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Title	Taming hazardous chemistry in flow: The continuous processing of diazo and diazonium compounds
Authors	Deadman, Benjamin J.;Collins, Stuart G.;Maguire, Anita R.
Publication date	2014-11-17
Original Citation	DEADMAN, B. J., COLLINS, S. G. & MAGUIRE, A. R. 2014. Taming Hazardous Chemistry in Flow: The Continuous Processing of Diazo and Diazonium Compounds. Chemistry – A European Journal, doi: 10.1002/chem.201404348
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1002/chem.201404348
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Download date	2026-11-12 06:20:44
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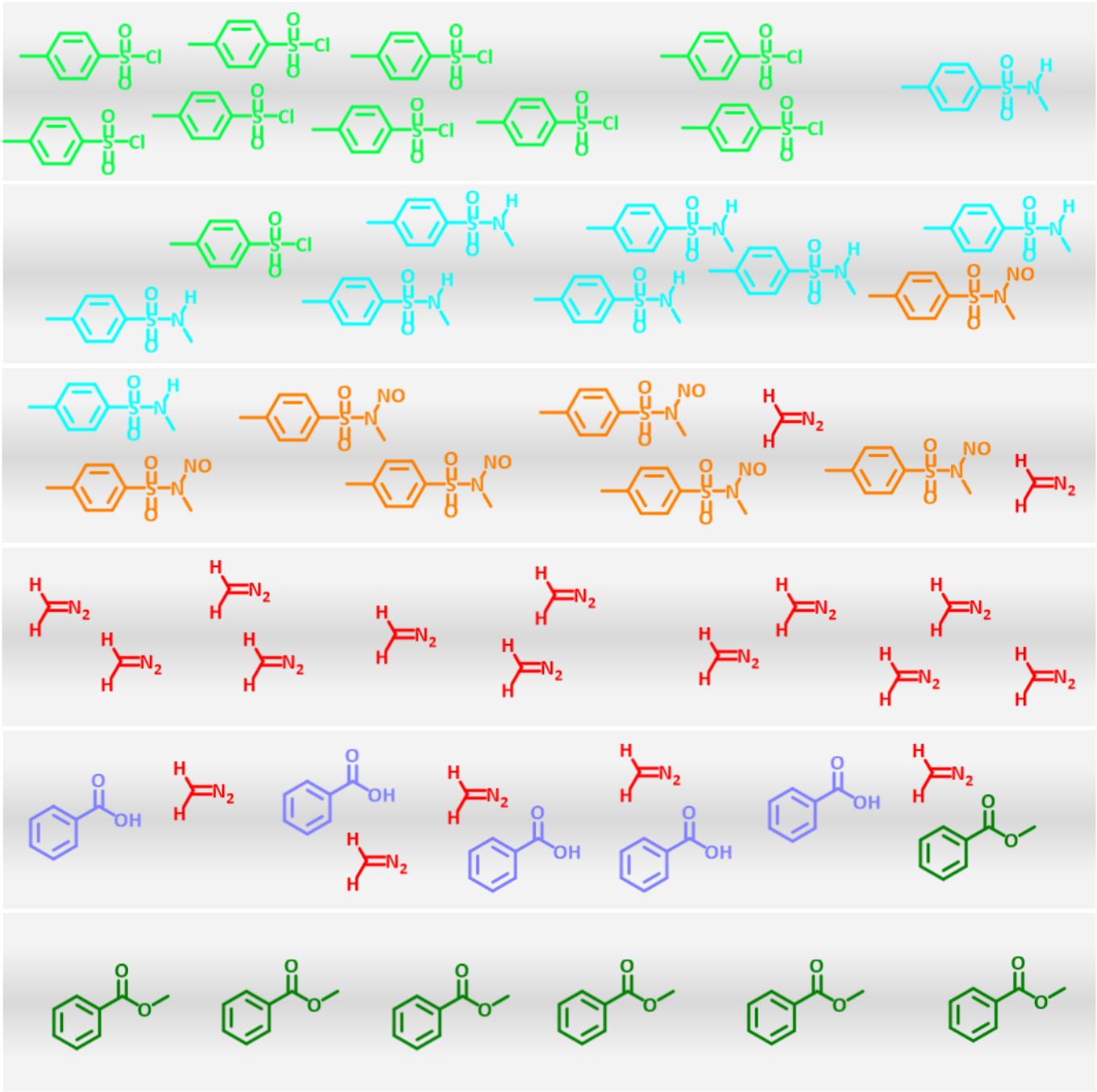
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Flow Chemistry

