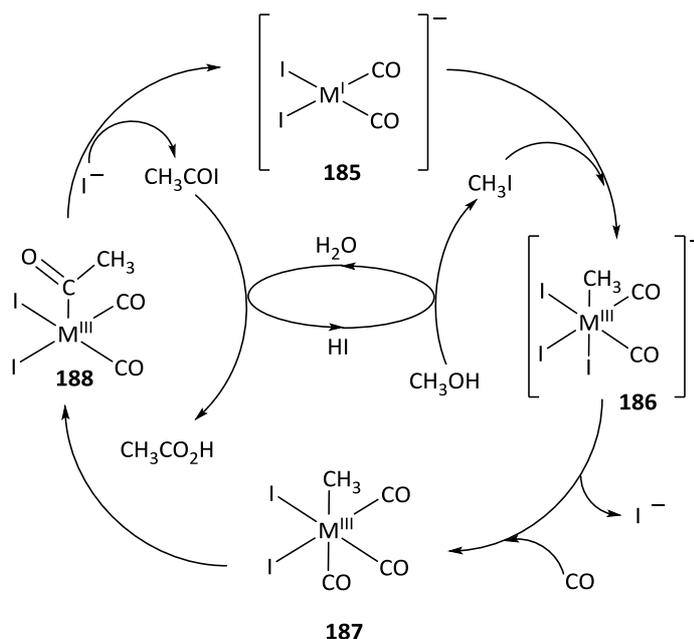


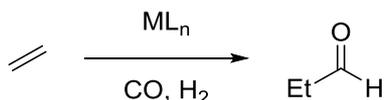
Figure 4.3: Catalytic cycle of the Monsanto (M = Rh) process and Cativa process (M = Ir).

Further industrial syntheses have been developed due to the success of such reactions to form anhydrides. Eastman chemicals developed a carbonylation of methyl acetate for the large scale production of acetic anhydride.^[215] This process is closely related to the rhodium catalysis of methanol to acetic acid and was made commercial in 1983.

In all of the various methods developed, conversion is usually dependent on catalysis by a transition metal to perform the transformation selectively and efficiently. All group 9 and 10 metals in combination with organic iodides show activity for carbonylations and many other metals such as group 11 have also shown great reactivity. Usual conditions for many of these reactions work at temperatures of 100-200 °C and pressures of 20-100 bar.

1.1.5 Hydroformylation of olefins

Another key area within carbonylation chemistry was the discovery of hydroformylation of olefins. Discovered by research conducted by Otto Roelen at BASF^[216], the reaction where in general formaldehyde is added across a double bond to form aldehydes and is referred to as the “oxo process” a phrase coined by Adkins (Scheme 4.1).^[217]



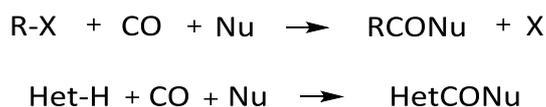
Scheme 4.1: Hydroformylation of ethene under metal catalysis with syn gas to produce propanal.

This process like many significant works was discovered by chance, while investigating the influence of olefins on the Fischer-Tropsch synthesis, using a silica supported cobalt oxide catalyst.^[218] This was later concluded to be a homogenous process when $\text{HCo}(\text{CO})_4$ was discovered to be formed *in situ* at high temperature and pressure, which is required for stability. Since then many metals have been shown to catalyse this process; Co, Rh, Pd and Pt have been shown to be most active.

1.1.6 Hetero-formylation conditions

As well as hydroformylation incorporation other simple modifications can be introduced to form different functional groups. Adding water or an alcohol to formylation conditions can produce carboxylic acids and esters and has been reported extensively. These processes were reported by Reppe and have been conducted most effectively with palladium.^[219]

One of the most commonly used metals in organic synthesis is palladium which has been used for a large amount of carbonyl insertion reactions due to its affinity to carbonyls and its ability to insert into R-X bonds, heteroatom-H bonds and C-H bonds (Scheme 4.2).

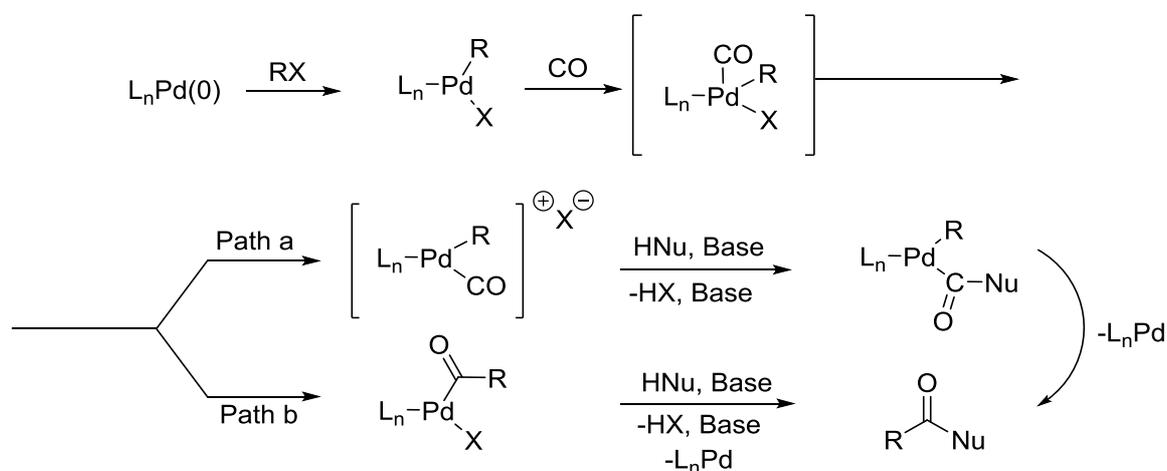


Scheme 4.2: Heck-type carbonylations by halide insertion and H activation of heteroatoms.

This field has grown largely due to the work of Heck since 1974^[220] and numerous carbonyl containing functional groups have been synthesised. Using the concepts formed under

hydroformylation conditions and the pioneering work established by the Nobel Prize winners in Pd cross-coupling reactions, Heck furthered carbonylation chemistry by showing that not only double bonds can be carbonylated; organic halides could also be exploited. The ability of palladium to oxidatively insert into organic halide bonds changed the way we synthesise molecules in the modern day and with the previous knowledge of carbonyl coordination chemistry carbonylations could be extended.

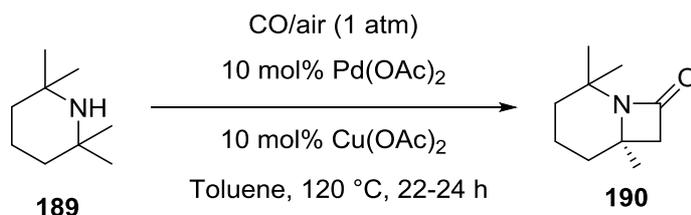
Mechanistically the process is fairly similar to that of a traditional cross coupling reaction where an oxidative insertion occurs with the organo halide. This is then followed by coordination of the CO. There are two schools of thought regarding the next step in the process. The first is that the halide dissociates to form a charged complex which is then followed by an attack of the nucleophile to form a palladium acyl complex. Reductive elimination of the organo compound from the acyl complex forms the product. The second process is thought to be a migratory insertion of the CO into the carbon palladium bond followed by reductive elimination to form an acyl halide. This is then quenched by the nucleophile to form the desired product.



Scheme 4.3: The two proposed pathways of Heck carbonylations.

Multiple studies have been conducted to support either claim and generally evidence points towards path B. It has also been shown that ligand concentrations play an important role. High concentrations of phosphine ligands promote greater formation of amide (if Nu is an amine Scheme 4.3) whereas lower concentrations tend to allow for a greater production of ester (if Nu is an alcohol Scheme 4.3). This suggests there are different mechanistic pathways for each functional group.^[221]

There are many examples of this versatility in the recent literature. Gaunt *et al.* showed the formation of strained β -lactam rings by the C-H activation of aliphatic amines **189**.^[222] Activation of the β -methyl group by the palladium species ($\text{Pd}(\text{OAc})_2$, 10 mol%) formed the four-membered cyclic intermediate (cyclopalladation). This was then followed by insertion of the CO under oxidation of air and finally a reductive elimination with the amine to cyclise onto the formyl group producing the β -lactam **190** (Scheme 4.4).



Scheme 4.4: Synthesis of β -Lactams via CH activation, carbonylation of aliphatic amines.

Temperatures of 120 °C were used in toluene with copper acetate ($\text{Cu}(\text{OAc})_2$) used as a co-catalyst in 10 mol%. Yields ranged from 55-87 % in 22-24 h reaction time.

4.1.3 Carbonylations in flow

As CO is highly toxic, modern techniques have looked at methods to harness this useful molecule in a safe and efficient fashion. The use of mass flow controllers (MFC) has led to introductions of gases into flow systems where the gas can be contained within the tubing, and thus if toxic or harmful cannot interact with the surrounding environment. Not only this, but due to the high surface-to-volume ratio, fewer equivalents are needed to allow for reaction. This is due to the superior interaction between the liquid and the gas phase at a much higher surface area. Recent examples of this can be split into metal catalysed and non-metal catalysed reactions.

4.1.3.1. Heterogeneous conditions

Heck amino carbonylations have attracted considerable attention in the last few decades and this is no different within flow chemistry. Many groups have demonstrated this transformation of aryl halides to amides via Pd cross coupling in the presence of amines. Two examples reported by Miller and Ryu were published in 2006.^{[223][224]} Both showed the coupling of aryl iodides with benzyl amines to produce the corresponding amides **191** and/or **192**. It was shown by Miller that relatively low pressures of CO were needed to obtain reasonable yields using PdCl₂(dppp) at 80 °C, obtaining a yield of 46% for **191** in 2 min Fig 4.4.

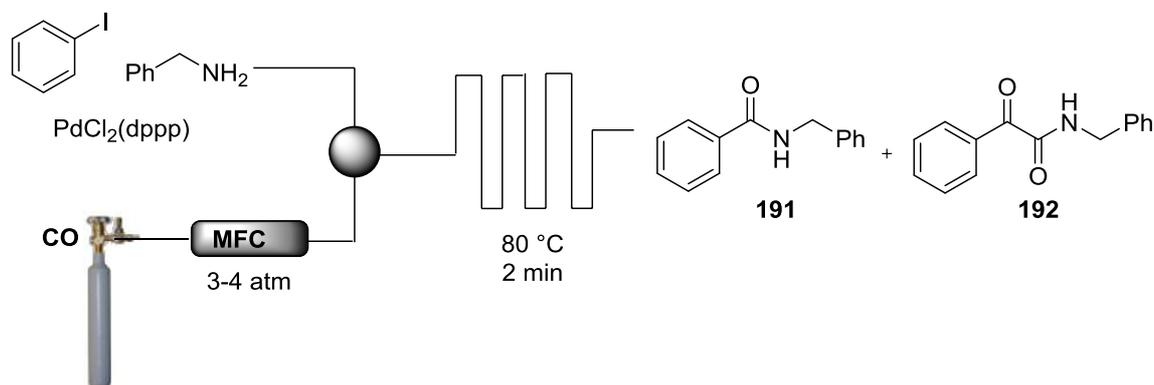


Figure 4.4: Formation of amides via Pd catalysed amino Heck carbonylation in flow.

Due to the general success of such a reaction, Miller and co-workers later used this reaction scheme to develop a rapid screening method in which a chip reactor was used. With a combination of varying temperatures and Pd/ligand complexes, it was shown that PdCl₂

complexed with Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) was the most effective for this transformation.^[225]

Ryu's method consisted of a Pd complex **193** dissolved in an ionic liquid which was premixed at a prior T-piece with CO via a MFC before introduction of the substrate mixture at a second T-piece (Figure 4.5).

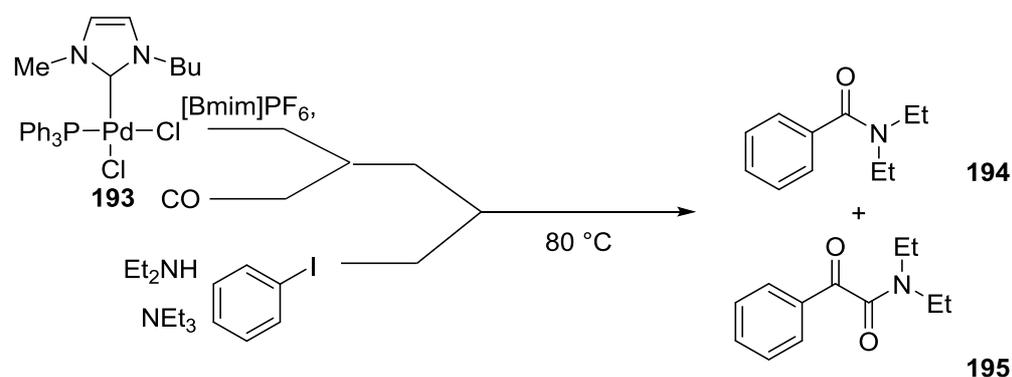
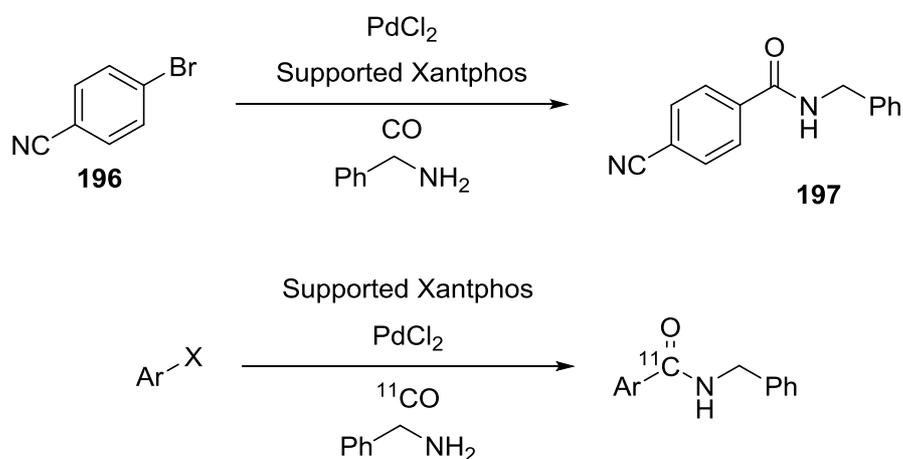


Figure 4.5: Aminocarbonylation of iodobenzene, CO_(g) and diethylamine by Pd catalysis in an ionic liquid. They compared their results to batch conditions where they showed an increase in yield and selectivity for the monocarbonylation product **194** as compared to the dicarbonylation product **195** of iodobenzene where the flow conditions resulted in 80% yield in 34 min as compared to 5 h and 63% yield under batch conditions.

An extremely efficient system using *p*-bromobenzonitrile (**196**) and benzylamine was devised by Long *et al.* using a gas-liquid-solid phase set-up to afford amides (**197**) in shorter times than the corresponding batch reaction (Scheme 4.5).^[226]



Scheme 4.5: Carbonylation of aromatic halides using ¹¹C to form amide PET tracers.

A reusable Pd silica-supported catalyst was used and was further demonstrated to be a proficient protocol for PET tracers forming very high purity radio-amides with ^{11}CO . They produced the labelled compound in a 79% radiochemical yield and in a second run producing it in a 65% radiochemical yield.

A similar system was then devised by Skoda-Foldes *et al.* using polymer-supported $\text{Pd}(\text{PPh}_3)_4$ as the catalyst.^[227] Using DBU as a base at a higher CO pressure of 40 atm and at 80 °C the aminodicarbonylation of arylhalide with amines was accomplished. As shown in Figure 4.6.

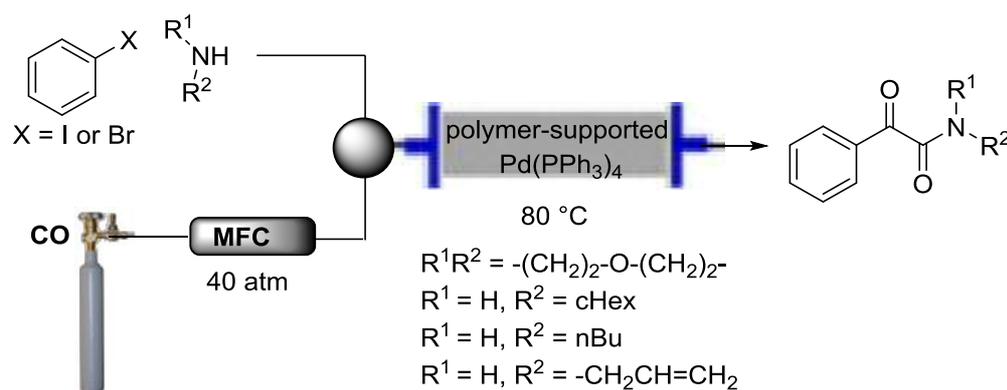


Figure 4.6: Aminodicarbonylation of aryl halide with an amine via supported Pd catalysis.

Another method (Figure 4.7) using solid-liquid-gas technique has been demonstrated in the commercial X-Cube™ using a supported Pd catalyst in a cartridge.^[228] Csajagi reported an aminocarbonylation of 2-iodobenzamide with pyrrolidine at 100 °C and 30 atm of CO. NEt_3 was used as the base and gave the corresponding amides in good yields with a residence time of 1.5 min.

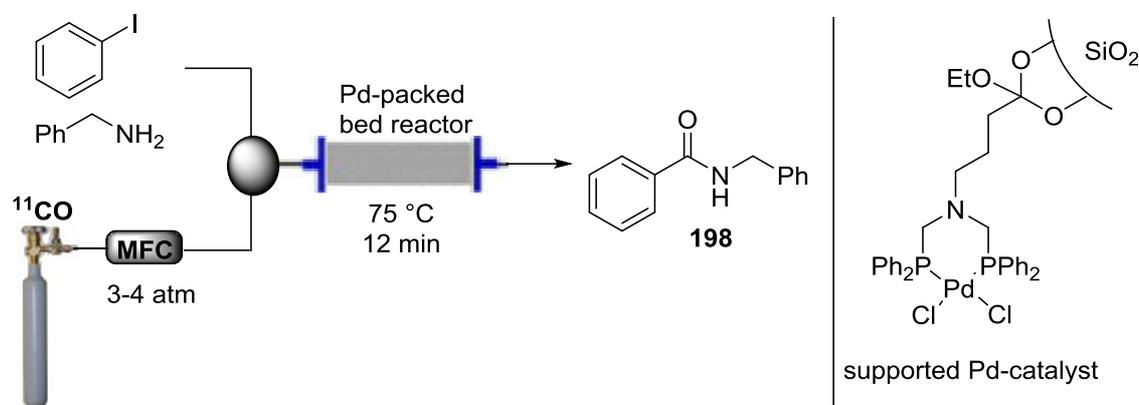
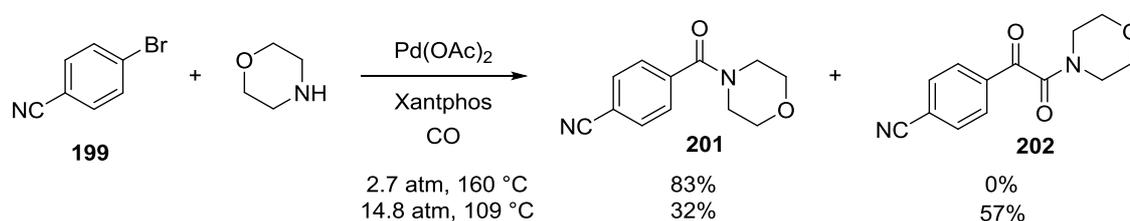


Figure 4.7: Gas, liquid and solid phase amino Heck carbonylation catalysed by a solid support Pd complex.

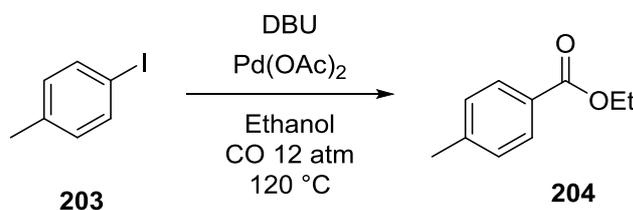
Buchwald *et al.* showed the coupling of *p*-bromobenzonitrile (**199**) using Pd(OAc)₂ with Xantphos for the aminocarbonylation with morpholine.^[229]



Scheme 4.6: Aminocarbonylation of *p*-iodobenzonitrile with morpholine under palladium catalysis in flow

A low pressure of CO was used of 2.7 atm at 160 °C in flow, to form the monocarbonylation product **201** in 83% yield and when the pressure was raised to 14.8 atm at a temperature of 109 °C the dicarbonylation product **202** occurred in 57% yield in addition to **201** in 32%. The varying pressure and temperatures can be attributed to the method of analysis. Using a sample loop and by collecting a sample at varying conditions the optimal yields could be obtained for each compound. In Scheme 4.6 the optimal condition for **201** and **202** are shown.

Not only have examples of aminocarbonylations been described in the literature but further Heck carbonylations using alcohols to form esters have been reported. Leadbeater *et al.* showed a meso-scale device for a larger scale reaction than conventional lab based syntheses in flow.^[230] Aryl esters were produced using Pd(OAc)₂, *p*-iodotoluene **203** and DBU in ethanol. 12 atm of CO were used at 120 °C in a residence time of 4 min to obtain **204** in an 86% yield (Scheme 4.7).



Scheme 4.7: Hydroxy-carbonylation of *p*-iodotoluene with ethanol by palladium and DBU under continuous flow conditions.

Another larger scale method was described by the Nihon Nohyaku Company, Ltd.^[231] They showed ester formation could be achieved on a gram scale. Furthermore, efficiency was high using near stoichiometric CO and still having quantitative yield.

It was also shown to be possible to synthesise ketones in this manner and the benefits of flow chemistry have been presented well by the carbonylative Sonogashira coupling of iodobenzene with phenylacetylene in the presence of CO.^[224] A low pressure of CO was needed at 3 atm with Pd and NEt₃ at 120 °C. This solely produced the ketone **205** as opposed to the batch Sonogashira coupling which forms 1,2-diphenylacetylene. (Figure 4.8) This is a prime example of the benefits of segmented flow and the greater interfacial area that is caused by microfluidics.

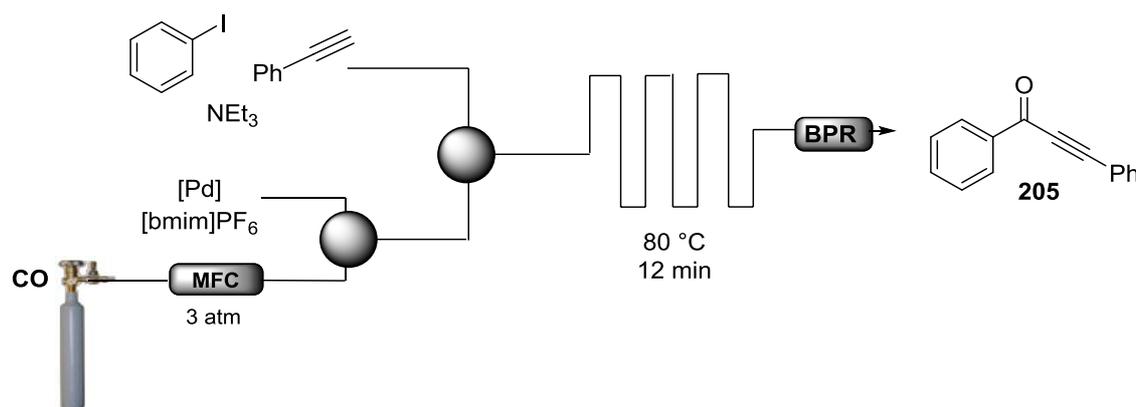
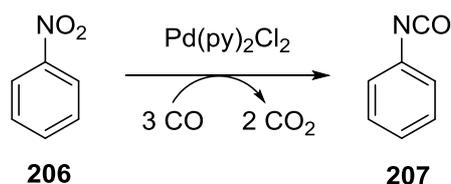


Figure 4.8: Pd-catalysed carbonylation for the formation of acetylene containing ketones in continuous flow.

Another demonstration of segmented flow has been shown by Takebayashi.^[232] They used CO as a reductant to form isocyanate **207** from nitrobenzene **206** (Scheme 4.8).

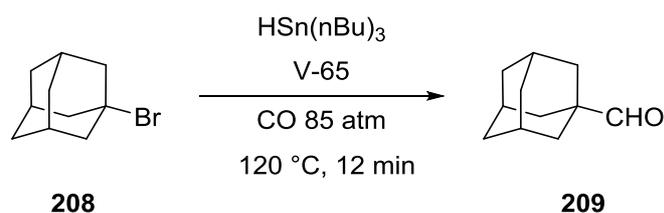


Scheme 4.8: Reductive carbonylation of nitrobenzene under Pd catalysis.