Taming Hazardous Chemistry in Flow: The Continuous Processing of Diazo and Diazonium Compounds

Benjamin J. Deadman,[a] Stuart G. Collins[a] and Anita R. Maguire*[b]



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Abstract: The synthetic utilities of the diazo and diazonium groups are matched only by their reputation for explosive decomposition. Continuous processing technology offers new opportunities to make and use these versatile intermediates at a range of scales with improved safety over traditional batch processes. In this minireview, the state of the art in the continuous flow processing of reactive diazo and diazonium species is discussed.

Introduction

Diazo and diazonium compounds are extremely versatile intermediates and reagents in organic synthesis. Diazoalkanes are important alkylating reagents,[1,2] while α-diazocarbonyls are important for their role in generating carbenes and metal carbenoids,[1,3–20] and also for providing access to reactive ketene and heteroanalogous intermediates *via* the Wolff rearrangement.[21–26] Diazo compounds are also important 1,3-dipoles for heterocycle-forming cycloaddition reactions.[27–32] The diazonium ion moiety is an important leaving group in Sandmeyer,[33–35] Meerwein,[36,37] Balz-Schiemann[38,39] and palladium catalysed cross coupling[40–42] chemistry; and is an essential reagent for the preparation of azo compounds, the backbone of the synthetic dye industry.[42,43]

The versatility of the diazo and diazonium moieties is matched only by their fearsome reputation. Diazoalkanes are highly toxic due to their potent alkylation of DNA.[44] Furthermore, diazo and diazonium compounds are highly energetic by nature and explosions can be triggered by shock, heat or exposure to concentrated acids.[44,45] α-Diazocarbonyls are considerably more stable than diazoalkanes and diazoniums due to the resonance stabilisation of adjacent carbonyls but detonation is still possible under more forcing conditions.[44,46] These safety concerns necessitate caution when using diazo and diazonium intermediates in the laboratory, and have limited their use on scale in industry. The synthetic utility of these hazardous compounds has led to a recent interest in developing safer alternative methods for their preparation and use.[1,44]

Continuous processing is rapidly growing in the academic, pharmaceutical and fine chemical sectors due to its favourable safety profile among other benefits such as efficient mixing, enhanced heat and mass transfer, access to extreme reaction conditions, reproducibility and scale up, in-line workups and automated operation.[47–54] The safety profile offered by continuous processing is perhaps the most compelling reason for its popularity in recent years. Sensitive and toxic reaction intermediates can be generated and consumed during a single flow process without the need for stockpiling hazardous quantities of material. Furthermore, the high surface area-to-volume ratio of tubular flow reactors also ensures rapid dissipation of heat and reduces the risk of reaction runaway.

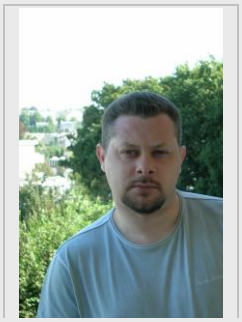
Continuous processing technology has allowed chemists to tame a number of hazardous chemistries including nitration,[55] use of azides[56–58] and fluorination.[59,60] The synthesis and use of diazo and diazonium compounds are no exception. There has been significant interest in the application of modern continuous processing technology to the generation and use of diazo and diazonium compounds at both laboratory and industrial scales. This minireview highlights the advances made in this area.