Under Pd catalysis and comparing two internal diameters of coil reactors (1 mm and 0.5 mm) it was shown again that the higher surface area caused by the smaller liquid plugs allowed a higher yield within the same residence time. Decreasing the size in tubing in-turn allowed for smaller segments which allows for this greater surface interaction between the gas and the liquid phases where they showed that more than double the amount of CO was absorbed allowing the reaction to progress quicker. This led to a higher yield within the same retention time.

4.1.3.2. Non-metal catalysed

Although the majority of examples in carbonylation chemistry has been reported with metal catalysed systems, there has been some research using other activation methods.^[233] Ryu *et al.* described a radical carbonylation of 1-bromoadamantane **208** using V-65 (2,2'-azobis(2,4-dimethylvaleronitrile) as the radical initiator and tributyltinhydride in the presence of CO to produce 1-carboxyaldehyde adamantane **209**. A steel tubular reactor was used to allow for the high pressure of 85 atm of CO and was heated to 120 °C for 12 min to afford the product **209** in 86% yield (Scheme 4.9).



Scheme 4.9: Radical carbonylation of 1-bromoadamantane by a tributyltinhydride, V-65 combination

A second example of a Pd-free system was the Koch-Haaf carbonylation of 1-adamantanol **210**.

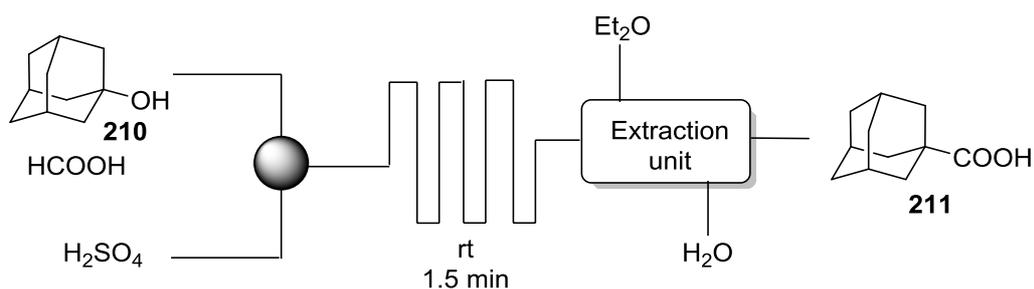
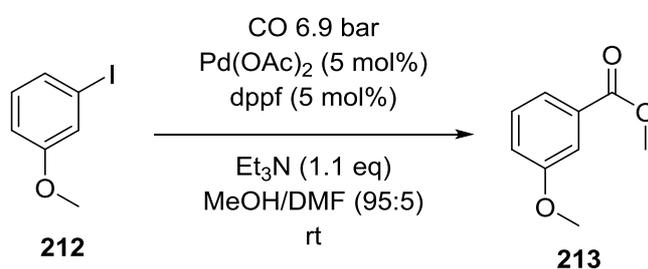


Figure 4.9: Koch-Haaf carbonylation of adamantanol using *in situ* formation of CO in a hasteel alloy reactor.

The system used the dehydration of formic acid with sulfuric acid to produce CO *in situ*. The dehydration of **210** led to the carbocation and with addition of CO followed by quenching with water produced the carboxylic acid **211** in 89% yield.^[234]

4.1.3.3. Homogeneous conditions

Another series of techniques utilizing flow chemistry are reactions with toxic gases. The advent of the AF-2400 tubing system pioneered by Ley *et al.* has allowed for many different gases to be produced *in situ* or introduced into solution without negatively affecting the subsequent reactions. Recent examples in carbonylation chemistry with this apparatus were shown by Ley where the tube in tube reactor approach was used to synthesise esters from aryl iodides (**212**).^[29,235] Two examples were shown where the solution was saturated with CO prior to entering the reactor coil. This was then subjected to the reaction conditions under Pd catalysis to produce the aryl esters such as **213** in very good yields of around 80% (Scheme 4.10).



Scheme 4.10: Methoxycarbonylation of 3-iodoanisole under palladium base catalysis.

Another approach taken by Ryu and co-workers was to use a method of CO production *in situ* (Figure 4.10).^[236]

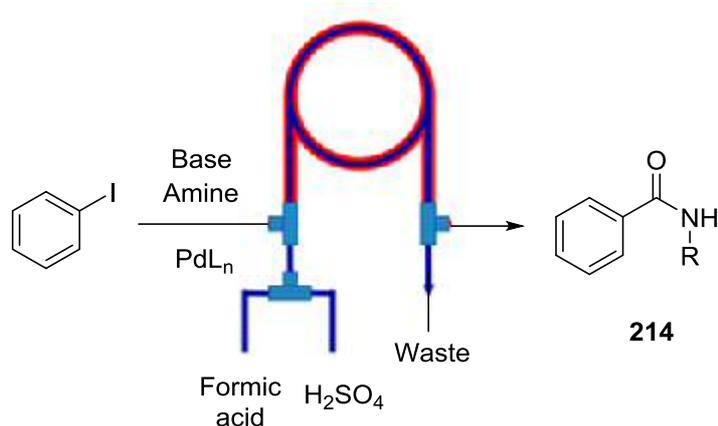


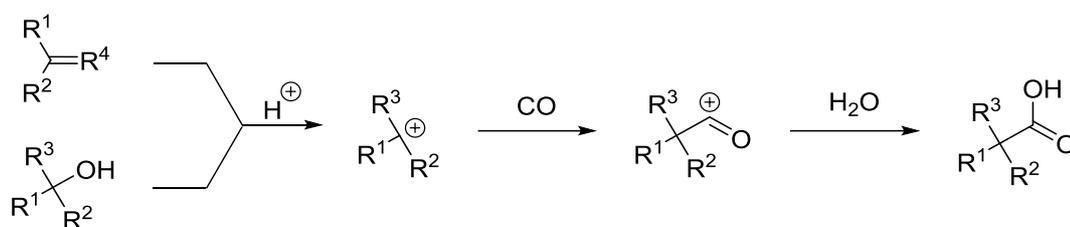
Figure 4.10: Aminocarbonylation of iodobenzene using in-situ formation of CO in a gastropod reactor.

Sulfuric acid and formic acid were used to generate CO in the inner tubing which was then passed through the membrane to the reaction mixture containing an aryl iodide, amine, a base

and the Pd catalyst complex. The reaction mixture was then subjected to the reaction conditions to afford the amide(**214**) in excellent yields of 59-100%.

4.1.4 Koch-Type carboxylations.

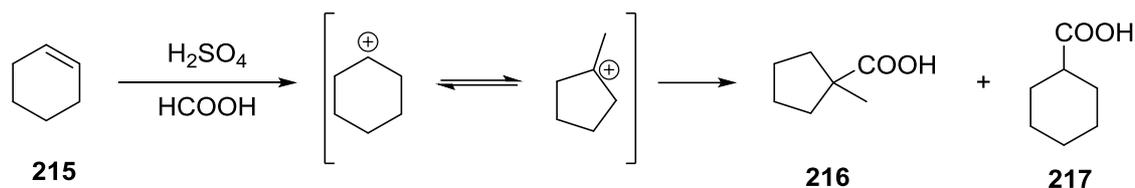
The Koch or Koch-Haaf carboxylation is the formation of carboxylic acids from either olefins or alcohols in strongly acidic media. Unlike many other carbonylation methods traditionally the formation of CO is an *in situ* process within Koch type reactions.^[237] This is prepared by the addition of formic acid to a concentrated sulfuric acid solution, although methods have been developed using CO gas introduction. As this reaction is in very acidic media, protonation easily occurs and therefore the reaction proceeds through either dehydration (alcohol) or simple protonation (olefin) to form a carbocation. The reaction of the carbocation with CO affords an oxo-carbenium ion (acyl cation) which is the key step in the formation of carboxylic acids via this method. As this is a reversible step, at this stage it is highly dependent on the concentration of CO in solution therefore larger concentrations of CO are needed to form the desired product (Scheme 4.11).



Scheme 4.11: Koch and Koch-Haaf conditions for formation of acids from alkenes and alcohols.

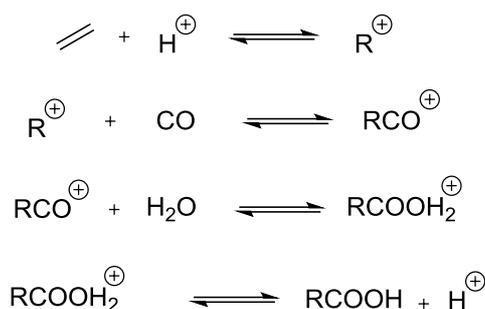
Traditionally Koch-type reactions were studied in concentrated H₂SO₄ solutions but to date numerous acid sources have been used from mineral and Lewis acids^[238], to solid acids^[239] and acidic ionic liquids^[240].

The original approach from Koch used hydrocarbon alkenes along with H₂SO₄ and formic acid to obtain the corresponding carboxylic acids in good yields.^[237] Simple alkenes such as hept-1-ene and cyclohexene **215** were used in the highly acidic medium (Scheme 4.12).



Scheme 4.12: Koch carbonylation of cyclohexene.

With the latter example it was observed that the carbocation formed initially rearranges from the secondary cyclohexyl cation to the more stable tertiary cyclopentyl methyl cation. The formation of such cations has been studied, and as a result it has been proposed that the rearrangement to the more stable cation is faster than the attack of the CO moiety. From this observation the rates of reaction of carbocations were tested in relation to their reaction with CO gas (Scheme 4.13).



Scheme 4.13: Equilibrium conditions for each step of the Koch carboxylation.

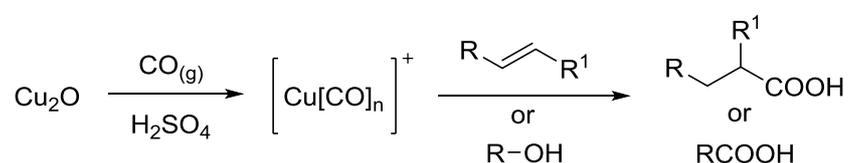
Although each step of the reaction is in equilibrium, the rate-determining step is considered to be the formation of the acyl cation. Therefore this is highly dependent on the stability of the carbocation formed and the concentration of CO within the solution.^[237] As a result, little work has been described with this method using highly stabilised carbocations.

4.1.4.1. Carbon monoxide scavenger complexes

As well as carbonylations from alkyl halides a few methods have been developed with metal catalysts for the carbonylation of carbocations. Souma *et al.* devised a copper (I) carbonyl system formed from copper oxide and carbon monoxide in concentrated sulfuric acid. They claimed that the unstable $[\text{CuCO}]^{\oplus}$ system could be used as a carrier for the CO, this reduced the equivalents needed as the CO would then be kept in solution bound to the metal. They showed various carbonylations of unsaturated hydrocarbons resulting in comparable yields as traditional methods.

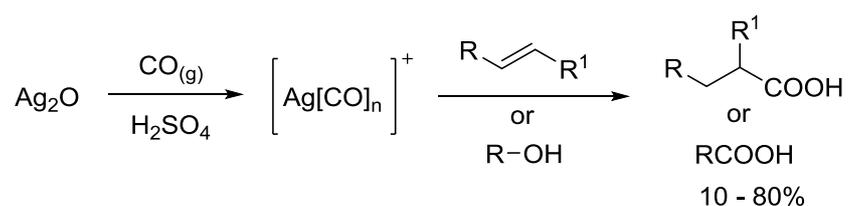
Metals have played an important role in many industrial carbonylation reactions and have shown strong tendencies to bind to carbonyls.^[241] The majority of processes use the typical Heck-type carbonylations with insertion into a double bond or carbon halide/pseudohalides bonds. Unlike these methods where the metal plays a direct role in the transfer of the carbonyl to the reactant there have been studies on using metals such as copper and silver in the +1 oxidation state to form complexes that can collect up to 4 molecules of carbon monoxide to

each metal centre. This allows for much higher concentrations of the gas within solution at any given time. These complexes tend to only be formed when there is an absence of counteranion basicity and so very strong acidic media are used for this but there are other conditions which can allow for this interaction. This ability to absorb CO and act in strong acidic media therefore allows these +1 metals to facilitate the Koch-type carbonylation, and has been shown in numerous publications by Souma et al.^[242] They originally showed that copper (I) oxide could be solvated in concentrated sulfuric acid, and that upon addition of CO_(g) from a bubbler a Cu[CO]⁺ complex could be formed. On addition of an olefin or alcohol the catalyst was able to transfer a CO onto the formed carbocation within the strong acidic media (Scheme 4.14). Substrates such as 1-hexene and 1-hexanol were shown to be carbonylated in moderate yield of up to 70%.



Scheme 4.14: Koch-type carbonylations using copper as a CO scavenger.

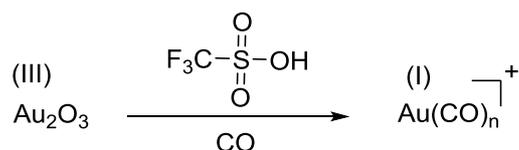
The same group then moved on to study additional transition metals for this method.^[243] They used silver (I) oxide for the same transformations whilst also studying the effect of acid concentration on the conversion and rate of reaction. Similar yields were obtained with the highest concentration of acid leading to the highest conversion and rate of reaction (Scheme 4.15).



Scheme 4.15: Koch-type carbonylations using silver as a CO scavenger.

It was shown that at acid concentrations of below 90 wt%, the rate of reaction was reduced significantly and therefore the method was virtually impractical.

They moved onto using gold where the formation of the active gold (I) species was *in situ* (Scheme 4.16).^[244]

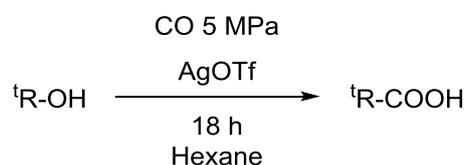


Scheme 4.16: Formation of the active gold (I) species via oxidation by CO triflic acid combination.

When Au_2O_3 was dissolved in concentrated trifluoromethane sulfonic acid, the introduction of $\text{CO}_{(\text{g})}$ allowed for the reduction of the gold (III) species to the active gold (I) species, which could then undergo catalysis. The active catalyst was then used to transfer the carbonyl to a variety of olefins demonstrating its increased rate compared to the absence of said catalyst. Results were compared to the copper catalyst with analogous results. Additional work showed the use of palladium under Koch-type conditions for the carbonylations of olefins and alcohols.^[245] They further investigated their catalytic system using computational calculations which showed that the stability of the catalytic system was in the sequence of $\text{Ag} < \text{Cu} < \text{Pd} < \text{Au}$ for mono-carbonylated complexes.

Later publications focused on rhodium^[246] and platinum^[247] complexes in which the same authors showed very similar results could be obtained but with only olefinic substrates. Unlike previous complexes, platinum showed a new characteristic of forming a dimer of hexacarbonyldiplatinum which would still undergo catalysis, although a large drop off in reaction rate was observed when using the *cis*-isomer of the dimer.

In addition, a report consisted of using silver(I) triflate^[238] without the presence of a strong Brønsted acids. The authors demonstrated that tertiary alkyl alcohols could be dehydroxylated to the corresponding tertiary alkyl cations. This was achieved using the Lewis acidity of the silver salt to form the carboxylic product after addition of CO (Scheme 4.17).



Scheme 4.17: Carboxylation of tertiary alkanes via silver triflate catalysis.

Although this was shown to be possible very high pressures of gas were needed to form the product which showed parity to the many conditions used with $\text{Mo}(\text{CO})_6$ and $\text{Fe}(\text{CO})_5$ in the past.

4.2 Results and Discussion

As previously mentioned the first Koch type carbonylation in continuous flow was reported by Ryu et al.^[234] They showed a simple flow system for the addition of in situ generated carbon monoxide in microreactors. With only a limited amount of CO produced at any time this could be seen as a very green method whilst being much safer than conventional batch type chemistry. Flow chemistry, due to its considerably higher surface to volume ratio and the absence of head space, allows for a much more efficient system.

Although a few Koch-type carbonylations have been reported in the literature the range of substrates is still very limited; mainly only aliphatic alcohols and olefins have been carbonylated to date using this method. The aim of this project is to explore these types of reactions and therefore increase the scope to systems such as benzylic alcohols. Only one publication has reported the carbonylation of such substrates under batch conditions and none have been reported in flow therefore these conditions using the system devised by Ryu, formed the basis for this project.

4.2.1 Traditional Koch-Haaf carbonylations

To first develop the initial system Ryu's experiments were repeated. Using 1-adamantanol dissolved in formic acid (syringe A) and concentrated sulfuric acid (97%) (syringe B) the reaction was performed in a simple PTFE tube reactor using a Comet mixer. A further inlet with a T-piece was used after the residence coil to allow for addition of diethyl ether (to prevent blockages on addition of water) and the mixture was finally dropped into a stirred beaker of water to collect the carboxylic acid Figure 4.11.

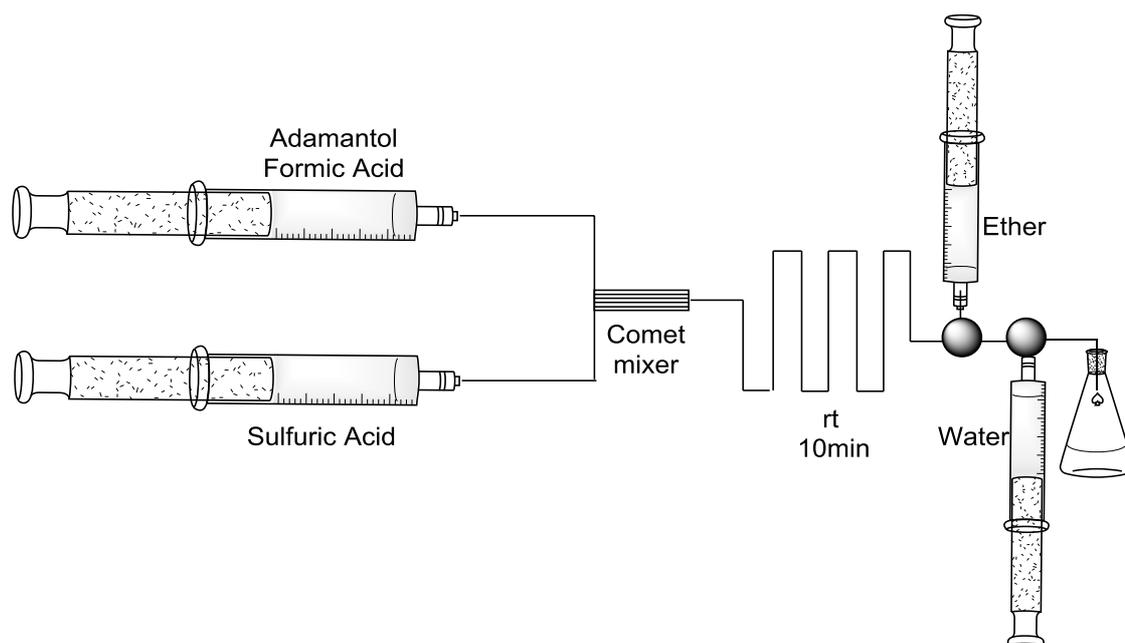
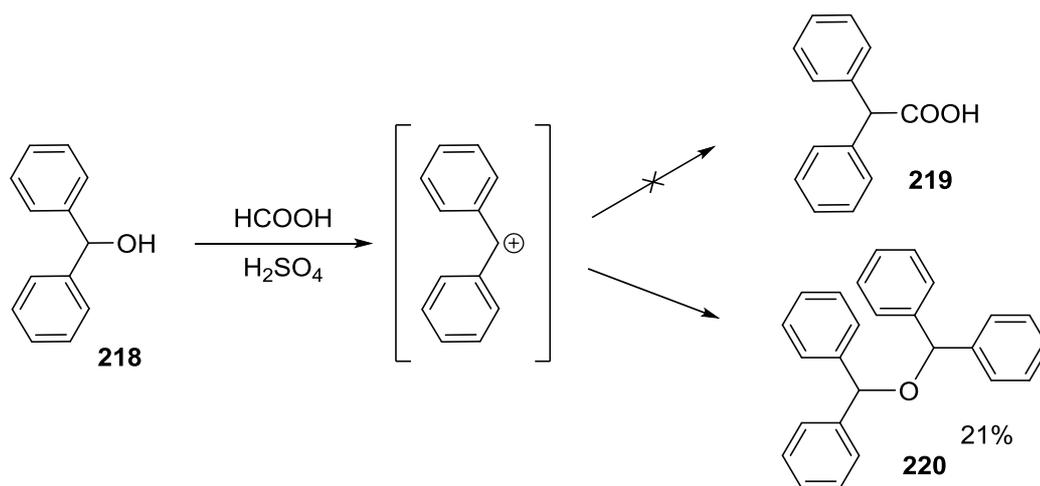


Figure 4.11: Flow set-up for Koch-Haaf carbonylations in flow as adapted from Ryu *et al.*

This produced the adamanylcarboxylic acid in 60% yield with a large amount of starting material remaining; this was because on addition of the formic acid to the sulfuric acid the CO gas produced caused a large plug flow of gas. This gave an inconsistent residence time within the coil. Although in Ryu's work no back pressure regulator (BPR) was stated, it is difficult to understand how similar problems did not occur within their work and therefore the results may be unreliable. Due to equipment limitations, we could also not install a BPR as their lack of acid resistance. It was therefore hoped that other methods could be used to solve this. By clamping the end of the outlet tube partially closed a small degree of control could be exerted, although this was not perfect.

The substrate of choice to further the scope of this transformation in continuous flow technology was benzhydrol **200**. Only one paper^[234] has been published on such systems under the Koch-Haaf conditions and thus this was considered a good starting point for further investigation. Benzhydrol was tested under the conditions established for 1-adamantanol.



Scheme 4.18: Scheme depicting the unexpected side reaction upon Koch-Haaf type carbonylation of benzhydrol in flow.

Unfortunately, diphenylacetic acid **218** was not produced and instead the major products were the decomposition or dimerization product **220** of the starting material (21%). Therefore on formation of the carbocation by dehydration, a second benzhydrol molecule must attack before introduction of the CO to the carbocation (Scheme 4.18).

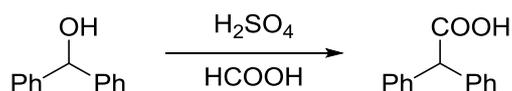
This is in concurrence with previously studied systems of benzhydrols in concentrated sulfuric acid where in high substrate to solvent concentration the formation of the ether occurs. Work from Takahashi^[248] confirmed this as when vigorous mixing was used, the yields of the carboxylic acids were essentially zero and dimerization occurred readily. Not only this, but as within a non-pressurised batch system, the mixing of the solution allowed for dissolution of the CO, which thus reduced the concentration of the CO and allowed the alcohol to react with the carbocation.

It was thought that the use of a micromixer had a negative effect on the formation of the acid and created more instances for dimerization. The comet micromixer was therefore removed from the set-up and replaced by a simple T-piece with the use of 0.5 mm I.D. tubing. This allowed for mixing only by diffusion through laminar flow and reduced the likelihood of dimerization. It was further hoped that using a T-piece mixer would reduce the CO gas being expelled from solution and cause less plug flow. Unfortunately the acid was not obtained and a mixture of small amounts of dimerization product was observed probably due to the poorer mixing, in addition to unidentifiable side products and a large amount of starting material.

To prevent this, two methods were devised. A lower concentration of substrate within solution, having less of the benzhydrol within the vicinity of the formed carbocation would

allow for the CO to have more time to attack the carbocation. The second approach was capping the end of the alcohol with a protecting group which still had the ability to leave to cause the formation of the desired carbocation.

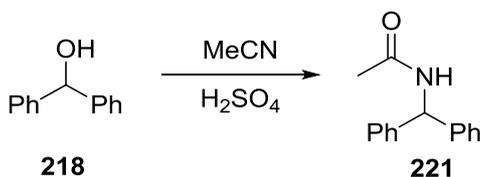
The easiest and quickest theory to test was the reduction in concentration. This was simply achieved by increasing the volume of formic acid in ratio to the alcohol in solution. This in turn would also increase the amount of CO produced, and thereby increase the likelihood of interaction with the carbocation Table 4.1.



| Entry | Concentration (M) | Yield (%) |
|-------|-------------------|-----------|
| 1 | 2 | 0 |
| 2 | 1 | 0 |

Table 4.1: Concentration effects on the Koch-Haaf reaction in flow.

Although from these conditions there was no formation of the bisdiphenylmethylether, the reaction was not successful and upon quenching with water, the starting material was recovered. This could have been attributable to CO not reacting with the carbocation or secondly, that the carbocation was not produced at these lower concentrations.

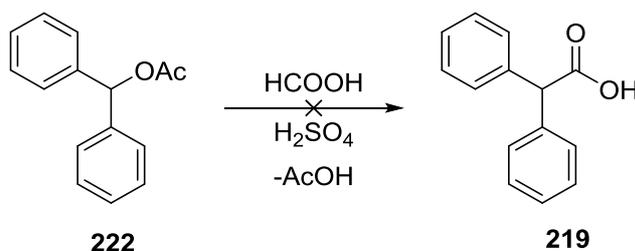


Scheme 4.19: Ritter conditions to test formation of carbocation in flow.

A similar reaction that proceeds through a carbocation intermediate and was earlier studied in flow within the Wirth group is the Ritter reaction, where addition of a nitrile to the carbocation followed by quenching with water forms an amide as the product (Scheme 4.19). To test the concentration of the reaction mixture the conditions were repeated although using acetonitrile instead of formic acid. This produced the amide **221** in very good yields 65%, therefore suggesting the formation of the carbocation at these concentrations.

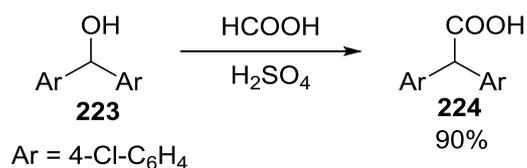
The second modification trialed was the protection of the alcohol to prevent the dimerization by blocking the nucleophilicity of the alcohols. As reported in previous works using Ritter-type chemistry, addition of an acetyl group was used to protect the alcohol. This has been shown to

still undergo elimination to form the carbocation and therefore undergo addition. It was then decided that this could be used for the carbonylation conditions, allowing for higher concentration of acid to substrate upon mixing and therefore a more electrophilic carbocation. Acetylation was accomplished through a simple procedure of benzhydrol in acetic anhydride at reflux to afford benzhydryl acetate **204** in 90 % yield. The conditions were then repeated using this for the *in situ* Koch type carbonylation.



Scheme 4.20: Proposed method to prevent dimerization pathway when using benzhydrol as a substrate. Upon mixing with the sulfuric acid a large colour change occurred, which implied the formation of a new species and therefore possibly the desired carbocation. When quenched with water and isolation, decomposition products were observed although dimerization was not (Scheme 4.20).

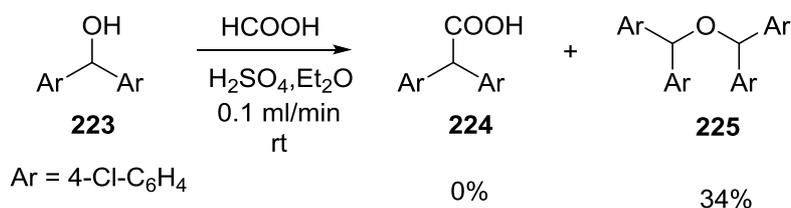
It was hence thought that CO is either too poor a nucleophile to react with such stabilised carbocations, or that not enough CO is in solution to react with the carbocation ion formed, which lead to a greater chance of decomposition and side reactions. One problem was assumed to have been the large mixing effect formed by the Taylor flow in the reactor coil. Mixing has been shown, in previous work with benzhydrol-type derivatives,^[248] to be detrimental to acid formation under batch conditions and further commented on the unsuitability of benzhydrol itself for this reaction.^[248] Takahashi's work mainly focused on using *para*-substituted systems such as 4,4' dichlorophenyl methanol **205** where the side products associated with benzhydrol were not observed or at least were observed to a much lower degree.^[248] The reaction was repeated under batch-type conditions using the chlorinated substrate with the absence of stirring. This resulted in a yield of 90% and showed the applicability of this reaction towards carbonylation.



Scheme 4.21: Koch carboxylation under batch conditions, alcohol (2 mmol), sulfuric acid (10 mL) and formic acid (0.5 mL) room temperature 2 h.

The next step was to try and replicate these conditions under continuous flow. This would minimise the expulsion of CO_(g) from the acid solution and reduce the effect of plug flow, in turn allowing for a much longer residence time. By reducing the flow rates and using AF2400 tubing it was thought that more optimal conditions could be achieved over a traditional type PTFE reactor. The AF2400 tubing would be used to release the pressure build up from the formation of gas and therefore prevent plug flow (Scheme 4.21).

Conditions replicating the batch procedure were used although a small amount of diethyl ether was introduced to the formic acid substrate syringe to allow for complete dissolution of the benzhydrol derivative **223** (Scheme 4.22, Figure 4.12).



Scheme 4.22: Reaction conditions for flow Koch-Haaf reaction using **205** (2 mmol), HCOOH (0.5 mL), Et₂O (0.5 mL) and H₂SO₄ (5 mL).

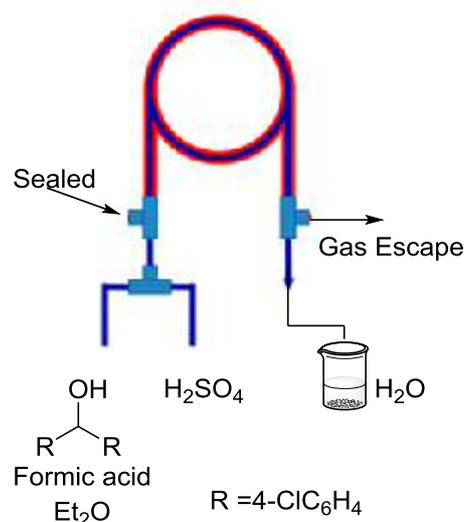
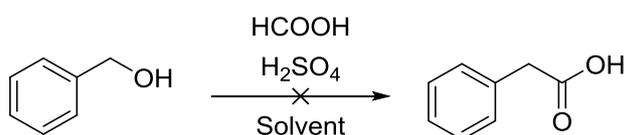


Figure 4.12: The use of AF-2400 tubing for the reduction of pressure and plug flow in Koch-type carbonylations.

Using the gas-permeable tubing, pressure was released and a reliable flow regime could be observed. This allowed for the reaction mixture to have a much longer residence time compared to the previous conditions where either starting material was recovered or a dimer was formed. The reaction was performed with a residence time of 40 min before being quenched into water. Upon analysis, a mixture of side products was prevalent, although the acid product had been formed in small amounts. The side products were determined to be decomposition products of the starting material. It was thought that as there was most likely too low a concentration of CO in solution that the formed carbocation began fragmentation into side products or dimerized. On further analysis the major side product was determined to be the di-(4,4'-dichlorobenzhydryl) ether suggesting that there indeed was a lack of CO in solution, it was therefore decided to change the system to less stabilised systems to allow for quicker reaction times once the carbocation is formed and to change to another synthon for the carboxylic acid formation.

Focus was given to the use of single aryl stabilised systems such as benzyl alcohols which would hopefully be more reactive towards CO and would not dimerise. Upon initial testing of these substrates under standard the conditions the alcohol dissolved in formic acid followed by addition of sulfuric acid, large amounts of precipitate were formed within the reactor coil and therefore blocking repeatedly occurred. This brought into use the addition of a co-solvent for the reaction (Table 4.2).



| Substrate | Co-solvent | Result |
|---------------------------------|-------------|---|
| Benzyl alcohol | Ether | Blockage |
| Benzyl alcohol | Acetic acid | Blockage |
| Benzyl alcohol | Chloroform | $(\text{C}_6\text{H}_4\text{CH}_2)_n$. |
| <i>p</i> -Methyl benzyl alcohol | Chloroform | $(\text{C}_6\text{H}_4\text{CH}_2)_n$. |
| Tri methyl benzyl alcohol | Chloroform | $(\text{C}_6\text{H}_4\text{CH}_2)_n$. |

Table 4.2: Carbonylation attempts using benzylic type substrates. Alcohol (1 eq), H_2SO_4 (excess), Formic acid (20 eq) in a concentration of 0.5 M with a residence time of 30 min at RT.

As shown in Table 4.2 CHCl_3 was shown to be the best solvent for prevention of precipitation as opposed to some the other solvents shown. Due to the harsh conditions solvent options were limited for such reactions. Upon quenching with water a colourless precipitate formed.

Solubility of the precipitate was extremely low, polar solvents such as methanol, acetonitrile and water showed no solvation of the precipitate for NMR studies. Chloroform was able to solvate the compound to some degree and therefore proton NMR could be measured.

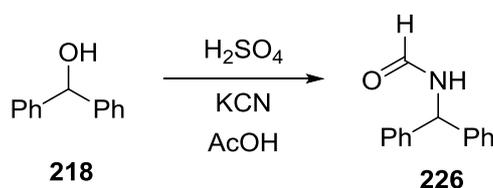
Upon measurement the spectrum showed large broadening of the peaks within the area of the aromatic and benzylic regions implying the benzyl group was intact and not simply decomposed. When referring to the literature^[249] similar conditions were used for another transformation using benzyl alcohols. The addition of sulfuric acid to benzyl alcohols in chloroform has been shown to form polymeric structures of the form $H(C_6H_5CH_2)_n$ arising from the formation of the benzyl cation. NMR data from this work supported the findings as broad peaks were shown within the same regions. Lower concentrations of acid proved to be just as unsuccessful at affording the phenyl acetic acid product with polymerisation occurring. Para methyl benzyl alcohol was further chosen to add a blocking site to the ring to prevent polymerisation through the para position. This unfortunately did not prevent the polymerisation. The original broad peaks were observed with the addition of a broad peak in the region of the methyl group. It was therefore thought that polymerisation could be accomplished through any site of the ring through electrophilic addition. When tested with trimethyl benzyl alcohol no desired products were formed, and thus it was confirmed that benzyl alcohols are unsuitable for Koch-Haaf carbonylations under these conditions.

4.2.2 Carboxylic acids through nitrile formation and hydrolysis

As CO seemed to lack sufficient nucleophilicity to react with previous carbocations it was thought that maybe an isotope of a carboxy group could be used in place. Cyanide is a typical group used in many organic syntheses for introducing a carboxyl group into a molecule by nucleophilic addition. Although like CO it is a useful one-carbon source of addition it has its drawbacks. Cyanide is very toxic and as well as being initially toxic, under these highly acidic conditions the reagents used can easily be protonated to form HCN. HCN is an extremely toxic gas and therefore a sealed continuous flow system is ideally suited for reaction in which it is used, as the gas cannot escape or form large concentrations in a head space.

It was thought that if the addition of the cyanide group to the carbocation was successful under these highly acidic conditions that it would subsequently be hydrolysed to the carboxylic acid. This would be beneficial in two ways. 1. A single-step flow protocol of carboxylic acids from alcohols and 2. the toxic cyanide group would be quenched without being released into the surrounding environment thus making this a relatively safe procedure.

The system was then adapted for this reaction. Formic acid was removed as the solvent of choice for the solvation of the alcohol and substituted with chloroform or acetic acid depending on the cyanide source. Conditions can be seen below in Table 4.3

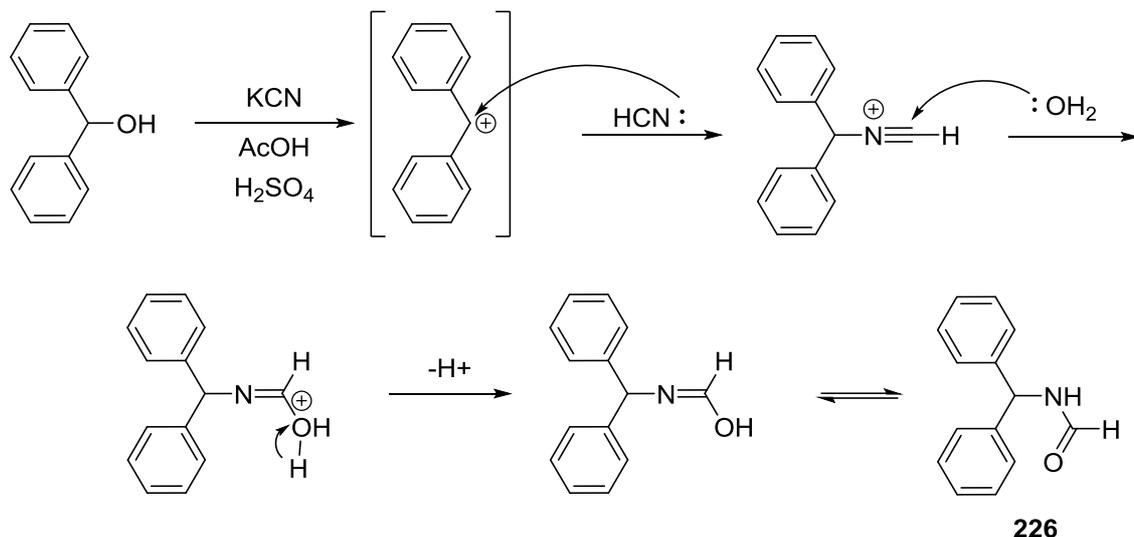


| Cyanide source | Acid | Solvent | Product |
|----------------|-----------------------------------|------------|------------------|
| KCN | H ₂ SO ₄ | AcOH | 226 (54%) |
| TMSCN | BF ₃ .OEt ₂ | Chloroform | 226 (48%) |
| TMSCN | AlCl ₃ | Chloroform | - |

Table 4.3: Conditions used were benzhydrol (1 eq), cyanide source (2 eq) at RT for 20 min residence time.

As shown from Table 4.3 the product of the reaction scheme was not the desired product (**226**) or an intermediate of the product. As with other nitrile sources such as acetonitrile the Ritter product **208** was observed, formation of the formamide. It was concluded that the

cyanide source must still attack the carbocation through the nitrogen opposed to the carbon (Scheme 4.23).

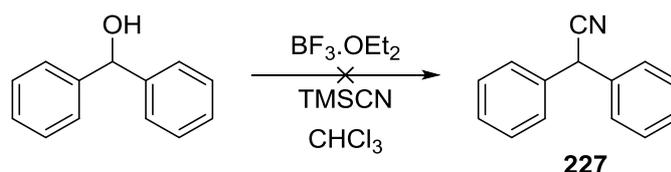


Scheme 4.23: Proposed formamide formation under Ritter conditions from Cyanide sources.

This is likely to be due to the highly acidic conditions of the system, where the large excess of H^+ prevents the formation of a naked ^-CN ion meaning HCN is prevalent. It is therefore more favourable to attack using the nitrogen lone pair, forming the Ritter product upon hydrolysis with water.

To remove this factor a change of conditions were applied under batch condition to search for an improved method. Instead of using Brønsted acids it was thought that using a Lewis acid could prevent the addition through the nitrogen as protonation of the cyanide group would be limited.

The Lewis acid of choice for these studies was chosen to be boron trifluoride diethyl etherate. $BF_3 \cdot OEt_2$ is a very strong Lewis acid and is hence capable of forming carbenium ions from alcohols effectively; it is additionally very soluble in the majority of organic solvents making it an obvious choice for flow chemistry (Scheme 4.24).



Scheme 4.24: Attempted conditions for the Lewis acid catalysed transformation of benzhydrol to **227**.

Benzhydrol was again used for the initial conditions in chloroform using TMS-CN as the cyanide source due to its increased solubility in organic solvent compared to KCN. Formation of the carbocation was prevalent upon addition of the Lewis acid and with subsequent addition of TMS-CN the reaction mixture was monitored by TLC until the starting material had been consumed. It was shown that the Ritter product had again been formed.

It was therefore thought that the governing force behind the reactivity of such a system was down to the characteristics of the electrophile and the nucleophile. As the substituted carbocation is quite a hard electrophile, it prefers to react with hard nucleophiles. In this case the nitrogen of the cyanide group is much harder than the carbanion; therefore addition goes through the nitrogen.

In recent times AF-2400 tubing has been a popular method for introducing gases to solutions within flow chemistry and as mentioned before numerous works have been shown within this area. It was sought to utilise such a system for the Koch-type carbonylations using CO gas as opposed to *in situ* formation where saturation of the solvent would allow for a much larger concentration of CO to counteract the low nucleophilicity. This would therefore allow for alternate dehydration conditions to be used without the use of the Brønsted acid system that previously caused dimerization.

Although this system can still aid in the dehydroxylation of the alcohols, Lewis acids have not been known to dehydrate formic acid to CO therefore *in situ* generation could not be applied to this system.

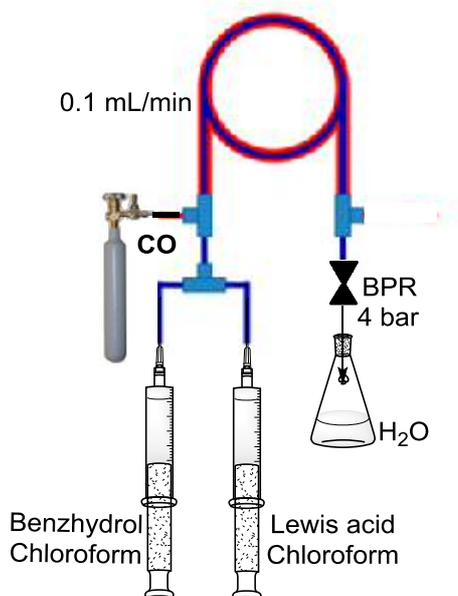
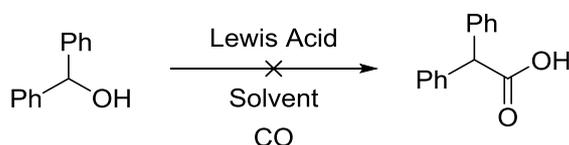


Figure 4.13: AF-2400 tube in tube gastropod for the introduction of CO gas in the carbonylation of benzhydrol derivatives in continuous flow under Lewis acid catalysis.

Using benzhydrol dissolved in chloroform, CO_(g) was introduced under pressure to enrich the solution within the AF-2400 tubing (Figure 4.13). The Lewis acid was then introduced via a second inlet at a mixer to dehydroxylate the alcohol in the presence of a saturated CO solution.



| Solvent | Lewis Acid | Residence time (min) | Yields (%) |
|-----------------|-----------------------------------|-------------------------|---------------|
| Dichloromethane | BF ₃ .OEt ₂ | 20 | N.R |
| Chloroform | BF ₃ .OEt ₂ | 40 | N.R |
| Chloroform | AlCl ₃ | 20 | N.R |
| Chloroform | AlCl ₃ | 40 | N.R |
| Chloroform | T ₃ P | 20 | N.R |

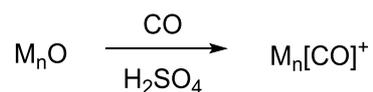
Table 4.4: Lewis acid catalysed Koch type carbonylations using CO gas from gas permeable tubing: Benzhydrol (2 mmol) in solvent (0.8M), Lewis acid (2.2 mmol) in solvent (0.88 M) with 4 bar of CO pressure at a flow rate of 0.1 mL/min. T₃P = Propylphosphonic anhydride

As shown from Table 4.4, when using BF₃.OEt₂ there was no formation of any product. This could be due to lack of interaction with the CO, leading to formation of the starting material

upon quenching with water. When using AlCl_3 similar results were obtained as no acid product was formed and only starting material was recovered. A single trial was performed with propylphosphonic anhydride (T_3P) dehydrating agent in an attempt to form the carbocation. Although T_3P has shown great aptitude in dehydrating for coupling reactions it was not efficient enough to allow for the formation of the carbocation in this case; no colour change was observed, unlike in other methods. Unfortunately due to limited time with the gastropod further conditions could not be trialled.

4.2.3 Metal catalysed Koch-type carbonylations

Due to the poor results when using traditional Koch-type conditions, it was believed that using a metal would benefit the reaction extensively. As shown from many industrial and laboratory procedures a large amount of work has been developed in the area of metal-catalysed carbonylations. Traditional methods that use a leaving group for oxidative insertion have shown to be very successful notably in the Monsanto process, but a hydroxyl is a very poor leaving group and it is difficult for metals to insert into the carbon-oxygen bond. Also with conditions such as highly acidic media dehydration occurs forming a carbocation. This then does not allow for oxidative insertion. A different class of metals have been used for the carbonylation of carbocations most notably from the work of Souma. Silver and copper oxides have been shown to be very useful for capture of CO gas and therefore have been reported as useful for Koch-type carbonylations (Scheme 4.25).



Scheme 4.25: Scavenging of CO_(g) into solution using transition metal with +1 oxidation state.

The method demonstrated the formation of a M_n[CO]⁺ complex formed *in situ* by bubbling CO gas through a solution of metal oxide dissolved in concentrated sulfuric acid. With the pre-catalyst formed and with addition of the alcohol carbonylation occurs. It is thought that as the metal captures the CO it can be in a higher concentration within the acid solution and upon dehydration to the carbocation the nucleophile is then readily available. It was decided that this could similarly help the case when using it within our system.

Two paths were devised: capture of CO *in situ* by formation upon dehydration of formic acid and preformation by bubbling into the acid solution followed by introduction to the alcohol.

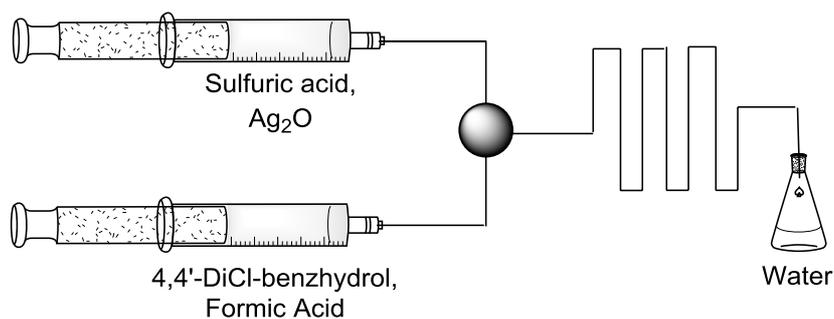
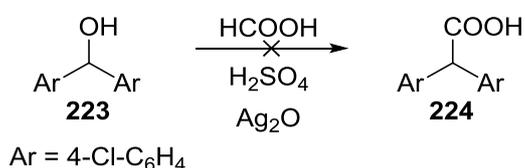


Figure 4.14: Proposed set-up for scavenging *in situ* formed CO gas using Ag^+ ions in concentrated H_2SO_4 .

The first system consisted of very similar conditions to the conditions of Ryu^[234] but with addition of a metal salt dissolved in the H_2SO_4 . (Figure 4.14, Scheme 4.26)



Scheme 4.26: Proposed reaction conditions for the Koch-Haaf reaction of alcohol **223** to acid **224** using silver oxide as a CO scavenger.

The reaction was then run in the same manner and the reaction mixture collected upon quenching with water. Although copper (I) showed a stronger ability to coordinate to CO than silver (I) it was shown to be completely inapplicable for flow chemistry due to the poor solubility in concentrated H_2SO_4 . Using silver (I) oxide (50 mol%) dissolved in H_2SO_4 were the chosen conditions for the first trial using the 4,4' dichlorophenyl methanol derivative. It was shown after analysis by NMR of the crude material that the acid product had not been produced although a mixture and the di-(4,4'-dichlorobenzhydryl) ether had been formed along with decomposition. Again this is likely due to the lack of $\text{CO}_{(g)}$ in solution therefore this method did not improve the concentration of gas in solution.

The second method was trialed in parallel. Formation of the pre-catalyst was prepared via the previously reported method of solvation of the metal catalyst in sulfuric acid and bubbling CO gas into the chamber. An *in situ* generation of CO was used in a second chamber attached to the catalyst chamber by a cannula. Formic acid was added slowly to a concentrated sulfuric acid and the evolved gas was then transferred to the first chamber via the cannula with an escape needle for safety (Figure 4.15).

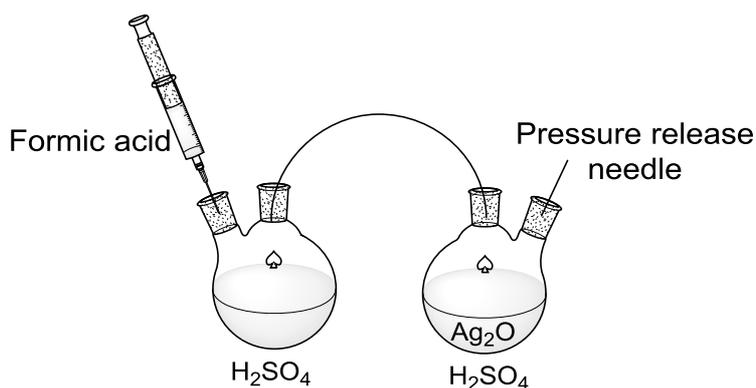
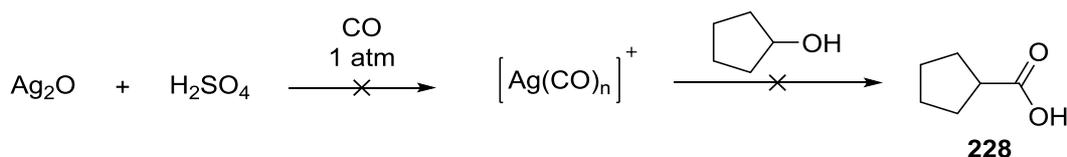


Figure 4.15: Method of introduction of CO gas for absorption onto M⁺ in highly acidic media.