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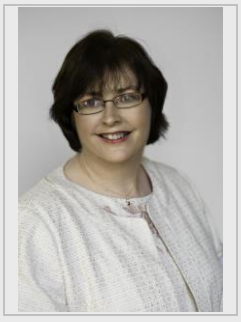
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Stuart G. Collins received a BSc. Degree in Chemistry, UCC in 1998 and then did his PhD. in Organic Chemistry at UCC under the supervision of Prof. Anita Maguire. He subsequently worked as a Postdoctoral Researcher on two projects, the first on development of novel methodology for the synthesis of phosphononucleosides as antiviral agents and the second on the asymmetric synthesis of unnatural amino acids. Stuart has been a lecturer in Organic and Pharmaceutical Chemistry in UCC since 2004.



Anita R. Maguire studied at University College Cork (B.Sc. 1985, PhD. 1989), focusing during her Ph.D on asymmetric catalysis in reactions of α-diazo ketones. Following postdoctoral research at Namur, Belgium and subsequently at Exeter, she returned to Cork in 1991. Her research interests include development of new synthetic methodology in α-diazocarbonyl chemistry, asymmetric synthesis including biocatalysis, and the design and synthesis of bioactive compounds.

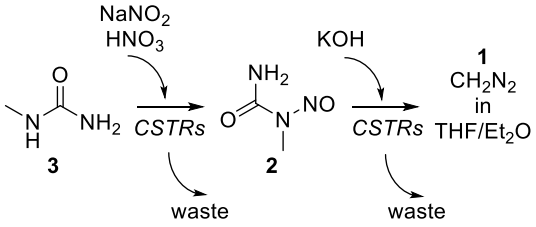
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Diazomethane (1)

The sensitivity of diazomethane (**1**) to shock and heat is such that its batch preparation has to be performed in specialised glass apparatus without ground glass joints. The Diazald® process can provide up to 200-300 mmol of diazomethane (**1**) per batch.[61] Early progress in developing continuous diazomethane (**1**) generation procedures appears to have been driven by a need to safely work at larger scales.

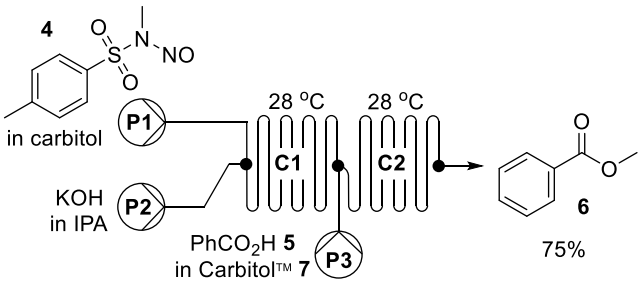
In 1998 Aerojet, a US manufacturer of rocket and missile propellants with a fine chemicals division (the division was later sold to become AMPAC Fine Chemicals), filed a patent for the continuous production of ethereal solutions of diazomethane (**1**).[62] Their process used a series of continuously stirred tank reactor (CSTR) stages to generate *N*-nitroso-*N*-methylurea (**2**, MNU) from non-hazardous *N*-methylurea (**3**) (Scheme 1). A phase separation stage facilitated the removal of the excess reagents into a treated aqueous waste stream while the ethereal solution of MNU (**2**) could be decomposed to diazomethane (**1**) in two CSTR stages by the addition of an aqueous KOH reagent stream. A final phase separation was reported to provide a continuous supply of 61 mol/h of diazomethane (**1**) in THF/Et_2O. The Aerojet process is notable for allowing the diazomethane precursor (**2**) to be generated, decomposed and used on-site. As the patent only described a laboratory scale model process it is unclear whether the process was ever operated at plant scale.