Batch studies were first attempted by dropwise addition of the alcohol to the preformed solution, before being stirred for the designated time Table 4.4. A number of reaction times and absorption times were trialled in order to allow for formation of the carboxylic acid product **210**. Cyclopentanol was chosen as the substrate to test the system as this had already been reported in similar work (Scheme 4.26).^[243]



Scheme 4.26: Reaction scheme for batch carbonylation of cyclopentane carboxylic acid. Ag₂O (0.5 eq), H₂SO₄ (10 mL), cyclopentanol (1 eq) at RT.

| CO absorption time (hrs) | Reaction time (hrs) | Yield (%) |
|--------------------------|---------------------|-----------|
| 1 | 1 | N.R |
| 1 | 2 | N.R |
| 2 | 2 | N.R |

Table 4.5: Batch attempts of Koch type carbonylations of cyclopentanol in the presence of Ag₂O (0.5 eq) dissolved in concentrated H₂SO₄ (Xs).

As shown in Table 4.5 this method was unsuccessful in introducing the CO gas into solution. Although absorption time was much longer than in the reported publication no formation of the carboxylic acid product was observed. Decomposition products with some starting material were recovered upon quenching with crushed ice. By changing the source of CO to a lecture bottle a cleaner source of CO could be introduced. This also allowed for evacuation of the flask to remove all air and moisture. By evacuating the air, balloons could be filled with CO and introduced to the evacuated flask thus creating a CO atmosphere in the flask. The solution

was stirred vigorously to allow for solvation of the CO atmosphere into the solution of H₂SO₄ containing Ag₂O (50 mol%). The solution was stirred overnight under atmospheric pressure of CO in order to allow for enough CO to be absorbed through equilibrium. On addition of the cyclopentanol the deep colour change occurred as associated with carbocation formation. Although the solution was allowed to stir for considerably longer than the reported procedure no formation of acid was detected and again it was thought that formation of the complex had not been successful. Unlike the previous method where a large volume of CO was bubbled through the solution, due to equipment limitations this could not be replicated to the same degree. It was therefore thought that as no formation of the acid product was observed then that the detrimental factor could be the low concentration of CO in solution.

4.2.4 Concluding remarks to Koch chemistry and future work

Due to time constraints the project was ended without further investigations. The work showed that diylalcohols are difficult substrates to perform the Koch-Haaf reaction with, where high concentrations or stronger nucleophiles are needed to react. By using the flow methods devised in previous Koch-type reactions, the systems struggled with large formations of gas therefore multiple methods were devised to alleviate this problem. Using AF-2400 tubing resulted in much more consistent flow regimes as pressure within the tubing was released although this likely resulted in much lower concentrations within solution and in the tubing. This promoted formation of side products or reformation of starting material. Using CO scavengers resulted in no formation of the product where as shown in the batch conditions a large volume of CO is needed to form the initial pre-catalyst in solution.

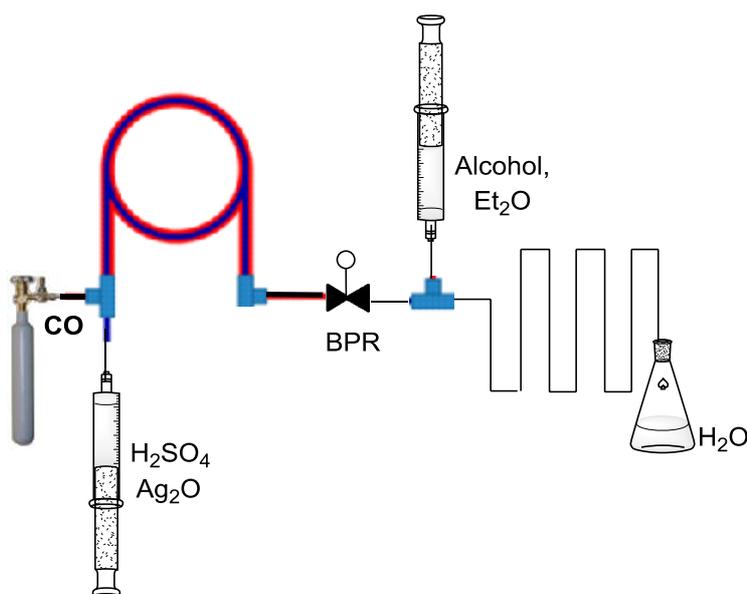


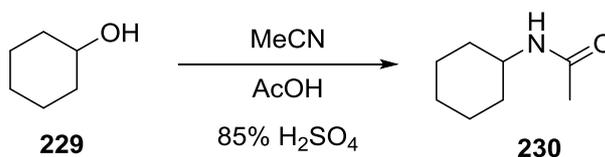
Figure 4.16: Set-up for Koch-Haaf carbonylations for future studies.

If the investigation was allowed to advance further it would likely result in the use of acid resistant back pressure regulators and HPLC pumps. This would allow for the containment of CO gas either within solution or controlled segmented flow. Furthermore by using the AF-2400 tubing to saturate the H₂SO₄ solution containing one of the CO scavenging metals such as Ag(I) the concentration of CO could circumvent the mixing problems that lead to dissolution of the CO_(g) and therefore prevent side reactions and potential dimerization (Figure 4.16).

5.1 Introduction to Ritter reactions

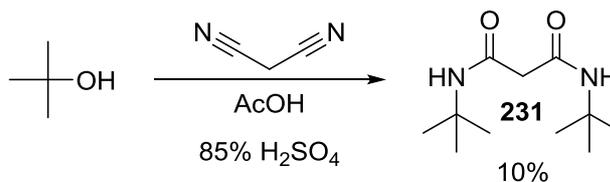
The Ritter reaction is the formation of amides,^[250,251] from the addition of nitriles to carbocations, and has a commonality with the Koch type reaction. The formation of the carbocation comes from dehydration of alcohols or protonation of alkenes and serves as a useful synthetic protocol for the synthesis of many amide containing products. Many works have been established in the last decade where catalysts, substrates and reaction media have been extended.^[252,253] Although this is the case in batch, only a few publications have been presented in continuous flow.^[254,255] The characteristics of the reaction conditions lend themselves to being used in continuous flow due to the highly exothermic nature of the reaction. The huge increase in surface-to-volume ratio created allows for considerably less need for cooling as within typical batch conditions, and therefore reaction times can be slashed. This is particularly apparent when moving to large scale synthesis as mentioned in previous chapters.

As mentioned, little has been demonstrated of the Ritter reaction in flow. Wirth *et al.*^[254,255] showed that alkyl type alcohols (**229**) and alkenes could be used to form a multitude of amides (**230**) from simple nitrile sources such as MeCN and EtCN in very good yields at 45 °C in 3 mins in their first publication (Scheme 5.1).



Scheme 5.1: Ritter condition demonstrated by Wirth *et al.* using cyclohexanol and acetonitrile.

This was later followed up with work that showed that the reaction system was not just limited to simple nitriles and even nitriles such as malononitrile could be used to form the diamide product **231** in 10% yield at 45 °C in 6 min (Scheme 5.2).



Scheme 5.2: Ritter reaction in flow of malononitrile and t-butanol by sulphuric acid.

5.2 Results and Discussion

As shown within the Koch type reactions when using acetonitrile with benzyl type alcohols the Ritter products were observed. As within the previous work within Ritter reactions in flow only one benzylic type substrate had been used and it was thought that this could be explored. Using conditions similar to that reported with benzhydrol 4-methylbenzyl alcohol was subjected to the Ritter conditions.

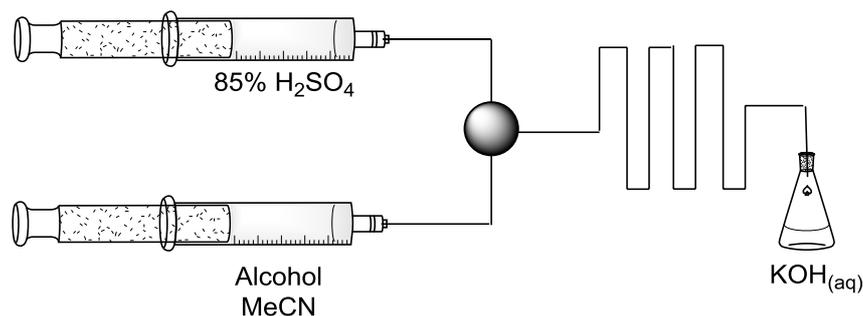
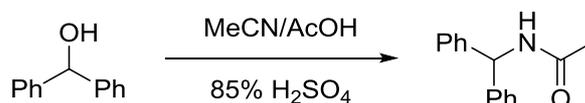


Figure 5.1: Schematic for the proposed Ritter reactions in flow.

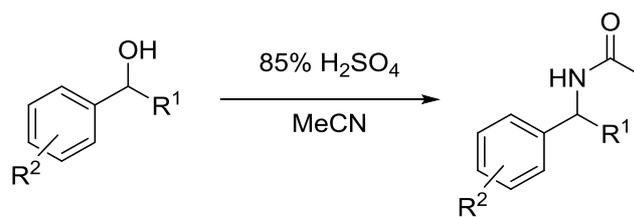
Initial conditions run at room temperature resulted in a very good yield using MeCN as the solvent (Figure 5.1). Decreasing the equivalents of MeCN using AcOH as the solvent resulted in a drastic drop in yield.



| Acetonitrile | Yield (%) |
|--------------|-----------|
| 5 mL | 80 |
| 1eq | 22 |
| 10 eq | 65 |

Table 5.1: Screening of nitrile equivalents for the Ritter reaction in flow. benzhydrol (2 mmol) in nitrile/AcOH (5 mL), sulfuric acid (5 mL) at room temperature for 30 min of residence time.

Once the conditions in flow had been found a small substrate scope was trialled as shown in Table 5.2 below.



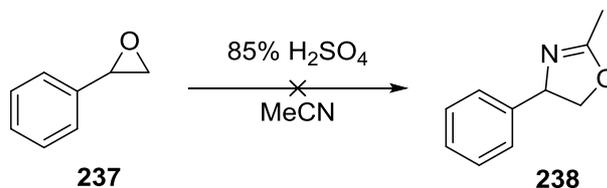
| Substrate | Product | Yield (%) |
|-----------------------------|----------------|---------------|
| 4-methylbenzylalcohol | 232 | 80 |
| 1-phenylethanol | 233 | 87 |
| di-p-tolylmethanol | 234 | 76 |
| bis(4-fluorophenyl)methanol | 235 | 74 |
| 2-phenyloxirane | 236 | Decomposition |

Table 5.2: Substrates used in the Ritter reaction in flow. Alcohol (2mmol) in nitrile (5 mL), sulfuric acid (5 mL) at room temperature for 30 min of residence time.

As shown from table 5.2 the yields of the Ritter products were generally good in all cases. The compound **232** was produced in good yield (80%). Secondary alcohols proved to work well as shown by the yield of **233** and furthermore the diarylamides **234** and **235** both showed

excellent yields with the electron rich and poor substituents. As shown, the stabilised nature of these substrates did not affect the overall yields of the reaction where very good yields were obtained throughout.

The reaction involving 2-phenyloxirane using the same Ritter conditions above resulted in a complex mixture of side products with no formation of the dihydrooxazole in Scheme 5.3.



Scheme 5.3: Ritter-type reaction of styrene epoxide using previously optimised conditions.

5.2.1. Conclusion

As shown by previous work by Wirth *et al* flow chemistry lends itself very well to the Ritter reaction, as the exothermic nature of the reaction is easily controlled by the large surface-to-volume ratio. This chapter looked to show that this chemistry is not just limited to alkyl alcohols. It was shown that benzyl alcohols lend themselves very well to the addition of acetonitrile under Ritter conditions. Reaction times were shown to be still quick with very good yields throughout.

Although attempted, the Ritter reaction to form the dihydrooxazole of 2-phenyloxirane was unsuccessful while only one trial was made, if sufficient time was allowed this could be a viable route to the formation of a large library of dihydrooxazole derivatives.

6. Supporting Information

6.1 General Methods

The reactions were carried out using standard laboratory equipment. Air and/or moisture sensitive experiments were performed under an inert atmosphere of argon and with flame dried glassware. All batch reactions were stirred by magnetic stirring, unless stated and when needed warmed to defined constant temperatures by hotplates with temperature probe control in dry heating blocks or silicone oil baths. Reactions performed in-flow were carried out on PTFE tubing (0.5 and 0.8 mm i.d.) using syringe pumps. Reactions performed at low temperatures were stirred in reaction vessels in a dry ice/acetone bath ($-78\text{ }^{\circ}\text{C}$), acetonitrile/dry ice bath ($-40\text{ }^{\circ}\text{C}$), ice/NaCl bath ($-15\text{ }^{\circ}\text{C}$), or ice/water ($0\text{ }^{\circ}\text{C}$). Rotary evaporators Büchi B-461, B-481 or B-490 were used for solvent evaporations (reduced pressure to 15 mbar); further drying was undertaken by the use of a high vacuum apparatus. A Büchi GKR-50 Kugelrohr distillation apparatus was employed for Kugelrohr distillations. For inert reactions, solvents were obtained from a solvent purification system and under inert atmosphere. Other chemicals were purchased from Acros, Aldrich, Alfa Aesar or Fluka and were used without further purification, except if indicated otherwise in the experimental procedure.

6.2 Chromatographic Methods

6.2.1 Thin Layer Chromatography

All reactions that were monitored by thin-layer chromatography (TLC) were performed on precoated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualised by UV radiation or by staining with ceric ammonium molybdate solution (CAM), potassium permanganate solution or iodine.

6.2.2 Column Chromatography

Column chromatography was performed with silica gel 60 (Merck, 230-400 mesh) under increased pressure (Flash Chromatography) or Biotage chromatography system using kp-sil.columns or biotage ultra silica columns.

6.2.3 High Pressure Liquid Chromatography (HPLC)

For HPLC measurements an arrangement from Shimadzu was used. The Shimadzu Class VP consisted of SIL-10ADVP (auto injector), LC-10 ATVP (liquid chromatograph), FCV-10ALVP (pump), DGU-14A (degasser), CTO-10ASVP (column oven), SCL-10AVP (system controller) and a SPD-M10A (diode array detector). The only solvents used were hexane and 2-propanol (both of HPLC grade purity, Fisher Scientific). Analytical chiral column *Chiracel*[®] *OD-H* (0.46 cm \varnothing x 25 cm) was used for separation of enantiomers at solvent flow rates of 0.5 ml/min.

6.3 Physical data characterisation techniques

6.3.1 ¹H NMR Spectroscopy

For NMR characterisation the Bruker DPX 600 (600 MHz), Bruker DPX 500 (500 MHz), Bruker DPX 400 (400 MHz), Bruker DPX 250 (250 MHz) or Oxford 300 were used. The chemical shifts δ are given in ppm downfield of tetramethylsilane ($\delta = 0$ ppm). Compounds and crude reaction mixtures were dissolved in either deuterated chloroform, deuterated acetone or deuterated dimethylsulfoxide. Coupling constants (J) are given in Hertz. The multiplicity of signals is designated: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dt = doublet of triplets, td = triplet of doublets, m = multiplet. Residual solvent peaks are assigned as follows: 7.26 ppm for chloroform, 2.54 ppm for dimethylsulfoxide, 2.05 ppm for acetone.

6.3.2 ¹³C NMR Spectroscopy

For NMR characterisation the Bruker DPX 500 (125 MHz), Bruker DPX 400 (100 MHz), Bruker DPX 250 (62.5 MHz) were used. The chemical shifts δ are given in ppm downfield of tetramethylsilane ($\delta = 0$ ppm). Compounds and crude reaction mixtures are dissolved in either deuterated chloroform, deuterated acetone or deuterated dimethylsulfoxide. Residual solvent peaks are assigned as follows: 77.4 ppm for chloroform, 40.5 ppm for dimethylsulfoxide, 29.8 ppm and 206.3 ppm for acetone.

6.3.3 Mass Spectrometry

Cardiff: Water LCR Premier XE-tof. Mass spectrometric measurement has been performed by the R. Jenkins/R. Hick at Cardiff University. Ions were generated by Electron Ionisation (EI). The molecular ion peaks values quoted for either molecular ion (M+), molecular ion plus hydrogen (M+H+)

6.3.4 IR Spectroscopy

IR spectra were recorded on a Perkin Elmer 1600 series FTIR (neat). Wavenumbers are quoted in cm^{-1} .

6.3.5 Melting Points

Melting Points were measured using a Gallenkamp variable heater with samples in open capillary tubes. All melting points are uncorrected.

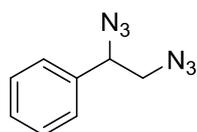
6.41 Experimental for diazidation of styrenes

General procedure for diazidation of styrenes in flow

Syringe A containing styrene (1.0 mmol), NaN_3 (2.5 mmol), made up to 2 mL with AcOH was placed in a syringe pump and connected to a reactor coil via a luer lock. Syringe B containing iodosylbenzene (1.5 mmol) dissolved in AcOH (2 mL) was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 60 min residence time within the reactor coil (1.0 mL, 0.8 mm I.D) at 50 °C, in a heated water bath. The mixture was quenched into saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution to allow for an accurate residence time once steady state had been reached. One residence volume was collected of 1 mL. The resulting mixture was dissolved into Et_2O (5 mL). The organic solution was washed with saturated NaHCO_3 (10 mL) and brine (10 mL). The organic solvent was then evaporated. The resulting mixture was then purified by Biotage column chromatography using a 10 g ultra Biotage column and a gradient of 0-15% EtOAc in hexane over 10 column volumes.

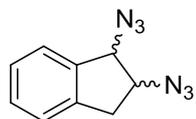
Yields were calculated by collecting a volume for a set time. This in combination with the flow rate of the reaction can then allow for the calculation of the moles of the starting material used within the volume collected. Therefore the yield is calculated from the theoretical full conversion of the used starting material from that volume. This is therefore used to calculate all flow method yields.

1,2-Diazido-1-phenylethane 118



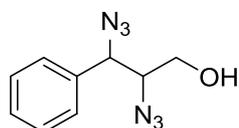
As a yellow oil (34 mg, 72%): $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 7.32-7.43 (m, 5H), 4.67 (dd, J = 7.8, 5.5 Hz, 1H), 3.46-3.51 (m, 2H) ppm; $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 136.3, 128.9, 128.8, 126.7, 65.6, 55.9 ppm. IR (neat): ν 2094, 1493, 1454, 758.0, 698.2 cm^{-1} . The spectroscopic data are within agreement of the literature.^[256]

1,2-Diazidoindane 125



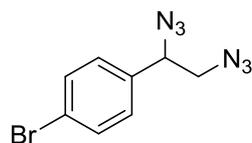
As a yellow oil (32 mg, 64%): A mixture of Syn:Anti 1:1: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.23-7.42 (m, 4H), 7.23-7.42 (m, 4H), 4.82 (d, J = 5.7 Hz, 1H), 4.76 (d, J = 5.6 Hz, 1H), 4.29 (dd, J = 12 Hz, 6.7, 1H), 4.16 (dd, J = 12 Hz, 6.7, 1H), 3.35 (dd, J = 16 Hz, 6.8, 1H),), 3.17 (d, J = 6.7 Hz, 2H), 2.94 (m, 2H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 139.6, 138.9, 137.7, 137.5, 129.6, 129.4, 127.6, 127.2, 125.2, 124.8, 124.2, 124.5, 70.3, 67.6, 66.9, 63.9, 36.0, 35.5 ppm. IR (neat): ν 2090, 1319, 1257, 754, 704, 533 cm^{-1} . The spectroscopic data are within agreement of the literature.^[256]

2,3-Diazido-3-phenylpropan-1-ol 130



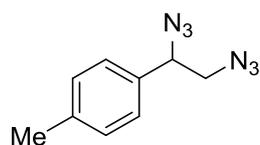
As a yellow oil (33 mg, 61%): A mixture of Syn:Anti 1:1: $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.36-7.43 (m, 5H), 4.68 (d, J = 9 Hz, 2H), 3.54-3.81 (m, 5H), 3.32-3.42 (m, 1H) ppm; $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ = 135.9, 135.8, 129.2, 129.1, 127.8, 127.5, 67.8, 67.0, 66.8, 65.6, 62.3, 62.2 ppm. IR (neat): ν 2098, 1608, 1213, 1178 cm^{-1} . The spectroscopic data are within agreement of the literature^[256]

1,2-Diazido-1-(4-bromophenyl)ethane 127



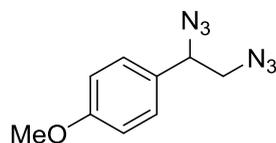
As a yellow oil (42 mg, 64%): $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.32-7.43 (m, 4H), 4.64 (dd, $J = 8.0, 5.6$ Hz, 1H), 3.34-3.54 (m, 2H) ppm; $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta = 158.8, 157.3, 128.8, 126.7, 94.1, 55.9$ ppm. IR (neat): $\nu 2091, 1381, 1257, 858, 690\text{ cm}^{-1}$. The spectroscopic data are within agreement of the literature.^[256]

1,2-Diazido-1-(4-methylphenyl)ethane 128



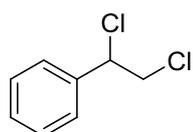
As a yellow oil (41 mg, 76%): $^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.22$ (s, 4H), 4.64 (dd, $J = 8.2, 5.1$ Hz, 1H), 3.4-3.5 (m, 2H), 2.37 (s, 3H) ppm; $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta = 139.6, 133.8, 130.2, 127.5, 65.9, 56.4$ ppm. IR (neat): $\nu 2098, 906, 725, 702\text{ cm}^{-1}$. The spectroscopic data are within agreement of the literature.^[256]

1,2-Diazido-1-(4-methoxyphenyl)ethane 129



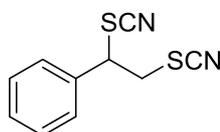
As a yellow oil (41 mg, 76%): $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta 7.26$ (d, $J = 8.3$ Hz, 2H), 6.93 (d, $J = 8.3$ Hz, 2H), 4.63 (dd, $J = 8.1, 5.2$ Hz, 1H), 3.82 (s, 3H), 3.42 (qd, $J = 8.1, 5.2$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): 160.0, 128.3, 128.2, 114.4, 65.0, 55.8, 55.3 ppm. IR (neat): $\nu 2102, 1514, 1255, 904.6, 725.2\text{ cm}^{-1}$. The spectroscopic data are within agreement of the literature.^[257]

Synthesis of (1,2-dichloroethyl)benzene 131



To a stirred solution of ICl_3 (277 mg, 1.20 mmol) in anhydrous CH_2Cl_2 (5 mL) was added styrene (115 μL , 1 mmol) at $-10\text{ }^\circ\text{C}$. The solution was stirred for 30 min at room temperature after addition and quenched with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) and extracted with EtOAc (2×10 mL). The combined extracts were dried over MgSO_4 and evaporated to give **131** as a colourless liquid (140 mg, 80%). $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 7.22$ (m, 5H), 5.01 (dd, $J = 7.8, 6.6$ Hz, 1H), 4.01 (dd, $J = 11.3, 6.6$ Hz, 1H), 3.94 (dd, $J = 11.3, 7.8$ Hz, 1H) ppm; $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): $\delta = 138.0, 129.1, 128.8, 127.4, 61.8, 41.3$ ppm. The spectroscopic data are within agreement of the literature.^[258]

Synthesis of (1,2-dithiocyanoethyl)benzene **137**



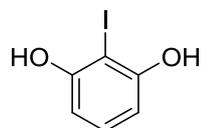
Syringe A containing styrene (1.0 mmol), NaN_3 (2.5 mmol) and MSCN (2.5 mmol) made up to 2.5 mL with AcOH was placed in a syringe pump and connected to a reactor coil via a luer lock. Syringe B containing oxidant (1.5 mmol) dissolved in AcOH (2.5 mL) was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 30 min residence time within the reactor coil (1.0 mL, 0.8 mm I.D) at $45\text{ }^\circ\text{C}$ (in a heated water bath). The mixture was quenched into saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) to allow for an accurate residence time once steady state had been reached. 2 mL of reaction mixture was collected.

| Oxidant | MSCN source | Mass /Yield(%) |
|-----------------|-------------------------|----------------|
| NaIO_4 | KSCN | 24 mg /27% |
| NaIO_4 | NH_4SCN | 30 mg /34% |
| DIB | KSCN | 18 mg /22% |
| Iodosyl | KSCN | 16 mg /17% |

As a yellow liquid $^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.22$ (m, 5H), 4.68 (dd, $J = 7.2, 4.1$ Hz, 1H), 3.54-3.69 (m, 2H) ppm. $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta = 135.6, 130.0, 129.5, 127.7, 111.1, 53.4, 29.9$ ppm. IR (neat): ν 2154, 1494, 1452, 1166, 1126, 1022, 869.9, 779.2, 694.4, 673.2, 582.5, 555.5 cm^{-1} . The spectroscopic data are within agreement of the literature.^[132]

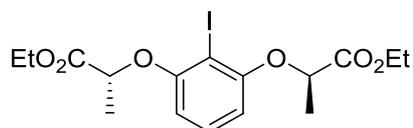
Synthesis of chiral hypervalent iodine reagents

2-Iodoresorcinol **120**



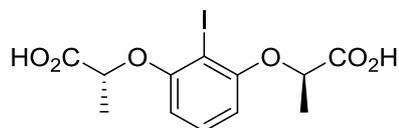
Compound **120** was synthesised using a previously reported procedure^[259]: resorcinol (5.5 g, 50 mmol) were added water (50 mL), iodine (13.6 g, 53 mmol), and NaHCO₃ (4.7 g, 56 mmol), and the mixture was stirred at room temperature for 20 min. After the reaction, the remaining iodine was quenched with aqueous sodium thiosulphate. The product was extracted with ether, the extracts were concentrated under reduced pressure, and the residue purified by column chromatography on silica gel with CH₂Cl₂/hexane (5/95) as eluent. 2-Iodoresorcinol was obtained as a colourless solid, (7.7 g, 65%): mp 101.2-104.0 °C [Lit^[259] mp 105-108 °C]; ¹H-NMR (400 MHz, CDCl₃): δ = 6.32 (d, *J* = 8.0 Hz, 2H), 6.91 (t, *J* = 8.0 Hz 1H), 10.1 (s, 1H) ppm.