Scheme 1. The Aerojet process for continuous generation of diazomethane (**1**).[62]

English company Phoenix Chemicals Ltd. developed an alternative plant for the continuous generation of diazomethane (**1**) from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (**4**, Diazald®).[45] They cited the solvent system to be a key limitation of the Aerojet process and came up with the alternative solution of extracting diazomethane (**1**) in the gas phase. In this process a continuous feed of Diazald® (**4**) is decomposed to diazomethane (**1**) by reaction with an aqueous KOH feed. Subsurface and headspace flows of nitrogen gas extract diazomethane (**1**) into the gas phase where it can intercept a flow of substrate as part of an integrated multistage continuous process for the production of halomethyl ketone intermediates. These intermediates are important building blocks in the synthesis of HIV protease inhibitor drugs such as nelfinavir mesylate. The Phoenix plant was designed to produce 60 metric tonnes of diazomethane (**1**) per year and operated without incident for a number of years before the company went into administration in 2011. It incorporated a number of safety features such as on-line monitoring of diazomethane (**1**), secondary fail safe monitoring, automated shutdown and was designed to safely quench the reactor contents in the worst-case scenario of a reactor burst failure.

There has also been considerable interest in using microreactors to access small quantities of diazomethane (**1**) in laboratories.[63–66] One of the earlier setups for producing diazomethane (**1**) in a laboratory scale continuous process was that reported by Stark and co-workers (Scheme 2).[64] In their microreactor a solution of Diazald® (**4**) was delivered into the reactor by a syringe pump (**P1**). A second syringe pump (**P2**) brought in an aqueous solution of KOH to induce decomposition of Diazald® (**4**) and release one equivalent of diazomethane (**1**). The efficient mixing of the two reaction streams inside the microreactor chip (**C1**) provided maximum conversion in 5 s. The substrate for methylation, in this case benzoic acid (**5**) was introduced by a third syringe pump (**P3**). Methylation occurred within 10 s inside the second stage of the microreactor chip (**C2**) and methyl benzoate (**6**) was obtained in 75% yield over a period of one hour. The unusual solvent system of 2-(2-ethoxyethoxy)ethanol (**7**, Carbitol™) and isopropanol was necessary to prevent precipitation of salts occurring inside the microreactor.



Scheme 2. Generation of diazomethane (**1**) and methylation in a microreactor.[64] **P** = syringe pump, **C** = microreactor chip.

The same group later published a follow-up work where they used a series of microreactors and liquid-liquid phase separations to prepare the precursor Diazald® (**4**) from *p*-toluenesulfonyl chloride and decompose it to diazomethane (**1**) for use in methylation of benzoic acid (**5**).[67] The extended microreactor system provided methyl benzoate (**6**) at a rate of 0.1 mol/h in a yield of 75%.

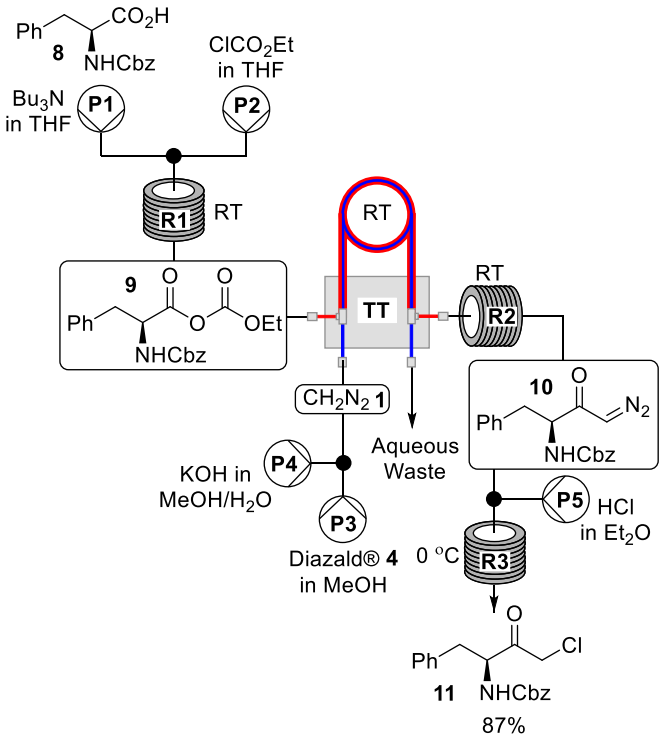
More recently Woehl, Maggini and co-workers scaled up a continuous diazomethane (**1**) generation in a Corning GEN1 flow reactor.[65] They utilised MNU (**2**) as the diazomethane (**1**) precursor and employed a biphasic solvent system of water, diethyl ether and diethylene glycol to prevent blockages in the flow reactor. The flow process was quickly scaled up from a 0.9 mL microreactor to a 25 mL flow reactor capable of generating 0.8 mol/h of diazomethane (**1**).

One of the greatest hazards associated with the generation of diazomethane (**1**) in batch mode comes from the required co-distillation of diazomethane (**1**) with diethyl ether. This is typically accomplished using specialty glassware (with rounded joints) and over a low heat such as that provided by a warm water bath. Microfluidic technology offers new methods of performing this separation safely in a continuous and convenient process. Kim and co-workers have developed a dual channel reactor where a hydrophobic poly(dimethylsiloxane) (PDMS) membrane allows

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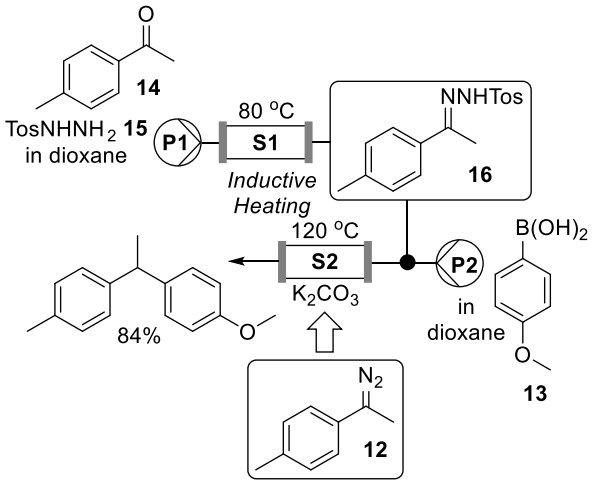
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the passage of organics between the two separate channels whilst retaining the aqueous phase.[66] The base-induced decomposition of Diazald® (**4**) could thus be performed in a water and dimethyl formamide (DMF) mixture in one channel of the reactor, and the released diazomethane (**1**) transferred across the membrane into the other reactor channel where it could be utilised to perform organic transformations under anhydrous conditions. Simple methylation of acetic acid or phenol proceeded in greater than 99% yield. The reactor could also be used to perform Arndt-Eistert reactions.



Scheme 3. Generation of anhydrous diazomethane (**1**) using a tube-in-tube membrane reactor.[68,69] **P** = pump, **R** = reactor coil, **TT** = tube-in-tube membrane reactor.