(2*R*, 2'*R*)-Diethyl 2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropionate **121**



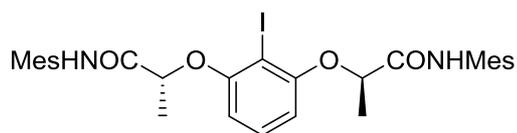
To a solution of 2-iodoresorcinol **120** (2.36 g, 10.0 mmol), PPh₃ (6.56 g, 25.0 mmol) and (-)-lactic acid ethyl ester (2.80 mL, 25.0 mmol) in THF (50 mL). DIAD (1.9 M in toluene, 13.2 mL, 25 mmol) was added slowly at 0 °C. The reaction was allowed to warm to room temperature while stirring overnight. The resulting mixture was then concentrated under vacuum before removal of triphenylphosphine oxide by re-dissolving in cold ether, filtering and again evaporated. The residue was purified by flash column chromatography on silica gel (eluent: hexane-EtOAc, 15:1) to give **121** as a colourless solid (2.70 g, 62%). ¹H-NMR (400 MHz, CDCl₃): δ = 7.14 (t, *J* = 8.2 Hz, 1H), 6.38 (d, *J* = 8.2 Hz, 2H), 4.75 (q, *J* = 6.8 Hz, 2H), 4.19 (dq, *J* = 7.1, 1.7, 4H), 1.68 (d, *J* = 6.8 Hz, 6H), 1.23 (t, *J* = 7.1 Hz, 6H) ppm. [α]_D²⁰ = -20.0 (c = 1.2, CHCl₃) (lit.^[260][α]_D²⁰ = -21.0 (c = 1.2, CHCl₃)). The spectroscopic data are within agreement of the literature^[260]

(2*R*, 2'*R*)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)dipropionic acid **122**



To a solution of **121** (2.6 g, 6.0 mmol in THF:MeOH (1:1, 40 mL) was added 2 N NaOH (20 mL) and the resulting mixture stirred at rt for 16 h. This was then cooled to 0 °C and quenched to pH 1 using 1 N HCl. The reaction was allowed to warm to room temperature while stirring for 16 h. The resulting mixture was then extracted by EtOAc (3 × 25 mL), the combined extracts were dried over MgSO₄ and concentrated under vacuum to give compound **122** which was used immediately without further purification.

(2*R*, 2'*R*)-2,2'-(2-iodo-1,3-phenylene)bis(oxy)bis(*N* mesitylpropanamide) **123**

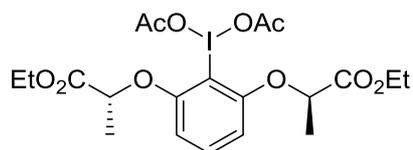


Compound **122** (2.0 g, 5.3 mmol) in SOCl₂ (6.0 mL, excess) was refluxed for 1 h. Benzene (10 mL) was added to the cooled mixture and the excess SOCl₂ was removed under vacuum. The residue was then dissolved in CH₂Cl₂ (25 mL) with the addition of mesityl amine (1.66 mL, 11.6 mmol) at 0 °C. The mixture was stirred at this temperature for 2 h before being allowed to warm to room temperature for 16 h. The resulting mixture was poured in to 1 N HCl, extracted with CHCl₃ (2 × 25 mL) and the combined extracts were dried over MgSO₄. The solution was evaporated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: CHCl₃:EtOAc, 4:1) to give **123** (3.36 g, 81% yield) as a colourless solid mp. 230-232 °C (lit.^[261] mp 231-233 °C) ¹H-NMR (400 MHz, CDCl₃): δ = 1.78 (d, *J* = 6.7 Hz, 6H), 2.15 (s, 12H), 2.27 (s, 6H), 5.01 (q, *J* = 6.7 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.3 Hz, 1H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ = 21.2, 55.7, 65.3, 126.8, 129.7, 133.2, 138.8 ppm. [α]_D = -118.0 (c = 1.01, CHCl₃). (lit.^[260] [α]_D = -121.0 (c = 1.01, CHCl₃)). The spectroscopic data are within agreement of the literature^[260]

General oxidation procedure for chiral iodine reagents to hypervalent iodine reagents

Aryl iodide (0.2 mmol) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate [Selectfluor[®]]) (354 mg, 1 mmol) were dissolved in AcOH (2mL) and CH₃CN (6.4 mL) and stirred at rt for 16 h. The solvents were evaporated under vacuum and water (100 mL) was added to the residue. The resulting suspension was then extracted with CH₂Cl₂ (3 × 50 mL) and the combined extracts were washed with water (25 mL). The extracts were dried over MgSO₄ and the solvents removed under vacuum to give the hypervalent reagents.

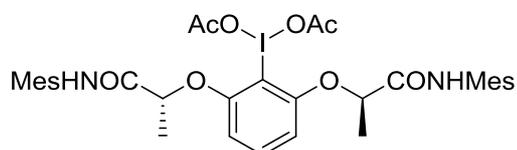
(2*R*, 2'*R*)-Diethyl 2,2'-{2-(diacetoxy)iodo-1,3-phenylene}bis(oxy)}dipropionate **121b**



Compound **121b** was made *in situ* prior to diazidation reaction using the method above.

¹H-NMR (400 MHz, CDCl₃): δ = 7.32 (t, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 2H), 4.77 (q, *J* = 6.8 Hz, 2H), 4.14 (q, *J* = 7.4, 4H), 1.91, (s, 6H), 1.61 (d, *J* = 6.8 Hz, 6H), 1.18 (t, *J* = 7.4 Hz, 6H) ppm. The spectroscopic data are in agreement with the literature.^[261]

(2*R*, 2'*R*)-2,2'-{2-(diacetoxy)iodo-1,3-phenylene}bis(oxy)}bis(oxy)bis(*N* mesitylpropanamide) **124**



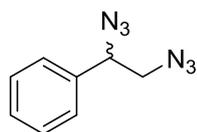
Compound **124** was made *in situ* prior to reaction using the method above.

¹H-NMR (400 MHz, CDCl₃): δ = 9.91 (s, 2H), 7.57 (t, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.79 (s, 4H), 5.15 (q, *J* = 6.7 Hz, 2H), 2.21 (s, 6H), 2.10 (bs, 12H), 1.88 (d, *J* = 6.7 Hz, 6H), 1.49 (s, 6H) ppm. The spectroscopic data are in agreement with the literature.^[261]

General procedure for chiral diazidation reactions

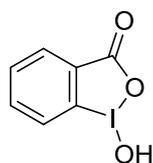
The chiral iodine reagent (0.1 mmol) was placed in a flask with Selectfluor® (177 mg, 0.5 mmol) in AcOH (1 mL) and MeCN (3.2 mL). The mixture was stirred at room temperature overnight (16 h). The solvents were evaporated under vacuum and the residue was suspended in water (25 mL). The resulting suspension was extracted with CH₂Cl₂ (3 × 25 mL) the extracts were dried over MgSO₄ and again concentrated under vacuum. The residue was then re-dissolved in CH₂Cl₂ (1 mL) and cooled to -40 °C. Once the temperature had been reached, TMSN₃ (29 mg, 0.25 mmol) was added and stirred for 5 min. Once the solution had become yellow the styrene (0.05 mmol) was added and allowed to warm to room temperature over 6 h. The resulting solution was then quenched into saturated Na₂S₂O₃ (2 mL) and extracted with CH₂Cl₂ (4 mL). The organic layer was dried over MgSO₄ and evaporated. The residue was then purified by Biotage column chromatography using a 10 g ultra Biotage column and a gradient of 0-15% EtOAc with hexane over 10 column volumes. The chiral compound was resolved using an OD-H chiral column 5% IPA to hexane at a flow rate of 0.1 mL/min at 20 °C. Retention times 1st: 35 min; 2nd::42 min

1,2-Diazido-1-phenylethane 118



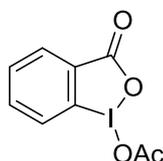
As a yellow oil (15 mg, 35%): ¹H-NMR (300 MHz, CDCl₃): δ = 7.32-7.43 (m, 5H), 4.67 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.46-3.51 (m, 2H) ppm; ¹³C-NMR (75 MHz, CDCl₃): δ = 136.3, 128.9, 128.8, 126.7, 65.6, 55.9 ppm. IR (neat): ν 2094, 1493, 1454, 758.0, 698.2 cm⁻¹. The spectroscopic data are within agreement of the literature.^[256]

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one



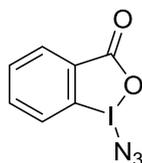
Following a reported procedure^[262], NaIO₄ (4.4 g, 20.2 mmol) and 2-iodobenzoic acid (5.0 g, 20.2 mmol) were suspended in 30% (v:v) aq. AcOH (90 mL). The mixture was vigorously stirred and left to reflux for 4 h. The resulting mixture was diluted with cold water (30 mL) and allowed to cool to room temperature. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 15 mL) and acetone (3 x 15 mL), and air-dried in the dark to give the pure product. (4.77 g, 17.7 mmol, 85% yield, reported 92%) as a colourless solid Decomposition at 263 °C, (Lit^[262] mp 260 °C). ¹H NMR (400 MHz, (CD₃)₂SO): 8.02 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.97 (m, 1H), 7.85 (dd, *J* = 8.2, 1 Hz, 1H), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H) ppm. NMR data correspond to the reported values.^[262]

1-Acetoxy-1,2-benziodoxol-3-(1H)-one



Using the reported procedure^[262], compound **100** (4.5 g, 18.3 mmol) was heated in Ac₂O (10 mL) to reflux until the solution turned clear (without suspension). The mixture was then left to cool down to induce crystallization. The crystallization was continued at -18 °C. The crystals were then collected via filtration and dried under high vacuum to give compound **101** as white crystalline solid (4.0 g, 13.1 mmol, 85% yield) m.p 161-163 °C [Lit^[263] mp 162-165 °C]; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.00 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.92 (dt, *J* = 7.0, 1.7 Hz, 1H), 7.71 (td, *J* = 7.6, 0.9 Hz, 1H) ppm. NMR data correspond to the reported values.^[262]

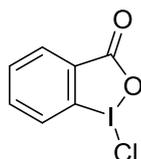
1-azido-1,2-benziodoxole-3-(1H)-one



Using the reported procedure,^[112] **101** (1.6 g, 5.2 mmol) in dry CH₂Cl₂ (4.5 mL) TMSN₃ (1.1 mL, 7.9 mmol) was then added. TMSOTf (4.7 μL, 0.03 mmol) was added last to the mixture which was then stirred for 30 minutes. The reaction mixture was then dried in vacuo to give a yellow precipitate, which was washed a few times with hexanes to give compound **102** (900 mg, 31.1

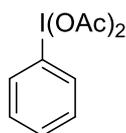
mmol, 60% yield) as a pure pale yellow crystals. ^1H NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$, 20:1) δ 8.32(d, $J = 8$ Hz, ArH, 1H), δ 8.05 (m, ArH, 2H), δ 7.85 (t, $J = 8$ Hz, ArH, 1H) ppm. ^{13}C NMR ($\text{CDCl}_3/\text{CF}_3\text{COOH}$, 20:1) δ 171.1, 137.3, 128.7, 126.7, 126.6, 118.8, 117.7 ppm. NMR data correspond to the reported values^[112]

1-chloro-1,2-benziodoxole-3-(1H)-one



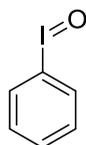
Using the reported procedure,^[264] concentrated HCl (50 mL) was added dropwise over 2 h to a stirred solution of 2-iodobenzoic acid (6.2 g, 25 mmol) and NaClO_2 (8.3 g, 75 mmol, 80% purity) in H_2O (125 mL) at room temperature. Stirring was continued overnight at room temperature. Light yellow solids gradually precipitated. When the reaction was complete, the light yellow solids were collected by filtration, washed with large amounts of H_2O and petroleum ether and then dried by suction at room temperature to obtain a yellow crystalline solid **103**. (6.18 g, 94%); m.p. 170-172 °C [Lit^[264] mp 172-173 °C]; ^1H NMR (400 MHz, CDCl_3): δ = 8.17-8.31 (m, 2 H), 8.00 (t, $J = 7.2$ Hz, 1 H), 7.80 (t, $J = 7.2$ Hz, 1 H) ppm.

Diacetoxyiodobenzene



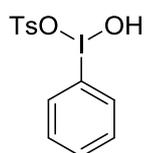
Using a reported literature procedure^[265], sodium perborate tetrahydrate (9.9 g, 100 mmol) was added portion-wise over 20 min to a stirred solution of the iodobenzene (1.1 g, 10 mmol) in glacial acetic acid (90 ml) at 45°C, and the mixture was stirred at this temperature for 4 h. The AcOH was evaporated under vacuum and the residue was washed with water (50 ml) under filtration to afford a colourless solid (2.25 g, 7 mmol, 70% yield); 163-166 °C (Lit Value 163-165 °C)^[266]; ^1H -NMR (400 MHz, CDCl_3): δ 2.01 (s, 6H), 7.47-7.54 (m, 2H), 7.58-7.61 (m, 1H), 8.08-8.10 (m, 2H) ppm.

Iodosobenzene



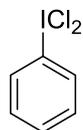
Using the reported procedure,^[267] a 15% aqueous solution of sodium hydroxide (3.7 mL, 14.0 mmol) was added dropwise to solid iodosobenzene diacetate (1.0g, 3.1 mmol) over a 5 min period. The resulting suspension was stirred for a further 2 h at room temperature. Water (6 mL) was then added and the reaction stirred vigorously for 5 min. The crude product was collected under suction, returned to the reaction flask and washed with further water (30 mL). The solid was then collected on a sinter funnel, washed with water (30 mL) and dried under vacuum. The pale yellow solid was triturated with chloroform (30 mL), filtered and dried to afford iodosobenzene (3.13 g, 92%) as an off-white solid

Koser's reagent



Using the reported procedure:^[268] To a stirred solution of iodoarene (0.10 mmol) in dichloromethane/TFE (1:1 v/v, 1 mL) was added mCPBA (0.10 mmol), followed by TsOH 3.H₂O (0.10 mmol). The resulting solution was stirred at room temperature for 30 min and concentrated under a stream of air, then diethyl ether (2 mL) was added to the remaining residue. The resulting precipitate was filtered off and dried in vacuum to give a solid 135-136 °C (Lit Value 134-136 °C)^[269]; ¹H NMR (400 MHz, CD₃OD) δ 8.32 (d, *J* = 8.3 Hz, 2H), 7.80 (m, 1H), 7.71-7.65 (m, 4H), 7.19 (d, *J* = 7.8 Hz, 2H), 2.33 (s, 3H) ppm.

Bischloriodobenzene



Using the reported procedure^[264]: Iodobenzene (2.0 g, 9.8 mmol), was suspended in 10% aqueous sodium hypochlorite (30 ml) at rt. The mixture was stirred vigorously and conc. HCl (20 mL) was added dropwise over 4 minutes. The yellow suspension was allowed to stir for 5 min, then the suspension was filtered. The resulting solid was washed with H₂O (200 mL) then petroleum ether (50 mL). The yellow solid is allowed to air-dry in the dark overnight in a desiccator. PhICl₂ is collected as a pale yellow solid (2.5 g, 93% yield). 110-112 °C (Lit^[270] mp 112-113 °C)

6.42 Experimental for Nitroaldol reactions and multi-steps: oxidations and reductions

General procedure for the preparation of 2-Nitro-1-alcohols A

Syringe A containing aldehyde (2 mmol), nitromethane (10 mmol) made up to 2 ml with ethanol was placed in a syringe pump and connected to a reactor coil via a luer lock. Syringe B containing KOH (0.6 mmol) dissolved in 1 mL of ethanol was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 10 min residence time within the reactor coil (0.5 mL, 0.8 mm I.D) at 60 °C. The mixture was quenched into dilute HCl to allow for accurate residence time once steady state had been reached. The resulting mixture was then extracted with CH₂Cl₂ (2 x 5 mL) the extracts washed with brine (10 mL) and the organic layers evaporated. The crude residue was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and Hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes.

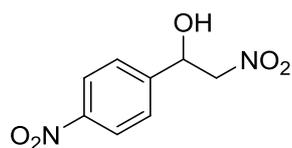
General procedure for the preparation of 2-Nitro-1-alcohols B

Syringe A containing aldehyde (2 mmol), nitromethane (10 mmol) made up to 2 ml with ethanol was placed in a syringe pump and connected to a reactor coil via a luer lock. Syringe B containing DBN (0.5 mmol) dissolved in 1 mL of ethanol was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 30 min residence time within the reactor coil (0.5 mL, 0.8 mm I.D) at RT °C. The mixture was quenched in to dilute HCl to allow for accurate residence time once steady state had been reached. The resulting mixture was then extracted with CH₂Cl₂ (2 x 5 mL) then washed with brine (10 mL) and the organic layers were evaporated. The crude mixture was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and Hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes.

General procedure for the preparation of 2-Nitro-1-alcohols C

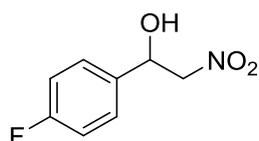
Syringe A containing aldehyde (2 mmol), nitromethane (10 mmol) made up to 2 ml with ethanol was placed in a syringe pump and connect to a reactor coil via a luer lock. Syringe B containing DBN (0.5 mmol) and Cu(OAc)₂ (0.2 mmol) dissolved in 1 mL of ethanol was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 30 min residence time within the reactor coil (0.5 mL, 0.8 mm I.D) at rt °C. The mixture was quenched in to dilute HCl to allow for accurate residence time once steady state had been reached. The resulting mixture was then extracted with CH₂Cl₂ (2 x 5 mL) then washed with brine (10 mL) and the organic layers were reduced under vacuo. The crude mixture was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and Hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes.

1-(4-Nitrophenyl)-2-nitroethanol 155



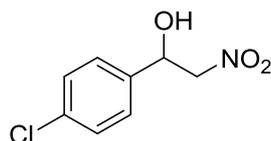
As a yellow solid method A:(97 mg, 92%), method C:(85 mg, 81%) 86-88 °C [Lit^[271] mp 85-86 °C]; ¹H NMR (300 MHz, CDCl₃): δ = 8.28 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 5.61 (dd, *J* = 7.5, 4.5 Hz, 1H), 4.61-4.58 (m, 2H), 3.30 (br s, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 148.0, 144.8, 126.9, 124.3, 80.6, 69.9 ppm. The spectroscopic data are within agreement of the literature^[272]

1-(4-Fluorophenyl)-2-nitroethanol 156



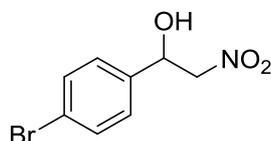
As a pale yellow oil method A: (65 mg, 70%), method C: (70 mg, 76%);¹H NMR (250 MHz, CDCl₃): δ = 7.39-7.31 (m, 4H), 5.43 (dd, *J* = 9.0, 3.3 Hz, 1H), 4.56 (dd, *J* = 13.2, 9.0 Hz, 1H), 4.47 (dd, *J* = 13.2, 3.3 Hz, 1H), 3.11 ppm (br s, 1H) ppm. The spectroscopic data are within agreement of the literature^[272]

1-(4-Chlorophenyl)-2-nitroethanol 157



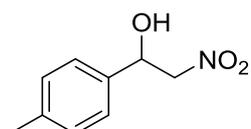
As a colourless oil method A: (65 mg, 65%), method C: (72 mg, 72%);¹H NMR (400 MHz, CDCl₃): δ = 7.37-7.32 (m, 4H), 5.43 (dd, *J* = 9.4, 3.1 Hz, 1H), 4.56 (dd, *J* = 13.3, 9.4 Hz, 1H), 4.48 (dd, *J* = 13.3, 3.1 Hz, 1H), 3.14 (br s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 137.0, 135.0, 129.5, 127.8, 81.4, 70.7 ppm. The spectroscopic data are within agreement of the literature^[272]

1-(4-Bromophenyl)-2-nitroethanol 158



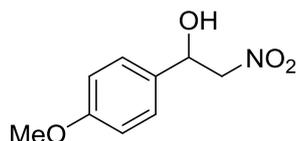
As a colourless oil method A: (92 mg, 72%), method B: (74 mg, 61%)¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, *J* = 8.4, 2H), 7.29 (d, *J* = 8.4, 2H), 5.38 (m, 1H), 4.56 (dd, *J* = 13.4, 9.4 Hz, 1H), 4.48 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.0 (br s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 136.7, 131.8, 127.9, 122.5, 80.5, 69.8 ppm. The spectroscopic data are within agreement of the literature^[272]

2-Nitro-1-*p*-tolylethanol 159



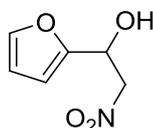
As a colourless solid method A:(36 mg, 40%), method B:(66 mg, 74%) method C: (55 mg, 61%) 44-46 °C (Lit Value 44-45 °C);¹H NMR (400 MHz, CDCl₃): δ = 7.32 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.45 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.63 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.52 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.95 (br s, 1H), 2.40 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 138.9, 135.1, 129.6, 125.8, 81.2, 70.8, 21.1 ppm The spectroscopic data are within agreement of the literature^[272]

(4-Methoxyphenyl)-2-nitroethanol 160



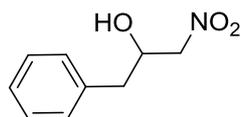
As a colourless oil method A:(12 mg, 12%), method B:(60 mg, 61%), method C: (10 mg, 10%) ¹H NMR (400 MHz, CDCl₃): δ = 7.30 (d, *J* = 8.4, 2H), 6.90 (d, *J* = 8.4, 2H), 5.38 (dd, *J* = 9.7, 3.1 Hz, 1H), 4.58 (dd, *J* = 13.1, 9.7 Hz, 1H), 4.46 (dd, *J* = 13.1, 3.1 Hz, 1H), 3.81 (s, 3H), 2.33 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 160.0, 130.2, 127.3, 114.4, 81.2, 55.4 ppm. The spectroscopic data are within agreement of the literature^[272]

1-(Furan-2-yl)-2-nitroethan-1-ol 161



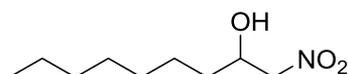
As a yellow oil method B:(35 mg, 61%) ^1H NMR (300 MHz, CDCl_3): δ = 7.50-7.46 (m, 1H), 7.25-7.22 (m, 2H), 5.64 (dd, J = 9.6, 2.7 Hz, 1H), 4.51 (dd, J = 13.5, 9.6 Hz, 1H), 4.39 (dd, J = 13.5, 2.7 Hz, 1H), 2.79 (br s, 1H) ppm ^{13}C NMR (75 MHz, CDCl_3): δ = 150.8, 143.1, 110.6, 108.1, 78.4, 64.7 ppm. The spectroscopic data are within agreement of the literature^[273]

1-Nitro-3-phenylpropan-2-ol 162



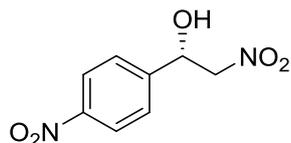
As a colourless oil method B: (60 mg, 61%) ^1H NMR (300 MHz, CDCl_3): δ = 7.50-7.46 (m, 1H), 7.25-7.22 (m, 2H), 7.17-7.15 (m, 1H), 5.64 (dd, J = 9.6, 2.7 Hz, 1H), 4.51 (dd, J = 13.5, 9.6 Hz, 1H), 4.39 (dd, J = 13.5, 2.7 Hz, 1H), 2.79 (br s, 1H), 2.35 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ = 135.7, 129.4, 128.6, 126.4, 79.3, 39.7 ppm The spectroscopic data are within agreement of the literature^[273]

1-Nitrononan-2-ol163



As a colourless oil method B: (39 mg, 42%)As a colourless oil ^1H NMR (300 MHz, CDCl_3): δ = 4.47-4.27 (m, 2H), 2.52 (br s, 1H), 1.60-1.47 (m, 4H), 1.26-1.29 (m, 9H), 0.88 ppm (t, J = 6.6 Hz, 3H); ^{13}C NMR (100MHz, CDCl_3): δ = 81.2, 69.8, 34.2, 32.1, 29.5, 29.3, 29.3, 28.0, 25.6, 22.9, 14.8 ppm. The spectroscopic data are within agreement of the literature^[272]

(S)-(+)-1-(4-Nitrophenyl)-2-nitroethanol



Syringe A containing aldehyde (2 mmol), nitromethane (10 mmol) made up to 2 ml with ethanol was placed in a syringe pump and connected to a reactor coil via a luer lock. Syringe B

containing $\text{Cu}(\text{OAc})_2$ (0.1 mmol) and 2,2-Bis((4S)-(-)-4-isopropylloxazoline)propane (0.1 mmol) dissolved in 1 mL of ethanol was placed on a second syringe pump and attached in the same manner. The solutions were then pumped at a rate as to achieve a 30 min residence time within the reactor coil (0.5 mL, 0.8 mm I.D) at RT °C. The mixture was quenched in to dilute HCl to allow for accurate residence times once steady state had been reached. To achieve steady state the reaction mixture was allowed to flow for one complete volume through the reactor coil, this therefore allows for a homogeneous mixture within the reactor before collection of the reaction mixture. The crude mixture was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes, to obtained the product in 9% yield. The chiral compound was resolved using an OD-H chiral column 10% IPA to hexane at a flow rate of 1.0 mL/min at 20 °C. Retention times S: $t_r = 36$ min R: $t_r = 28$ min Lit^[272]

General reduction procedure of nitroalcohols by zinc in batch Method A

To a suspension of of nitro alcohol (5 mmol) and Zn dust (6 mmol) in ethanol (5 mL) was stirred with ammonium formate (0.5 g) or 90% HCOOH (2.5 mL) at room temperature. After completion of the reaction (1 h), the organic layer was evaporated and the residue dissolved in CHCl_3 and washed with saturated NaCl. The organic layer upon evaporation gave the desired amino alcohol.

General reduction procedure of nitroalcohols by Pd/C in batch Method B

To a suspension of of nitro alcohol (5 mmol) and Pd/C (0.1 mmol) in ethanol (5 mL) was stirred with ammonium formate (1.5 g) at room temperature. After completion of the reaction (2 h). The mixture was filtered through celite and the organic solvent was evaporated and the residue re-dissolved in CHCl_3 and the solution washed with saturated NaCl. The organic layer was evaporated under vacuum to give the desired amino alcohol.

General reduction procedure of nitroalcohols by zinc in flow Method C

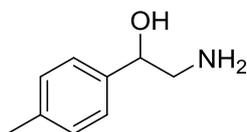
A syringe containing nitroalcohol (2 mmol), NH_4Cl (424 mg, 8 mmol) or HCOONH_4 (504 mg, 8 mmol) made up to 2.5 mL with EtOH was placed in a syringe pump and connected to a reactor coil via a luer lock. The solution was then pumped through a column (L × I.D. 150 mm × 10 mm) containing zinc dust (1.6 g, 25 mmol) at a rate as to achieve a 30 min residence time (40

$\mu\text{L}/\text{min}$) at $40\text{ }^\circ\text{C}$. The mixture was quenched into water once steady state had been reached collecting the second column volume of 1.2 mL . The resulting mixture was poured into a separating funnel and the product extracted using EtOAc ($3 \times 10\text{ mL}$) The crude mixture was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and Hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes.

General reduction procedure of nitroalcohols by Pd/C in flow Method D

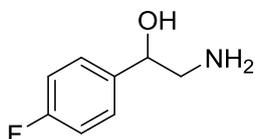
A syringe containing nitroalcohol (1 mmol), HCOONH_4 (252 mg , 4 mmol) made up to 2 mL with EtOH was placed in a syringe pump and connected to the reactor via a luer lock. The solution was then pumped through a column (L \times I.D. $150\text{ mm} \times 10\text{ mm}$) containing Pd/C (150 mg in 1.2g of celite) at a rate as to achieve a 30 min residence time at $40\text{ }^\circ\text{C}$. The mixture was quenched into water once steady state had been reached and the second column volume of 1 mL was collected. The resulting mixture was poured into a separating funnel and the product extracted using EtOAc ($3 \times 10\text{ mL}$) The crude mixture was purified using a Biotage column system. Using a Biotage ultra 10g silica gel cartridge and Hexane:EtOAc running a gradient of 0-30% EtOAc over 20 column volumes.

2-Amino-1-(*p*-tolyl)ethan-1-ol 172



As a white solid Method A: (600 mg , 80%), method B: (639 mg , 85%), method C: (100 mg , 83%), method D: (64 mg , 85%), mp $66\text{--}69\text{ }^\circ\text{C}$ [lit.^[274] mp $68\text{--}69\text{ }^\circ\text{C}$], ($^1\text{H NMR}$ (400 MHz , CDCl_3): $\delta = 7.18$ (d, $J = 7.9\text{ Hz}$, 2H), 7.08 (d, $J = 7.8\text{ Hz}$, 2H), 4.70 (dd, $J = 8.4, 2.8\text{ Hz}$, 1H), 3.57 (br s, 3H), 2.99 (dd, $J = 12.7, 3.4\text{ Hz}$, 1H), 2.84 (dd, $J = 12.6, 8.8\text{ Hz}$, 1H), 2.30 ppm (s, 3H) ppm $^{13}\text{C NMR}$ (100 MHz , CDCl_3): $\delta = 140.0, 137.2, 129.1, 126.1, 74.2, 49.3, 21.0\text{ ppm}$ The spectroscopic data are within agreement of the literature.^[274]

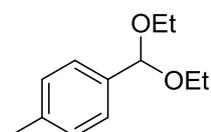
2-Amino-1-(*p*-fluorobenzene)ethan-1-ol



As a white solid Method C: (96 mg, 78%), (^1H NMR (400 MHz, CDCl_3): δ = 7.31 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 4.72 (dd, J = 8.9, 2.7 Hz, 1H), 2.94 (dd, J = 11.6, 4.2 Hz, 1H), 2.74 (dd, J = 11.6, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 163.2, 161.0, 138.4, 138.3, 127.5, 115.2, 115.1, 73.8, 49.0 ppm The spectroscopic data are within agreement of the literature.^[274]

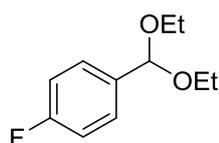
Side products from the attempts to do a 2-step, inline reduction following the nitro aldol reaction.

1-(Diethoxymethyl)-4-methylbenzene 173



^1H NMR (400 MHz, CDCl_3): δ = 7.42 (m, 2H), 7.03 (m, 2H), 5.47 (s, 1H), 3.49-3.54 (m, 4H), 2.99 (t, J = 7.1 Hz, 6H) ppm. The spectroscopic data are within agreement of the literature^[275]

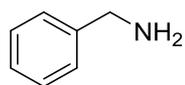
1-(Diethoxymethyl)-4-fluorobenzene 174



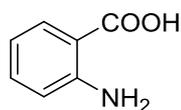
^1H NMR (400 MHz, CDCl_3): δ = 7.41 (m, 2H), 7.01 (m, 2H), 5.45 (s, 1H), 3.53 (m, 4H), 2.99 (t, J = 7.06, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 138.9, 135.1, 129.6, 125.8, 81.2, 70.8, 21.1 ppm The spectroscopic data are within agreement of the literature^[276]

General Procedure for reductions.

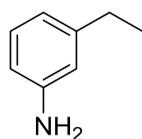
Nitro compound or olefin (5 mmol) and hydrogen source (25 mmol) were dissolved in 10 mL of MeOH (0.5 M). After flushing the column with MeOH, the substrate/reagent solution was pumped through the column (L \times I.D. 150 mm \times 10 mm) at the specified temperature with a flow rate of 0.108 mL/min using the Vapourtec E-series equipment (with a peristaltic pump). The first column volume was discarded, the second was collected (2.1 mL). The solvent was evaporated, the residue added to distilled water (20 mL), and extracted with diethyl ether or dichloromethane (3 \times 15 mL). The combined organic phases were dried over MgSO_4 , filtered, and the solvent removed in vacuo. The resulting mixture was then purified by Biotage column chromatography using a 10g ultra Biotage column and a gradient of 0-20% EtOAc with Hexane over 20 column volumes.

Benzylamine: 177b

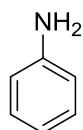
Yield: 113 mg (1.06 mmol) 98%; colourless liquid; ^1H NMR (CDCl_3 , 400 MHz) δ = 7.18-7.31 (5H, m), 3.81 (2H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ = 143.3, 128.6, 127.1, 126.8, 46.2 ppm; in agreement with reported literature data^[277].

Anthranilic acid: 174b

Yield: 133 mg (0.98 mmol) 90%; off white solid; mp.: 147-150 °C [lit ^[278]mp: 146-148 °C]; ^1H NMR (CDCl_3 , 400 MHz) δ = 7.93 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 6.67 (d, J = 7.2 Hz, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ = 173.6, 151.6, 135.6, 132.6, 117.2, 116.9, 109.9 ppm; in agreement with reported literature data^[279].

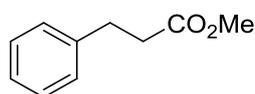
3-Ethylaniline 175b

Yield: 128 mg (1.06 mmol) 98%; pale yellow liquid; ^1H NMR (CDCl_3 , 400 MHz) δ = 7.08 (t, J = 7.7 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.57-6.50 (m, 2H), 3.25 (bs, 2H), 2.57 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ = 146.4, 145.7, 129.2, 118.4, 115.0, 112.5, 28.9, 15.5 ppm; in agreement with reported literature data^[280]

Aniline: 176b

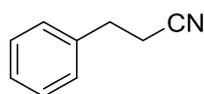
Yield: 0.73 g (7.85 mmol) 78%; pale yellow liquid; ^1H NMR (CDCl_3 , 400 MHz) δ = 7.17 (d, J = 7.5 Hz, 2H), 6.77 (t, J = 7.4 Hz, 1H), 6.70 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ = 146.5, 129.4, 118.7, 115.2 ppm. in agreement with reported literature data^[281]

Methyl 3-phenylpropanoate 179b



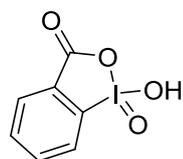
Yield: 172 mg (1.05 mmol) 97%; colourless oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.25-7.30 (m, 2H), 7.18-7.21 (m, 3H), 3.66 (s, 3H), 2.95 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 173.4, 140.5, 128.5, 128.3, 123.7, 51.7, 35.7, 30.9 ppm; in agreement with reported literature data^[282]

3-Phenylpropanenitrile:180b



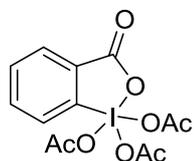
Yield: 113 mg (0.86 mmol) 80%; pale yellow liquid; ^1H NMR (CDCl_3 , 400 MHz) δ = 7.25-7.31 (m, 5H), 2.99 (t, J = 7.4 Hz, 2H), 2.64 (t, J = 7.4 Hz, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ = 138.3, 129.2, 128.6, 127.8, 119.5, 32.1, 19.6 ppm; in agreement with reported literature data.^[283]

2-Iodoxybenzoic acid (IBX)



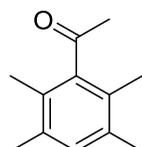
2-Iodobenzoic acid (5.0 g, 20 mmol) was added to a solution of Oxone (18.1g, 29 mmol) in water (65 mL). The reaction mixture was warmed to 70 °C stirred at this temperature for 3 h. The suspension was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered through sintered-glass funnel, and the solid was repeatedly rinsed with water (5 × 20 mL) and acetone (2 × 10 mL). The white, crystalline solid was left to dry at room temperature overnight to produce a fluffy white solid 70% (3.9g, 13.9 mmol); ^1H NMR (300 MHz, CDCl_3): δ = 7.29-7.55 (m, 5H), 4.65 (dd, J = 5.4, 7.8 Hz, 1H), 3.37-3.55 (m, 2H) ppm

Dess-Martin periodinane (DMP)



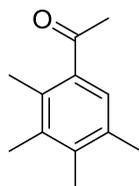
The solid iodine oxide (3.9 g, 13.9 mmol) was suspended in glacial AcOH (7.5 mL), and Ac₂O (15 mL) under an argon atmosphere. The mixture was stirred and heated to 85°C for 30 min until all the solids dissolve to afford a colourless to clear yellow solution. Heating and stirring are discontinued and the reaction mixture was allowed to cool slowly to room temperature in the heat block for 16 h. The resulting crystalline solids are isolated by vacuum filtration in the reaction vessel under argon using a fritted adapter followed by washing the solids with anhydrous ether (3 × 80-mL). Residual solvent is removed under vacuum giving 4.17g, 9.8 mmol, (71% yield) of DMP as a white solid.

2,3,5,6-Tetramethylacetophenone



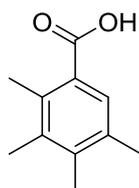
To a suspension of AlCl₃ (8.25 g, 61.1 mmol) in 22 mL of CCl₄ cooled to 5 °C was added acetyl chloride (4 mL, 56.0 mmol) slowly. The resulting solution was allowed to stir for 1 h. Durene (7.5 g, 61.1 mmol) dissolved in 23 mL of CCl₄ was slowly added to the solution, while the temperature was held below 5 °C. The resulting reaction mixture was allowed to stir at 0–10 °C for 2 h and then at 30 °C for another 2 h. It was then poured into crushed ice, and concentrated HCl (6.5 mL) was added. The organic residue was extracted with CHCl₃ (3 × 75 mL), washed with NaHCO₃ (50 mL) and brine (50 mL), dried over anhydrous MgSO₄, and concentrated under vacuum to obtain the crude product, which was purified by Kugelrohr distillation (80 °C, 0 mbar) to isolate a further crude mixture (containing a mixture of the starting material and unidentifiable side products by NMR) as an off white solid (8 g) which was subsequently used without further purification.

2,3,4,5-Tetramethylacetophenone



The 2,3,5,6-tetramethylacetophenone mixture (8 g), AlCl₃ (16.0 g, 112 mmol), NaCl (1.1 g, 17.1 mmol), and H₂O (12 mol %) was heated at 100 °C for 2 h. The reaction mixture was quenched with water. The organic matter was extracted with CHCl₃ (3 × 50 mL), washed with NaHCO₃ (50 mL) and brine (50 mL), dried over anhydrous MgSO₄, and concentrated in vacuo to obtain the crude product, which was purified by column chromatography (hexane 100%) to isolate 2,3,4,5-tetramethylacetophenone as a colourless liquid in 75% yield (6.1 g, 31.5 mmol): ¹H NMR (CDCl₃, 300 MHz) δ = 7.20 (s, 1H), 2.54 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.23 (s, 6H) ppm. The spectroscopic data are within agreement of the literature^[182]

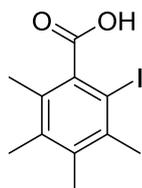
2,3,4,5-Tetramethylbenzoic Acid



Water (40 mL) was charged with potassium hydroxide (17.5 g, 310 mmol) and bromine (4.8 mL, 94.5 mmol) one after the other at 0 °C. The resulting mixture was allowed to stir for 20 min. The solution was slowly added to a solution of 2,3,4,5-tetramethylacetophenone (5.5 g 31.3 mmol) in dioxane (80 mL), and the mixture was allowed to stir for another 1 h at room temperature. The resultant mixture was heated at reflux for 1 h. Subsequently, the reaction mixture was acidified with dilute HCl (pH 1) and extracted with EtOAc (3 × 75 mL), washed with brine (100 mL) and saturated Na₂S₂O₃ (50 mL) solution, and dried over anhydrous Na₂SO₄. The combined extract was concentrated in vacuo, and the residue was subjected to silica gel

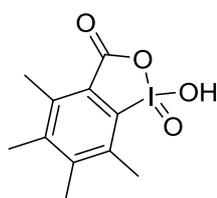
chromatography to isolate 2,3,4,5- tetramethylbenzoic acid as a colourless solid in 65% yield (4.8g, 27.3 mmol): mpt 171–173 °C [Lit^[182] mp 165-167 °C], ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (s, 1H), 2.53 (s, 3H), 2.30 (s, 3H), 2.26 (s, 6H) ppm. The spectroscopic data are within agreement of the literature^[182]

2-Iodo-3,4,5,6-tetramethylbenzoic Acid



To a solution of 2,3,4,5-tetramethylbenzoic acid (2.8 g, 16.0 mmol) in acetonitrile (25 mL), N-iodosuccinimide (3.8 g, 17.0 mmol) was added. Subsequently, 0.25 mL of concentrated H₂SO₄ and TFA (0.35 mL, 4.7 mmol) were introduced at room temperature. The resulting reaction mixture was allowed to stir at room temperature overnight. It was subsequently quenched by adding crushed ice. Filtration of the solid by washing with a small amount of H₂O (2 × 5 mL) and petroleum ether (2 × 10 mL), followed by drying under vacuum, led to the pure product in 75% yield (4.0 g, 12.3 mmol): mp 205–207 °C [Lit^[182] mp 204-207 °C], ¹H-NMR (300 MHz, CDCl₃): δ 2.20 (s, 2H), 2.32 (s, 1H), 2.33 (s, 1H), 2.51 (s, 1H) ppm The spectroscopic data are within agreement of the literature^[182]

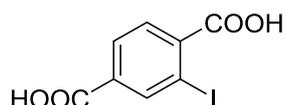
2,3,4,5-Tetramethyliodosybenzoic acid



To a solution of Oxone (8.1 g, 13.2 mmol) dissolved in water (50 mL) and acetonitrile (10 mL) was added 2-iodo-3,4,5,6-tetramethylbenzoic acid (2.0 g, 6.58 mmol), and the resultant suspension was heated at 70 °C for 3.5 h with vigorous stirring. The white precipitate that formed was collected by filtration. The precipitate was washed with water (15 mL) and acetone (10 mL) and dried under vacuum to obtain 3,4,5,6- tetramethyl-2-iodoxybenzoic acid as a colorless solid in 82% yield (1.81 g, 5.4 mmol): mp 136–139 °C; (Lit^[182] mp 138-140 °C), ¹H-

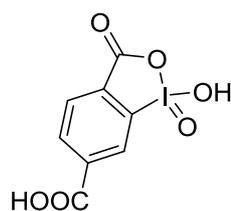
NMR (300 MHz, DMSO-d₆): δ 2.28 (s, 2H), 2.62 (s, 1H), 2.67 (s, 1H) ppm The spectroscopic data are within agreement of the literature^[182]

2-Iodoterephthalic acid



To a suspension of 2-aminoterephthalic acid (3.0 g, 16.6 mmol) in H₂O (100mL) conc. HCl (1;1,v/v) was added drop wise at 0 °C a solution of NaNO₂ (2.85 g, 41.3 mmol) over a period of 45 min during which time the solution became clear. After being stirred for an additional 30 min at 0 °C, the diazonium salt was poured into a solution of KI (16.5 g, 99.4 mmol) in water (150 mL) and the resulting dark solution was left stirring at room temperature for 18 h. To the stirred solution was then added solid NaHSO₃ in portions till the dark colour of the solution was discharged leaving a suspension a tan coloured solid in the solvent mixture. The solid was filtered and triturated with of 1:1(v/v) CH₂Cl₂:H₂O (150 mL) to give 4.18 g (86%) as a yellow coloured solid, mp 289-296 °C [Lit^[284] mp 299-300°C] ¹H NMR (300 MHz, (CD₃)₂CO): 8.61 (d, *J* = 1.5 Hz, 1H), 8.13 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.96 (d *J* = 7.0 Hz, 1H) ppm

1-hydroxy-1,3-dioxo-1,3-dihydro-1*H*-benzo[d][1,2]iodooxazole-6-carboxylic acid



A mixture of 2-iodoterephthalic acid, 9 (7.0 g, 24.0 mmol) and Oxone (44.3 g, 72.0 mmol) in 400 mL water was maintained at reflux for 3 h during which time the solution became clear. The hot solution was poured into a 1L beaker and allowed to cool to room temperature overnight. The precipitated cream coloured solid was filtered and dried to yield (4.8 g, 62%); mp 258-261°C ¹H NMR (300 MHz, D₂O): 8.71 (d, *J* = 1.0 Hz, 1H), 8.38 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H) ppm The spectroscopic data are within agreement of the literature.^[284]

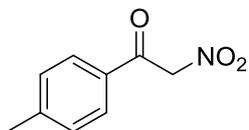
Batch oxidation conditions for nitroalcohols

To a stirred solution of 2-nitro-1-*p*-tolylethanol (91 mg, 0.5 mmol) in MeCN (2 mL) was added IBX (210 mg, 0.75 mmol) and kept at room temperature for 2 h. The reaction mixture was then quenched with saturated Na₂S₂O₃ solution (5 mL) before being extracted with CH₂Cl₂ (3 × 10mL). The organic combines were then evaporated under vacuum to afford 2-nitro-1-(*p*-tolyl)ethan-1-one (63 mg, 0.35 mmol, 70%)

To a stirred solution of 2-nitro-1-*p*-tolylethanol (91 mg, 0.5 mmol) in CH₂Cl₂ (2 mL) was added IBX (210 mg, 0.75 mmol) and kept at room temperature for 2 h. The reaction mixture was then quenched with saturated Na₂S₂O₃ solution before being extracted with CH₂Cl₂ (3 × 10mL). The organic combines were then evaporated under vacuum to afford 2-nitro-1-(*p*-tolyl)ethan-1-one (49 mg, 0.28 mmol, 54%)

To a stirred solution of 2-nitro-1-*p*-tolylethanol (91 mg, 0.5 mmol) in CH₂Cl₂ (2 mL) was added DMP (210 mg, 0.75 mmol) and kept at room temperature for 2 h. The reaction mixture was then quenched with saturated Na₂S₂O₃ solution before being extracted with CH₂Cl₂ (3 × 10mL). The organic combines were then evaporated under vacuum to afford 2-nitro-1-(*p*-tolyl)ethan-1-one (49 mg, 0.28 mmol, 76%)

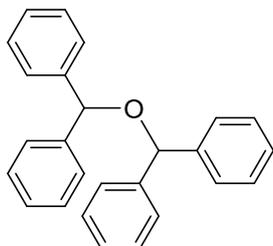
2-nitro-1-(*p*-tolyl)ethan-1-one 181



¹H NMR 300 MHz, (CDCl₃): 7.78 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 5.88 (s, 2H), 2.44 (s, 3H) ppm. ¹³C NMR 100 MHz, (CDCl₃): 185.3, 130.1, 128.5, 81.4, 21.9 ppm. The spectroscopic data are within agreement of the literature ^[285]

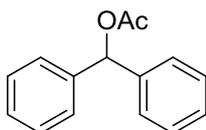
6.43 Experimental procedures for Koch Haaf carbonylations:

Bis(benzhydryl) ether 220



To a flask containing benzhydrol (368 mg, 2 mmol) in sulfuric acid (10 mL) was added formic acid (0.5 mL) slowly. The resulting solution was then stirred for 1 h and poured into ice. The resulting mixture was extracted with Et₂O (2 × 50 mL) dried over MgSO₄ and reduced under vacuum. The residue was purified by silica gel chromatography (99:1, Hex:EtOAc) to obtain Bis(benzhydryl) ether as a colourless solid: mp 106-109 °C, [Lit^[286] mp 108.9-109.4 °C], ¹H NMR (300 MHz, CDCl₃): δ = 7.49–7.17 (m, 20H), 5.41 (s, 2H) ppm The spectroscopic data are within agreement of the literature^[287]

Synthesis of benzhydryl acetate 222

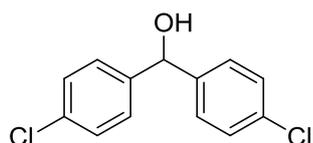


To a flask containing benzhydrol (1.84 g, 10 mmol) was added acetic anhydride (20 mL) the mixture was then reflux for 2 h. The resulting solution was then cooled and quenched with sat. NaHCO₃ (50 mL) until effervescence ceased. The resulting mixture was extracted with Et₂O (2 × 50 mL) dried over MgSO₄ and reduced under vacuum. The residue was purified by silica gel chromatography (99:1, Hex:EtOAc) to obtain benzhydryl acetate as a colourless solid (2.03 g, 9 mmol, 90%). mp 40-43 °C, [Lit^[288] mp 39-41 °C] ¹H NMR (300 MHz, CDCl₃): δ = 7.28-7.33 (m, 10H), 6.88 (s, 1H), 2.16 (s, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 170.1, 140.2, 128.5, 128.3, 127.9, 21.3 ppm. The spectroscopic data are within agreement of the literature. ^[289]

General procedure for reductions of benzophenones

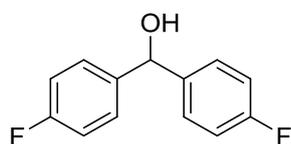
To a stirred solution of 4,4'-Dihalobenzophenone (4 mmol) in methanol (10 mL) was added portion-wise sodium borohydride (453 mg, 12 mmol) over 40 min. The subsequent reaction mixture was allowed to stir for 2 h until all benzophenone had been consumed by TLC. The methanol was reduced under vacuo. The resulting mixture was dissolved into Et₂O (10 ml) and washed with water (20 mL) and brine (10 mL). The organic layer was reduced under vacuo to produce pure product.