A limitation of Kim's microfluidic process is the small quantities of anhydrous diazomethane (**1**) which it produces (1 mmol in 8 hours operation).[66] The same membrane separation concept was later employed by Kappe and co-workers in a tubular mesofluidic system capable of producing 3.6 mmol of anhydrous diazomethane (**1**) per hour.[68] The membrane separator in this case was the gas permeable AF-2400 tube-in-tube reactor (**TT**) originally developed by Ley and co-workers.[70,71] The anhydrous diazomethane (**1**) generated in this system was successfully utilised in simple methylation reactions of aromatic acids and tetrazoles (80-99% yield), cycloaddition with *N*-phenylmaleimide (76% yield), cyclopropanation of an alkene (59% yield) and the Arndt-Eistert transformation of three acyl chlorides to the corresponding *α*-chloroketones (78-93% yield).[68] In a follow-up publication they demonstrated that chiral intermediates of HIV protease inhibitors could be prepared in a telescoped flow process (Scheme 3) incorporating four distinct operations.[69] Firstly, a solution of Diazald® (**4**) in MeOH (**P3**) was combined with a solution of KOH in MeOH/water (**P4**) inside a simple T-piece mixer to induce rapid decomposition of the Diazald® nitroso urea (**4**) to release diazomethane (**1**). As the solution flows through the inner tube of the membrane reactor (**TT**) the volatile diazomethane (**1**) is quickly transferred across the AF-2400 membrane. At the same time the amino acid (**8**) was activated as the anhydride (**9**) as it passed through reactor **R1**. The anhydride (**9**) subsequently reacts with the diazomethane (**1**) which diffused through the membrane tubing (**TT**). Formation of the α-diazoketone (**10**) was complete after the solution had passed through the coiled tube reactor **R2**. Finally, a flow stream of ethereal hydrochloric acid (**P5**) was introduced *via* a T-piece mixer and hydrohalogenation occured in reactor **R3** to provide the α-chloroketone intermediate (**11**) in 87% yield after flash column chromatography. An alternative continuous flow procedure for preparing α-chloroketone intermediates (such as **11**) has been developed by Liotta and co-workers.[72] They made use of the less explosive trimethylsilyldiazomethane to form the α-diazoketone. This alternative reagent could be used in a homogeneous flow regime using ethyl acetate as the reaction solvent.



Scheme 4. Continuous generation of diazoalkanes (**12**) by the Bamford-Stevens decomposition of arylsulfonylhydrazones (**16**) telescoped with a continuous metal-free coupling reaction of the diazoalkane intermediates (**12**) with boronic acids (**13**).[73] **P** = pump, **S** = inductively heated solid reactor.

Other Diazoalkanes

While diazomethane (**1**) is the most commonly used diazoalkane, it is by no means the only useful member of this reactive family. The decomposition of arylsulfonylhydrazones proceeds *via* diazoalkanes in a Bamford-Stevens type mechanism. In this way it is possible to transform a ketone into a diazoalkane intermediate. The Kirschning group have recently performed this decomposition in a continuous flow system where the diazo intermediate (**12**) participates in a metal-free coupling with boronic acids (**13**) (Scheme 4).[73] In the first of the two flow steps a solution of ketone (**14**) and tosylhydrazide (**15**) in dioxane was pumped (**P1**) through a column of steel beads (**S1**) subjected to inductive heating at 80 °C in order to form the tosylhydrazone intermediate (**16**). A second stream containing the boronic acid

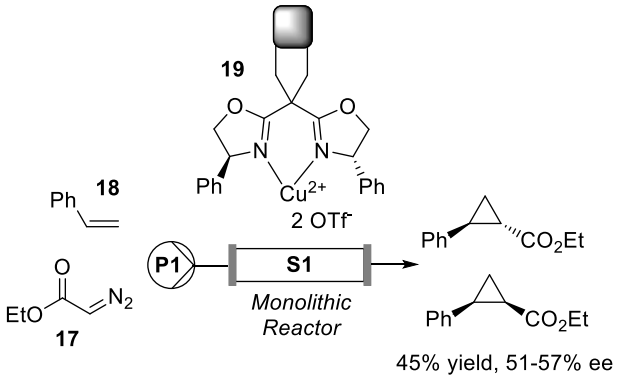
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(**13**) was pumped (**P2**) into the system *via* a T-piece before the mixed solution passed through a second inductively heated column containing steel beads and potassium carbonate (**S2**). Under the superheated conditions (120 °C) made possible by operating under pressurised conditions, the tosylhydrazone (**16**) was quickly decomposed to the diazo intermediate (**12**). Reductive coupling of the diazoalkane (**12**) with the boronic acid (**13**) was efficient and proceeded in 84% yield. The telescoped flow process was operated continuously over a period of 21 hours.