4,4'-Dichlorobenzhydrol 223



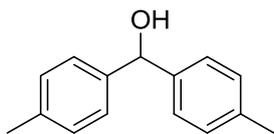
As a white solid: (1.01 g, 3.9 mmol, 99%) 89-92 °C, [lit^[290] mp 91.5-93 °C] ¹H NMR (300 MHz, CDCl₃): δ = 7.30 (d, *J* = 8.7, 4H), 7.22 (d, *J* = 8.7, 4H), 4.97 (s, 1H) ppm. ¹³C NMR (75.0 MHz, CDCl₃): δ = 177.6, 135.9, 135.5, 130.2, 128.8, 55.6 ppm. The spectroscopic data are within agreement of the literature.^[291]

4,4'-Difluorobenzhydrol



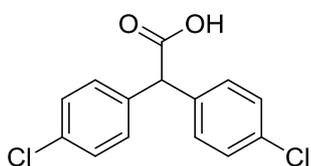
As a pale yellow solid: (863 mg, 3.9 mmol, 99%), 49-52 °C [Lit^[292] mp 47-49 °C] ¹H NMR (300 MHz, CDCl₃): δ = 7.32 (m, 4H), 7.02 (m, 4H), 5.8 (s, 1H), 2.35 (br s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 163.8, 160.6, 139.4, 128.2 (d), 115.5 (d), 74.9 ppm. The spectroscopic data are within agreement of the literature.^[291]

4,4'-Dimethylbenzhydrol



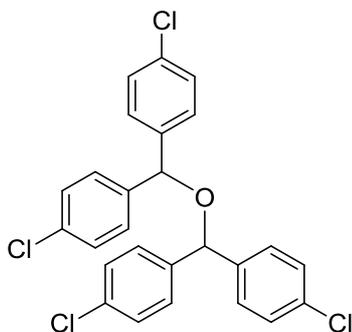
As a colourless solid: (827 mg, 3.9 mmol, 99%) mp 70-72 °C [Lit^[290] mp 69-70 °C] ¹H NMR (300 MHz, CDCl₃): δ = 7.27 (d, *J* = 9 Hz, 4H), 7.14 (d, *J* = 9 Hz, 4H), 5.8 (s, 1H), 2.32 (s, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 141.1, 137.1, 129.1, 126.4, 77.2 ppm. The spectroscopic data are within agreement of the literature.^[293]

Synthesis of 4,4'-Dichloro(diphenylacetic acid) 206



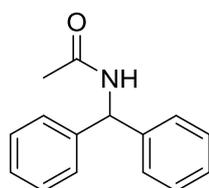
To a un-stirred solution of 4,4'-Dichlorobenzhydrol (506 mg, 2 mmol) in concentrated sulphuric acid (10 mL) was added formic acid (0.5 mL) slowly. The solution was left undisturbed for 1 h before being poured into crushed ice and extracted with diethyl ether (3 × 25 mL). The resulting organic solution was dried of MgSO₄ and concentrated under vacuum to afford an off-white solid (534 mg, 1.8 mmol, 95% yield) mp 166–169°C [Lit^[294] mp 167-168°C]; ¹H NMR (400 MHz, CDCl₃): δ = 7.31 (m, 2H), 7.23 (m, 2H), 5.00 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 177.6, 135.9, 133.8, 130.6, 129.0, 55.6 ppm. The spectroscopic data are within agreement of the literature.^[294]

Di-(4,4'-dichlorobenzhydryl) ether 224



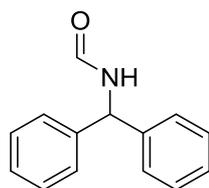
Syringe A contacting a solution of 4,4'-Dichlorobenzhydrol (506 mg, 2 mmol) in Formic acid (0.5 mL) and Et₂O (0.5 mL) was placed into a syringe pump and connected via luer lock fittings. Syringe B containing sulphuric acid (5 mL) was placed in a second syringe pump and connect in the same way to the reactor. The solution was eluted, once 1 reactor volume had been reached, into crushed ice. The reaction mixture was collected for 40 min and then extracted with diethyl ether (2 × 25 mL). The resulting organic solution was dried of MgSO₄ and concentrated under vacuum. Colourless solid (74 mg, 34 %); mp 125-128 °C, [Lit.^[295] mp 126-127 °C]; ¹H NMR (500 MHz, CDCl₃): δ = 7.31 (m, 2H), 7.23 (m, 2H), 5.28 (s, 1H) ppm.¹³C NMR (125 MHz, CDCl₃): δ = 139.8, 133.8, 129.9, 128.8, 79.1; MS EI+ calcd for C₂₆H₁₈O(35)Cl₄ (M+) 486.0112, found 487.0135.

N-benzhydrylacetamide 221



Syringe A containing H₂SO₄ (85%, 5mL) was placed in a syringe pump and connected to the reactor via luer lock fittings. Syringe B containing alcohol (2 mmol) dissolved in MeCN (2.5 mL) was placed in a second syringe pump and connect in the same way to the reactor. The contents of the syringe were then pump at a rate as to achieve a residence time of 20 min within a PTFE reactor coil (0.5 mm i.d, 1 mL vol). The reaction mixture was quenched into NaOH (aq, 10 mL) after steady state had been reached. The resulting mixture was extracted with EtOAc (2 ×20 mL), dried over MgSO₄ and reduced under vacuum. The residue was purified by silica gel chromatography (10:1, Hex:EtOAc) to obtained the desired amide product. As a colourless solid; mp 154–155°C; (Lit.^[296] mp 147-149 °C); ¹H NMR (300 MHz, CDCl₃): δ= 7.19–7.38 ppm (m, 10H), 6.26 (s, 1H), 2.04 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) 169.1, 141.5, 128.7, 127.4, 57.0, 23.3 ppm.^[294]

N-benzhydrylformamide 226



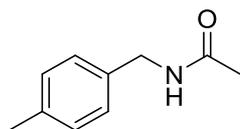
Syringe A containing H₂SO₄ (85%, 5mL) was placed in a syringe pump and connected to the reactor via luer lock fittings. Syringe B containing alcohol (368 mg, 2 mmol) and KCN (260mg, 4 mmol) dissolved in AcOH (2.5 mL) was placed in a second syringe pump and connect in the same way to the reactor. The contents of the syringe were then pumped at a rate as to achieve a residence time of 20 min within a PTFE reactor coil (0.5 mm i.d, 1 mL vol). The reaction mixture was quenched into NaOH (aq, 10 mL, 1M) after steady state had been reached. The resulting mixture was extracted with EtOAc (2 ×20 mL), the combined extracts were dried over MgSO₄ and evaporated. The residue was purified by Biotage column chromatography using a 10g Biotage ultra cartridge running a gradient of 0-10%:EtOAc with hexane over 10 cv to obtain the desired amide product, as a colourless solid (228 mg, 54%); mp.: 134–136 °C; [Lit.^[297] mp132-134 °C] Two rotamers (ratio 76:24) was observed. ¹H NMR (CDCl₃, 400 MHz) δ 8.33 and 8.25 (s and d, J = 11.3 Hz, total 1H), 7.39-7.23 (m, 10H), 6.35 (d, J = 8.23 Hz, total 1.8H), 6.08 (br s, 1H), 5.79 (d, J = 8.27 Hz, 0.2H) ppm.¹³C NMR (CDCl₃, 100 MHz) δ 164.5, 160.3, 140.9, 140.8, 128.9, 128.5, 128.0, 127.7, 127.4, 127.3, 60.0, 55.7. The spectroscopic data are within agreement of the literature.^[298]

6.44 Experimental procedures for Ritter reactions of benzylic alcohols:

General procedure for the Ritter reaction in continuous flow.

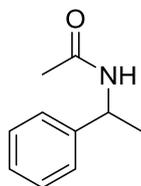
Syringe A containing H₂SO₄ (85%, 5mL) was placed in a syringe pump and connected to the reactor via luer lock fittings. Syringe B containing alcohol (2 mmol) dissolved in MeCN (2.5 mL) was placed in a second syringe pump and connect in the same way to the reactor. The contents of the syringe were then pump at a rate as to achieve a residence time of 20 min within a PTFE reactor coil (0.5 mm i.d, 1 mL vol). The reaction mixture was quenched into NaOH (aq, 10 mL) after steady state had been reached. The resulting mixture was extracted with EtOAc (2 ×20 mL) then dried over MgSO₄ and evaporated. The residue was purified by Biotage chromatography using a 10g snap ultra Biotage column using a gradient of EtOAc 0-10% with hexane.

N-(4-Methylbenzyl)acetamide 232



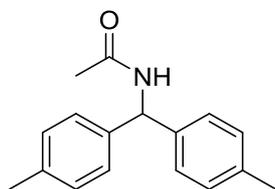
As colourless needles (82.6, 72%); mp 112-113 °C [Lit.^[299] mp 110.5-111.5 °C]; ¹H-NMR (400 MHz, CDCl₃) δ = 7.16-7.23 (m, 5H), 5.70 (br s, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 2.39 (s, 3H), 2.01 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.1, 137.5, 135.2, 129.6, 128.0, 43.7, 23.5 ppm. The spectroscopic data are within agreement of the literature^[287]

N-(1-Phenylethyl)acetamide 233



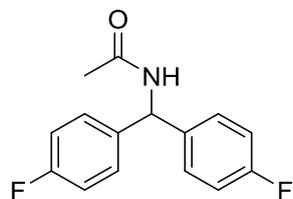
As a colourless oil (99 mg, 87%); ¹H-NMR (300 MHz, CDCl₃) δ: 7.27-7.36 (m, 5H), 5.93 (1H, br s), 5.12 (m, 1H), 1.97 (s, 3H), 1.48 (d, *J* = 6.9 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 169.1, 143.3, 128.6, 127.2, 126.2, 48.8, 23.5, 21.7. The spectroscopic data are within agreement of the literature^[287]

N-(bis(4-Tolyl)methyl)acetamide 234



As colourless solid (135 mg, 76%); mp 145-147 °C, [Lit ^[300] mp 149 °C]; ¹H-NMR (300 MHz, CDCl₃) δ = 7.09-7.14 (m, 8H), 6.18 (d, *J* = 7.9 Hz, 1H), 5.98 (br s, 1H), 2.33 (s, 6H), 2.06 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 169.8, 164.5, 160.5, 137.0, 129.1, 155.6, 55.8. The spectroscopic data are within agreement of the literature^[287]

N-(bis(4-Fluorophenyl)methyl)acetamide 235



As a tan solid (147 mg, 80%); mp 159-163 °C [Lit.^[296] mp 160-162 °C]; ¹H-NMR (300 MHz, CDCl₃) δ = 7.16 (m, 4H), 7.02 (t, *J* = 8.2, 8.2 Hz, 4H), 6.20 (d, *J* = 6.4 Hz, 1H), 6.09 (br s, 1H), 2.09 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): 169.8, 164.5, 160.5, 137.0, 129.1(d), 155.6(d), 55.8 ppm The spectroscopic data are within agreement of the literature^[287]

Bibliography

- [1] P. Watts, C. Wiles, *Chem. Commun.* **2007**, 443–467.
- [2] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318.
- [3] J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57.
- [4] I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519–552.
- [5] B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728.
- [6] J. Yoshida, *Flash Chemistry*, Wiley, Tokyo, **2008**.
- [7] F. Darvas, V. Hessel, G. Dorman, *Flow Chemistry- Fundamentals*, De Gruyter, Berlin, **2014**.
- [8] A. J. deMello, *Nature* **2006**, *442*, 394–402.
- [9] L. Ducry, D. M. Roberge, *Angew. Chemie* **2005**, *117*, 8186–8189.
- [10] D. R. J. Acke, C. V. Stevens, *Org. Proc. Res. Dev.* **2006**, *10*, 417–422.
- [11] J. Yoshida, *Chem. Commun.* **2005**, 4509–4516.
- [12] J. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450–7459.
- [13] J. Yoshida, *Chem. Rec.* **2010**, *10*, 332–341.
- [14] J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896–9904.
- [15] A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 14149–14158.
- [16] T. Fukuyama, I. Ryu, in *Encycl. Radicals Chem. Biol. Mater.*, John Wiley & Sons, Ltd, Chichester, UK, **2012**.
- [17] T. Noel, V. Hessel, in *New Trends Cross-Coupling Theory Appl.*, Colacot, Thomas J, Cambridge, **2015**, pp. 610–645.
- [18] R. Duque, E. Öchsner, H. Clavier, F. Caijo, S. P. Nolan, M. Mauduit, D. J. Cole-Hamilton, *Green Chem.* **2011**, *13*, 1187.
- [19] A. Corma, H. García, *Chem. Rev.* **2003**, *103*, 4307–4366.
- [20] Y. Zhang, T. F. Jamison, S. Patel, N. Mainolfi, *Org. Lett.* **2011**, *13*, 280–283.
- [21] B. Ahmed-Omer, D. A. Barrow, T. Wirth, *Tetrahedron Lett.* **2009**, *50*, 3352–3355.
- [22] B. Ahmed, D. Barrow, T. Wirth, *Adv. Synth. Catal.* **2006**, *348*, 1043–1048.
- [23] C. J. Mallia, I. R. Baxendale, *Org. Proc. Res. Dev.* **2015**, 150901080230009.
- [24] M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362.
- [25] K. Kin Yeong, A. Gavriilidis, R. Zapf, V. Hessel, *Chem. Eng. Sci.* **2004**, *59*, 3491–3494.
- [26] V. Hessel, P. Angeli, A. Gavriilidis, H. Löwe, *Ind. Eng. Chem. Res.* **2005**, *44*, 9750–9769.
- [27] X. Gong, P. W. Miller, A. D. Gee, N. J. Long, A. J. de Mello, R. Vilar, *Chem. Eur. J.* **2012**, *18*, 2768–2772.
- [28] B. Gutmann, P. Elsner, T. Glasnov, D. M. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2014**, *53*, 11557–11561.
- [29] P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2011**, *9*, 6903.

- [30] F. Mastronardi, B. Gutmann, C. Oliver Kappe, *Org. Lett.* **2013**, *15*, 5590–5593.
- [31] X. Liu, B. Ünal, K. F. Jensen, *Catal. Sci. Tech.* **2012**, *2*, 2134.
- [32] D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120–1125.
- [33] T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287.
- [34] T. Razzaq, T. N. Glasnov, C. O. Kappe, *Eur. J. Org. Chem.* **2009**, 1321–1325.
- [35] T. Razzaq, T. N. Glasnov, C. O. Kappe, *Chem. Eng. Technol.* **2009**, *32*, 1702–1716.
- [36] N. Ambreen, T. Wirth, *Eur. J. Org. Chem.* **2014**, *2014*, 7590–7593.
- [37] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675.
- [38] K. Arai, T. Wirth, *Org. Proc. Res. Dev.* **2014**, *18*, 1377–1381.
- [39] D. R. Snead, T. F. Jamison, *Angew. Chem. Int. Ed.* **2015**, *54*, 983–987.
- [40] T. Brodmann, P. Koos, A. Metzger, P. Knochel, S. V. Ley, *Org. Proc. Res. Dev.* **2012**, *16*, 1102–1113.
- [41] J. S. Moore, K. F. Jensen, *Org. Proc. Res. Dev.* **2012**, *16*, 1409–1415.
- [42] C. J. Welch, X. Gong, J. Cuff, S. Dolman, J. Nyrop, F. Lin, H. Rogers, *Org. Proc. Res. Dev.* **2009**, *13*, 1022–1025.
- [43] D. M. Roberge, M. Gottsponer, M. Eyholzer, N. Kockmann, *Chem. Today* **2009**, *27*, 8–11.
- [44] S. Vyawahare, A. D. Griffiths, C. A. Merten, *Chem. Biol.* **2010**, *17*, 1052–1065.
- [45] S. Lee, G. Robinson, *Process Development: Fine Chemicals from Grams to Kilograms*, Oxford University Press, Oxford, **1995**.
- [46] P. Styring, A. I. R. Parracho, *Beilstein J. Org. Chem.* **2009**, *5*, DOI 10.3762/bjoc.5.29.
- [47] P. Griess, *Proc. R. Soc. London* **1863**, *13*, 375–384.
- [48] T. Curtius, *Chem. Ber.* **1890**, *23*, 3023–3033.
- [49] T. Curtius, *J. für Prakt. Chemie* **1894**, *50*, 275–294.
- [50] A. Hantzsch, *Chem. Ber.* **1933**, *66*, 1349–1354.
- [51] G. L'abbe, *Chem. Rev.* **1969**, *69*, 345–363.
- [52] E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297–368.
- [53] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240.
- [54] S. Bräse, K. Banert, *Organic Azides: Syntheses and Applications*, John Wiley & Sons, Ltd, Chichester, **2010**.
- [55] P. L. Marinkas, *Organic Energetic Compounds*, Nova Science Publishers, Michigan, **1996**.
- [56] R. Haiges, J. A. Boatz, A. Vij, M. Gerken, S. Schneider, T. Schroer, K. O. Christe, *Angew. Chem. Int. Ed.* **2003**, *42*, 5847–5851.
- [57] M. H. V. Huynh, M. A. Hiskey, D. E. Chavez, D. L. Naud, R. D. Gilardi, *J. Am. Chem. Soc.* **2005**, *127*, 12537–12543.
- [58] T. Uchida, T. Katsuki, *Chem. Rec.* **2014**, *14*, 117–129.
- [59] A. Hassner, F. W. Fowler, *J. Am. Chem. Soc.* **1968**, *90*, 2869–2875.
- [60] R. Huisgen, *Proc. Chem. Soc.* **1961**, 357–396.

- [61] J. S. Mihina, R. M. Herbst, *J. Org. Chem.* **1950**, *15*, 1082–1092.
- [62] E. Leyva, M. S. Platz, G. Persy, J. Wirz, *J. Am. Chem. Soc.* **1986**, *108*, 3783–3790.
- [63] M. Regitz, *Angew. Chem. Int. Ed.* **1967**, *6*, 733–749.
- [64] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646.
- [65] H. Tanimoto, K. Kakiuchi, *Nat. Prod. Commun.* **2013**, *7*, 1021–1034.
- [66] J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249.
- [67] P. H. Seeberger, A. G. O'Brien, F. Lévesque, Y. Suzuki, *Chem. Today* **2011**, 57–61.
- [68] H. R. Sahoo, J. G. Kralj, K. F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5704–5708.
- [69] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith, J. P. Tierney, *Org. Biomol. Chem.* **2008**, *6*, 1577–1586.
- [70] M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1587–1593.
- [71] C. F. Carter, H. Lange, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode, N. L. Gaunt, *Org. Proc. Res. Dev.* **2010**, *14*, 393–404.
- [72] A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849–854.
- [73] A. R. Bogdan, K. James, *Org. Lett.* **2011**, *13*, 4060–4063.
- [74] L. Kupracz, J. Hartwig, J. Wegner, S. Ceylan, A. Kirschning, *Beilstein J. Org. Chem.* **2011**, *7*, 1441–1448.
- [75] S. B. Ötvös, Á. Georgiádes, I. M. Mándity, L. Kiss, F. Fülöp, *Beilstein J. Org. Chem.* **2013**, *9*, 1508–1516.
- [76] R. P. Jumde, C. Evangelisti, A. Mandoli, N. Scotti, R. Psaro, *J. Catal.* **2015**, *324*, 25–31.
- [77] W.-H. Song, M.-M. Liu, D.-W. Zhong, Y. Zhu, M. Bosscher, L. Zhou, D.-Y. Ye, Z.-H. Yuan, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4528–4531.
- [78] B. Gutmann, J.-P. Roudit, D. Roberge, C. O. Kappe, *Angew. Chem. Int. Ed.* **2010**, *49*, 7101–7105.
- [79] B. Gutmann, T. N. Glasnov, T. Razaq, W. Goessler, D. M. Roberge, C. O. Kappe, *Beilstein J. Org. Chem.* **2011**, *7*, 503–517.
- [80] A. G. O'Brien, F. Lévesque, P. H. Seeberger, *Chem. Commun.* **2011**, *47*, 2688–2690.
- [81] C. Willgerodt, *J. Prakt. Chem.* **1886**, *33*, 154–160.
- [82] M. S. Yusubov, V. V. Zhdankin, *Resour. Technol.* **2015**, *1*, 49–67.
- [83] T. Wirth, *Hypervalent Iodine Chemistry*, Springer Berlin Heidelberg, Berlin, Heidelberg, **2016**.
- [84] J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587.
- [85] H. Li, R. A. Widenhoefer, *Tetrahedron* **2010**, *66*, 4827–4831.
- [86] U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462–3465.
- [87] H. J. Kim, S. H. Cho, S. Chang, *Org. Lett.* **2012**, *14*, 1424–1427.
- [88] C. Röben, J. A. Souto, Y. González, A. Lishchynskiy, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478–9482.
- [89] C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2013**, *15*, 1008–1011.
- [90] A. Lishchynskiy, K. Muñiz, *Chem. Eur. J.* **2012**, *18*, 2212–2216.

- [91] H.-T. Yang, X.-W. Lu, M.-L. Xing, X.-Q. Sun, C.-B. Miao, *Org. Lett.* **2014**, *16*, 5882–5885.
- [92] K. B. Hong, J. N. Johnston, *Org. Lett.* **2014**, *16*, 3804–3807.
- [93] W. E. Fristad, T. A. Brandvold, J. R. Peterson, S. R. Thompson, *J. Org. Chem.* **1985**, *50*, 3647–3649.
- [94] T. Suzuki, A. Shibata, N. Morohashi, Y. Ohba, *Chem. Lett.* **2005**, *34*, 1476–1477.
- [95] R. Galli, V. Malatesta, *Org. Prep. Proced. Int.* **1971**, *3*, 231–233.
- [96] S. P. Chavan, Y. T. Subbarao, *Tetrahedron Lett.* **1999**, *40*, 5073–5074.
- [97] R. M. Moriarty, J. S. Khosrowshahi, *Tetrahedron Lett.* **1986**, *27*, 2809–2812.
- [98] R. M. Moriarty, R. K. Vaid, V. T. Ravikumar, B. K. Vaid, T. E. Hopkins, *Tetrahedron* **1988**, *44*, 1603–1607.
- [99] M. Tingoli, M. Tiecco, D. Chianelli, R. Balducci, A. Temperini, *J. Org. Chem.* **1991**, *56*, 6809–6813.
- [100] Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka, T. Yakura, *Tetrahedron Lett.* **1991**, *32*, 4321–4324.
- [101] P. Magnus, J. Lacour, W. Weber, *J. Am. Chem. Soc.* **1993**, *115*, 9347–9348.
- [102] P. Magnus, A. Evans, J. Lacour, *Tetrahedron Lett.* **1992**, *33*, 2933–2936.
- [103] P. Magnus, C. Hulme, W. Weber, *J. Am. Chem. Soc.* **1994**, *116*, 4501–4502.
- [104] P. Magnus, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1995**, 263.
- [105] P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406–3418.
- [106] H. Tohma, *Chem. Commun.* **1998**, 173–174.
- [107] D.-J. Chen, Z.-C. Chen, *Tetrahedron Lett.* **2000**, *41*, 7361–7363.
- [108] X.-Q. Li, X.-F. Zhao, C. Zhang, *Synthesis* **2008**, 2589–2593.
- [109] R. Chung, E. Yu, C. D. Incarvito, D. J. Austin, *Org. Lett.* **2004**, *6*, 3881–3884.
- [110] A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem. Int. Ed.* **1999**, *38*, 2594–2596.
- [111] N. V. Tsarevsky, *J. Polym. Sci. Part A Polym. Chem.* **2010**, *48*, 966–974.
- [112] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, M. S. Formanek, J. T. Bolz, *Tetrahedron Lett.* **1994**, *35*, 9677–9680.
- [113] M. V. Vita, J. Waser, *Org. Lett.* **2013**, *15*, 3246–3249.
- [114] H. Liang, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2011**, *50*, 11849–11851.
- [115] V. V. Zhdankin, K. J. Hanson, A. E. Kuposov, E. Blomquist, R. R. Tykwinski, *Mendeleev Commun.* **2001**, *11*, 51–52.
- [116] P. Theerthagiri, A. Lalitha, P. N. Arunachalam, *Tetrahedron Lett.* **2010**, *51*, 2813–2819.
- [117] P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910–9913.
- [118] J. N. Moorthy, K. N. Parida, *J. Org. Chem.* **2014**, *79*, 11431–11439.
- [119] Z. Li, C. Zhang, L. Zhu, C. Liu, C. Li, *Org. Chem. Front.* **2014**, *1*, 100–104.
- [120] B. Zhang, A. Studer, *Org. Lett.* **2013**, *15*, 4548–4551.
- [121] X.-F. Xia, Z. Gu, W. Liu, H. Wang, Y. Xia, H. Gao, X. Liu, Y.-M. Liang, *J. Org. Chem.* **2015**,

80, 290–295.

- [122] L. Xu, X.-Q. Mou, Z.-M. Chen, S.-H. Wang, *Chem. Commun.* **2014**, 10676–10679.
- [123] P. Chouthaiwale, P. Karabal, G. Suryavanshi, A. Sudalai, *Synthesis* **2010**, 3879–3882.
- [124] M. Bruno, R. Margarita, L. Parlanti, G. Piancatelli, M. Trifoni, *Tetrahedron Lett.* **1998**, *39*, 3847–3848.
- [125] P. D. Woodgate, H. H. Lee, P. S. Rutledge, R. C. Cambie, *Tetrahedron Lett.* **1976**, *17*, 1531–1534.
- [126] N. Thoai, M. Rubinstein, C. Wakselman, *J. Fluor. Chem.* **1982**, *21*, 437–444.
- [127] T. Ando, J. H. Clark, D. G. Cork, M. Fujita, T. Kimura, *J. Am. Chem. Soc.* **1987**, *10*, 1301–1302.
- [128] V. Nair, L. G. Nair, *Tetrahedron Lett.* **1998**, *39*, 4585–4586.
- [129] V. Nair, T. G. George, L. G. Nair, S. B. Panicker, *Tetrahedron Lett.* **1999**, *40*, 1195–1196.
- [130] V. Nair, L. G. Nair, T. G. George, A. Augustine, *Tetrahedron* **2000**, *56*, 7607–7611.
- [131] K. Liu, D.-P. Li, S.-F. Zhou, X.-Q. Pan, A. Shoberu, J.-P. Zou, *Tetrahedron* **2015**, *71*, 4031–4034.
- [132] J. S. Yadav, B. V. Reddy, M. K. Gupta, *Synthesis* **2004**, 1983–1986.
- [133] V. K. Jadhav, R. R. Pal, P. P. Wadgaonkar, M. M. Salunkhe, *Synth. Commun.* **2001**, *31*, 3041–3045.
- [134] G. Wu, W. Wu, R. Li, Y. Shen, L. Wu, *Chem. Lett.* **2007**, *36*, 188–189.
- [135] A. Icar, “Liquid Explosives review,” can be found under http://www.aiexplosives.com/inspections_articles.asp?id=23, **n.d.**
- [136] J. Sullivan, W. Sunderland, *Liquid Explosive in Pipes*, Springfield, **1994**.
- [137] “Oklahoma Bombing (1995 Bombing of Alfred P. Murrah Building).,” can be found under <http://www.encyclopedia.com/doc/1G2-3448300419.html>, **2005**.
- [138] T. Sugiyama, *Bull. Inst. Chem. Res.* **1989**, *67*, 112–120.
- [139] G. A. Olah, P. Ramaiah, C.-S. Lee, G. K. Surya Prakash, *Synlett* **1992**, 337–339.
- [140] M. Carmeli, S. Rozen, *J. Org. Chem.* **2006**, *71*, 4585–4589.
- [141] G. W. Kabalka, G. M. H. Laila, R. S. Varma, *Tetrahedron* **1990**, *46*, 7443–7457.
- [142] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **2000**, *2*, 4257–4259.
- [143] L. Henry, *Acad. Sci. Ser. C.* **1895**, 1265.
- [144] L. Henry, *Bull. Soc. Chim. Fr.* **1895**, *13*, 999.
- [145] F. a. Luzzio, *Tetrahedron* **2001**, *57*, 915–945.
- [146] Y. Alvarez-Casao, E. Marques-Lopez, R. P. Herrera, *Symmetry* **2011**, *3*, 220–245.
- [147] J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymm* **2006**, *17*, 3315–3326.
- [148] A. V. Biradar, K. K. Sharma, T. Asefa, *Appl. Catal. A Gen.* **2010**, *389*, 19–26.
- [149] K. Kawai, T. Ebata, T. Kitazume, *J. Fluor. Chem.* **2005**, *126*, 956–961.
- [150] K. Hashimoto, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 3496–3499.
- [151] W. A. Nugent, *Org. Lett.* **2002**, *4*, 2133–2136.
- [152] X. Wu, X. Li, M. McConville, O. Saidi, J. Xiao, *J. Mol. Cat. A* **2006**, *247*, 153–158.
- [153] M. C. Etter, T. W. Panunto, *J. Am. Chem. Soc.* **1988**, *110*, 5896–5897.

- [154] R. J. Rahaim, R. E. Maleczka, *Org. Lett.* **2005**, *7*, 5087–5090.
- [155] K. Wang, X. Qian, J. Cui, *Tetrahedron* **2009**, *65*, 10377–10382.
- [156] M. J. Guttieri, W. F. Maier, *J. Org. Chem.* **1984**, *49*, 2875–2880.
- [157] W. E. Noland, *Chem. Rev.* **1955**, *55*, 137–155.
- [158] **n.d.**
- [159] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.
- [160] A. Odedra, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2009**, *48*, 2699–2702.
- [161] “<http://thalesnano.com/publication>,” List of reductiona using thales nano can be found under <http://thalesnano.com/publication>.
- [162] M. Irfan, T. N. Glasnov, C. O. Kappe, *ChemSusChem* **2011**, *4*, 300–316.
- [163] P. J. Cossar, L. Hizartidis, M. I. Simone, A. McCluskey, C. P. Gordon, *Org. Biomol. Chem.* **2015**, *13*, 7119–7130.
- [164] K. Gilmore, S. Vukelić, D. T. McQuade, B. Kocsch, P. H. Seeberger, *Org. Proc. Res. Dev.* **2014**, *18*, 1771–1776.
- [165] S. G. Newman, L. Gu, C. Lesniak, G. Victor, F. Meschke, L. Abahmane, K. F. Jensen, *Green Chem.* **2014**, *16*, 176–180.
- [166] J. de M. Muñoz, J. Alcázar, A. de la Hoz, A. Díaz-Ortiz, *Tetrahedron Lett.* **2011**, *52*, 6058–6060.
- [167] D. Webb, T. F. Jamison, *Org. Lett.* **2012**, *14*, 568–571.
- [168] J. de M. Muñoz, J. Alcázar, A. de la Hoz, A. Díaz-Ortiz, *Eur. J. Org. Chem.* **2012**, *52*, 260–263.
- [169] C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett.* **2013**, *15*, 2278–2281.
- [170] A. S. Kleinke, T. F. Jamison, *Org. Lett.* **2013**, *15*, 710–713.
- [171] B. Pieber, S. T. Martinez, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2013**, *52*, 10241–10244.
- [172] S. De Angelis, M. De Renzo, C. Carlucci, L. Degennaro, R. Luisi, *Org. Biomol. Chem.* **2016**, *14*, 4304–4311.
- [173] J. Sedelmeier, S. V. Ley, I. R. Baxendale, *Green Chem.* **2009**, *11*, 683.
- [174] B. Elamin, J.-W. Park, G. E. Means, *Tetrahedron Lett.* **1988**, *29*, 5599–5600.
- [175] C. H. Hornung, B. Hallmark, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Adv. Synth. Catal.* **2010**, *352*, 1736–1745.
- [176] R. Javaid, S. Kawasaki, A. Suzuki, T. M. Suzuki, *Beilstein J. Org. Chem.* **2013**, *9*, 1156–1163.
- [177] P. Falus, Z. Boros, G. Hornyánszky, J. Nagy, F. Darvas, L. Üрге, L. Poppe, *Tetrahedron Lett.* **2011**, *52*, 1310–1312.
- [178] V. R. Jumde, E. Petricci, C. Petrucci, N. Santillo, M. Taddei, L. Vaccaro, *Org. Lett.* **2015**, *17*, 3990–3993.
- [179] S. Saaby, K. R. Knudsen, M. Ladlow, S. V. Ley, *Chem. Commun.* **2005**, 2909.
- [180] M. Mirza-Aghayan, R. Boukherroub, M. Bolourtchian, *Appl. Organomet. Chem.* **2006**, *20*, 214–219.

- [181] N. Ambreen, R. Kumar, T. Wirth, *Beilstein J. Org. Chem.* **2013**, *9*, 1437–1442.
- [182] J. N. Moorthy, K. Senapati, K. N. Parida, S. Jhulki, K. Sooraj, N. N. Nair, *J. Org. Chem.* **2011**, *76*, 9593–9601.
- [183] R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith, T. Wirth, *Angew. Chem. Int. Ed.* **2007**, *46*, 6529–6532.
- [184] A. Ozanne, L. Pouységu, D. Depernet, B. François, S. Quideau, *Org. Lett.* **2003**, *5*, 2903–2906.
- [185] E. J. Corey, M. Ishiguro, *Tetrahedron Lett.* **1979**, *20*, 2745–2748.
- [186] Z.-G. Wang, Y.-G. Xia, Y. Jin, M. Lu, *Appl. Organomet. Chem.* **2015**, *29*, 109–112.
- [187] H. Tomioka, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1982**, *23*, 539–542.
- [188] A. B. Leduc, T. F. Jamison, *Org. Proc. Res. Dev.* **2012**, *16*, 1082–1089.
- [189] B. Perlmutter-Hayman, Y. Weissmann, *J. Am. Chem. Soc.* **1969**, *91*, 668–672.
- [190] T.-L. Ho, M. Fieser, L. Fieser, in *Fieser Fieser's Reagents Org. Synth.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2006**, pp. 58–59.
- [191] C. Battilocchio, J. M. Hawkins, S. V. Ley, *Org. Lett.* **2014**, *16*, 1060–1063.
- [192] N. M. Roda, D. N. Tran, C. Battilocchio, R. Labes, R. J. Ingham, J. M. Hawkins, S. V. Ley, *Org. Biomol. Chem.* **2015**, *13*, 2550–2554.
- [193] D. M. Allwood, D. C. Blakemore, A. D. Brown, S. V. Ley, *J. Org. Chem.* **2014**, *79*, 328–338.
- [194] A. Shaabani, P. Mirzaei, S. Naderi, D. G. Lee, *Tetrahedron* **2004**, *60*, 11415–11420.
- [195] T. A. Elmaaty, L. W. Castle, *Molecules* **2005**, *10*, 1458–1461.
- [196] C. Bhat, S. G. Tilve, *Tetrahedron* **2013**, *69*, 6129–6143.
- [197] H. W. Pinnick, in *Org. React.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **1990**, pp. 655–792.
- [198] J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618–3621.
- [199] P. Ceccherelli, M. Curini, M. C. Marcotullio, F. Epifano, O. Rosati, *Synth. Commun.* **1998**, *28*, 3057–3064.
- [200] M. Hawkins, *Eur. J. Anaesthesiol.* **1999**, *16*, 585.
- [201] S. T. Omaye, *Toxicology* **2002**, *180*, 139–150.
- [202] G. B. Vásquez, X. Ji, C. Fonticelli, G. L. Gilliland, *Acta Crystallogr. Sect. D* **1998**, *54*, 355–366.
- [203] *WHO Air Quality Guidelines for Europe*, Copenhagen, **2000**.
- [204] T. Baird, J. R. Fryer, B. Grant, *Carbon N. Y.* **1974**, *12*, 591–602.
- [205] L. Mond, C. Langer, F. Quincke, *J. Chem. Soc. Trans.* **1890**, *57*, 749.
- [206] W. C. Roberts-Austin, *Nature* **1898**, *59*, 63–64.
- [207] J. Huheey, E. Keiter, R. Keiter, *Metallcarbonyle Anorganische Chemie*, De Gruyter, Berlin/New York, **1995**.
- [208] S. T. Gadge, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 10367–10389.
- [209] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, University Press: New York, Oxford, **1998**.
- [210] D. Forster, in *Mech. Pathways Catal. Carbonylation Methanol by Rhodium Iridium Complexes*, **1979**, pp. 255–267.

- [211] G. J. Sunley, D. J. Watson, *Catal. Today* **2000**, *58*, 293–307.
- [212] P. Ellwood, *Chem Eng News* **1969**, 148.
- [213] J. Falbe, *Carbon Monoxide in Organic Synthesis*, Springer Berlin Heidelberg, Berlin, Heidelberg, **1970**.
- [214] R. Kummer, *Angew. Chemie* **2006**, *94*, 156–156.
- [215] S. W. Polichnowski, *J. Chem. Educ.* **1986**, *63*, 206.
- [216] O. Roelen, *Angew. Chemie* **1948**, *60*, 62.
- [217] H. Adkins, G. Krsek, *J. Am. Chem. Soc.* **1948**, *70*, 383–386.
- [218] I. Wender, M. Orchin, H. H. Storch, *J. Am. Chem. Soc.* **1950**, *72*, 4842–4843.
- [219] W. Reppe, H. Vetter, *Liebigs Annalen* **1953**, *582*, 133–161.
- [220] A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318–3326.
- [221] Y.-S. Lin, A. Yamamoto, *Organometallics* **1998**, *17*, 3466–3478.
- [222] A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129–133.
- [223] P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, J. Passchier, A. Gee, *Chem. Commun.* **2006**, 546–548.
- [224] M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236–2238.
- [225] P. Miller, L. Jennings, A. DeMello, A. Gee, N. Long, R. Vilar, *Adv. Synth. Catal.* **2009**, *351*, 3260–3268.
- [226] P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, H. Audrain, D. Bender, J. Passchier, A. Gee, *Angew. Chem. Int. Ed.* **2007**, *46*, 2875–2878.
- [227] J. Balogh, Á. Kuik, L. Üрге, F. Darvas, J. Bakos, R. Skoda-Földes, *J. Mol. Cat. A* **2009**, *302*, 76–79.
- [228] C. Csajági, B. Borcsek, K. Niesz, I. Kovács, Z. Székelyhidi, Z. Bajkó, L. Üрге, F. Darvas, *Org. Lett.* **2008**, *10*, 1589–1592.
- [229] E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1734–1737.
- [230] C. B. Kelly, C. Lee, M. A. Mercadante, N. E. Leadbeater, *Org. Proc. Res. Dev.* **2011**, *15*, 717–720.
- [231] T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.* **2014**, *16*, 2042.
- [232] Y. Takebayashi, K. Sue, S. Yoda, T. Furuya, K. Mae, *Chem. Eng. J.* **2012**, *180*, 250–254.
- [233] T. Fukuyama, M. T. Rahman, N. Kamata, I. Ryu, *Beilstein J. Org. Chem.* **2009**, *5*, DOI 10.3762/bjoc.5.34.
- [234] T. Fukuyama, Y. Mukai, I. Ryu, *Beilstein J. Org. Chem.* **2011**, *7*, 1288–1293.
- [235] U. Gross, P. Koos, M. O'Brien, A. Polyzos, S. V. Ley, *Eur. J. Org. Chem.* **2014**, 6418–6430.
- [236] C. Brancour, T. Fukuyama, Y. Mukai, T. Skrydstrup, I. Ryu, *Org. Lett.* **2013**, *15*, 2794–2797.
- [237] H. Koch, W. Haaf, *Liebigs Annalen* **1958**, *618*, 251–266.
- [238] H. Mori, A. Mori, Q. Xu, Y. Souma, *Tetrahedron Lett.* **2002**, *43*, 7871–7874.
- [239] N. Tsumori, Q. Xu, Y. Souma, H. Mori, *J. Mol. Cat. A* **2002**, *179*, 271–277.
- [240] K. Qiao, C. Yokoyama, *Catal. Commun.* **2006**, *7*, 450–453.

- [241] F. A. Cotton, *Helv. Chim. Acta* **1967**, *50*, 117–130.
- [242] Y. Souma, H. Sano, *J. Org. Chem.* **1973**, *38*, 3633–3635.
- [243] Y. Souma, H. Sano, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1717–1719.
- [244] Q. Xu, Y. Imamura, M. Fujiwara, Y. Souma, *J. Org. Chem.* **1997**, *62*, 1594–1598.
- [245] Q. Xu, Y. Souma, J. Umezawa, M. Tanaka, H. Nakatani, *J. Org. Chem.* **1999**, *64*, 6306–6311.
- [246] Q. Xu, H. Nakatani, Y. Souma, *J. Org. Chem.* **2000**, *65*, 1540–1543.
- [247] Q. Xu, M. Fujiwara, M. Tanaka, Y. Souma, *J. Org. Chem.* **2000**, *65*, 8105–8107.
- [248] Y. Takahashi, N. Yoneda, H. Nagai, *Chem. Lett.* **1985**, 1733–1734.
- [249] T. M'Hiri, C. Catusse, R. Catusse, J. L. Janier Dubry, *React. Kinet. Catal. Lett.* **1983**, *22*, 425–428.
- [250] J. J. Ritter, P. P. Minieri, *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048.
- [251] F. R. Benson, J. J. Ritter, *J. Am. Chem. Soc.* **1949**, *71*, 4128–4129.
- [252] A. Guérinot, S. Reymond, J. Cossy, *Eur. J. Org. Chem.* **2012**, 19–28.
- [253] D. Jiang, T. He, L. Ma, Z. Wang, *RSC Adv.* **2014**, *4*, 64936–64946.
- [254] L. Audiger, K. Watts, S. C. Elmore, R. I. Robinson, T. Wirth, *ChemSusChem* **2012**, *5*, 257–260.
- [255] J. Brandt, S. Elmore, R. Robinson, T. Wirth, *Synlett* **2010**, 3099–3103.
- [256] D. A. Kamble, P. U. Karabal, P. V. Chouthaiwale, A. Sudalai, *Tetrahedron Lett.* **2012**, *53*, 4195–4198.
- [257] M.-Z. Lu, C.-Q. Wang, T.-P. Loh, *Org. Lett.* **2015**, *17*, 6110–6113.
- [258] R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* **2010**, *12*, 4678–4681.
- [259] T. Kitamura, K. Otsubo, *J. Org. Chem.* **2012**, *77*, 2978–2982.
- [260] M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem. Int. Ed.* **2010**, *49*, 7068–7071.
- [261] M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177.
- [262] D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457–9461.
- [263] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586.
- [264] X.-Q. Li, C. Zhang, *Synthesis* **2009**, 1163–1169.
- [265] A. McKillop, D. Kemp, *Tetrahedron* **1989**, *45*, 3299–3306.
- [266] A. N. Chulin, I. L. Rodionov, L. K. Baidakova, L. N. Rodionova, T. A. Balashova, V. T. Ivanov, *J. Pept. Sci.* **2005**, *11*, 175–186.
- [267] H. Saltzman, J. Sharefkin, *Org. Synth.* **1963**, *43*, 60.
- [268] E. A. Merritt, V. M. T. Carneiro, L. F. Silva, B. Olofsson, *J. Org. Chem.* **2010**, *75*, 7416–7419.
- [269] M. S. Yusubov, T. Wirth, *Org. Lett.* **2005**, *7*, 519–521.
- [270] X.-F. Zhao, C. Zhang, *Synthesis* **2007**, 551–557.
- [271] S. Jammi, M. A. Ali, S. Sakthivel, L. Rout, T. Punniyamurthy, *Chem Asian J* **2009**, *4*, 314–320.
- [272] G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725–

4730.

- [273] K. Kanagaraj, P. Suresh, K. Pitchumani, *Org. Lett.* **2010**, *12*, 4070–4073.
- [274] G. Shang, D. Liu, S. E. Allen, Q. Yang, X. Zhang, *Chem. Eur. J.* **2007**, *13*, 7780–7784.
- [275] T. Maegawa, K. Otake, A. Goto, H. Fujioka, *Org. Biomol. Chem.* **2011**, *9*, 5648.
- [276] Y. Luan, N. Zheng, Y. Qi, J. Yu, G. Wang, *Eur. J. Inorg. Chem.* **2014**, 4268–4272.
- [277] H. P. Hemantha, V. V. Sureshbabu, *Org. Biomol. Chem.* **2011**, *9*, 2597.
- [278] C. H. V. Kumar, K. N. Shivananda, C. N. Raju, R. V. Jagadeesh, *Synth. Commun.* **2010**, *40*, 3480–3487.
- [279] E. Regulska, M. Samsonowicz, R. Świśtocka, W. Lewandowski, *J. Mol. Struct.* **2009**, *936*, 162–170.
- [280] U. Sharma, P. Kumar, N. Kumar, V. Kumar, B. Singh, *Adv. Synth. Catal.* **2010**, *352*, 1834–1840.
- [281] Z. Garkani-Nejad, M. Poshteh-Shirani, *Can. J. Chem.* **2011**, *89*, 598–607.
- [282] M. Hayashi, H. Kawabata, K. Yoshimoto, T. Tanaka, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2007**, *182*, 433–445.
- [283] N. Mori, H. Togo, *Synlett* **2005**, 1456–1458.
- [284] A. Kommreddy, M. S. Bowsher, M. R. Gunna, K. Botha, T. K. Vinod, *Tetrahedron Lett.* **2008**, *49*, 4378–4382.
- [285] Y. Hamada, K. Ando, T. Shioiri, *Chem. Pharm. Bull.* **1981**, *29*, 259–261.
- [286] C. M. Welch, H. A. Smith, *J. Am. Chem. Soc.* **1953**, *75*, 1412–1415.
- [287] M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, *Eur. J. Org. Chem.* **2009**, *2009*, 430–436.
- [288] S. Farhadi, S. Panahandehjoo, *Eur. J. Chem.* **2010**, *1*, 335–340.
- [289] M. Barbero, S. Cadamuro, S. Dughera, P. Venturello, *Synthesis* **2008**, 3625–3632.
- [290] D. K. Yung, M. L. Gilroy, D. E. Mahony, *J. Pharm. Sci.* **1978**, *67*, 900–905.
- [291] C. Azerraf, D. Gelman, *Chem. Eur. J.* **2008**, *14*, 10364–10368.
- [292] V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymm* **2007**, *18*, 400–405.
- [293] R. Popielarz, D. R. Arnold, *J. Am. Chem. Soc.* **1990**, *112*, 3068–3082.
- [294] J. R. Coats, J. W. Williams, C. Chang, A.-H. Lee, R. L. Metcalf, *Environ. Toxicol. Chem.* **1989**, *8*, 45–52.
- [295] O. Grummitt, A. Buck, *J. Am. Chem. Soc.* **1945**, *67*, 693–693.
- [296] R. Sanz, A. Martínez, V. Guilarte, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Eur. J. Org. Chem.* **2007**, 4642–4645.
- [297] G. W. H. Cheeseman, *J. Chem. Soc.* **1957**, 115.
- [298] T. V. Q. Nguyen, W.-J. Yoo, S. Kobayashi, *Angew. Chem. Int. Ed.* **2015**, *54*, 9209–9212.
- [299] Y. Yamamoto, H. Hasegawa, H. Yamataka, *J. Org. Chem.* **2011**, *76*, 4652–4660.
- [300] N. Ibrahim, A. S. K. Hashmi, F. Rominger, *Adv. Synth. Catal.* **2011**, *353*, 461–468.