α-Diazocarbonyls

α-Diazocarbonyls are considered to be more stable than diazoalkanes due to the resonance stabilising effect of the carbonyl group, but detonation is still possible under more forceful conditions.[44,46] Furthermore the reagents used to prepare these compounds can be explosive in their own right. A number of groups have published research making or using α-diazocarbonyls reagents in flow.

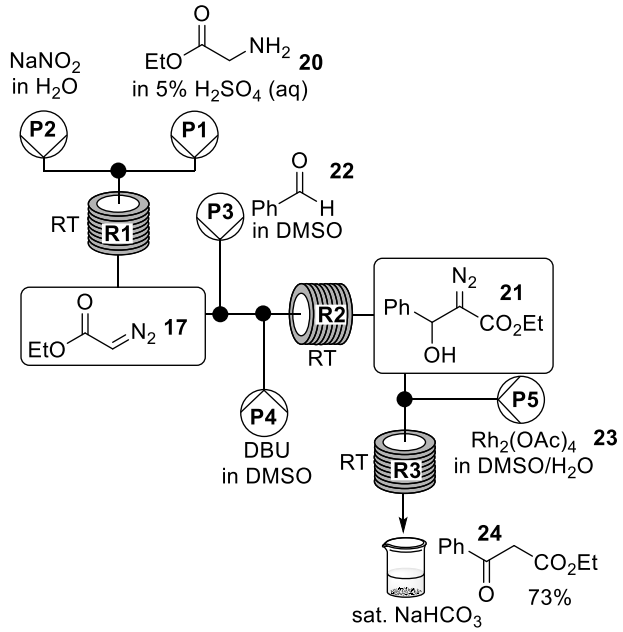
Ethyl diazoacetate (**17**) is one of the few commercially available diazo compounds and a useful C2 synthon.[1] It is therefore no surprise that the first examples of α-diazocarbonyl chemistry in continuous processing make use of this reagent.



Scheme 5. Continuous use of ethyl diazoacetate (**17**) in a cyclopropanation reaction catalysed by a monolithic bisoxazoline (BOX) copper (II) catalyst (**19**, **S1**).[74] **P** = pump, **S** = monolithic solid reactor.

Burguete *et al.* reported the use of ethyl diazoacetate (**17**) in a continuous cyclopropanation of styrene (**18**), pumping the reagents through a monolithic bisoxazoline (BOX) copper (II) catalyst (**19**, **S1**) to generate the metal carbenoid from the diazoacetate (**17**) (Scheme 5).[74] The heterogeneous monolithic catalyst **S1** is a single piece of porous, functionalised polystyrene which was prepared by co-polymerisation of a chiral monomer with styrene and divinylbenzene in the presence of a porogen. The monolithic catalyst **S1** could be employed under batch or flow conditions, but with a reduced reaction rate compared to the equivalent homogeneous catalyst. Asymmetric induction by the catalyst was not impaired by its immobilisation in a monolith and the flow reaction could be carried out in dichloromethane, under solvent free conditions, or in super-critical CO_2 with comparable results. The stability of the monolith **S1** was demonstrated by continuous operation of the flow reactor over a period of 5 hours with no decrease in product yield or enantioselectivity being observed.

Hayes and co-workers have reported the condensation of ethyl diazoacetate (**17**) with aldehydes in a flow system producing β-keto esters.[75] The β-keto esters generated in flow were combined with amidine hydrochlorides to provide the corresponding pyrimidin-4-ol products in a subsequent batch process. The process, as described, is limited to small scale (0.5 mmol) plug flow reactions where the reagents are introduced *via* injection valves. The benefits of utilising flow processing in the scale up of the nucleophilic addition of diazoesters was recently demonstrated by the Wirth group (Scheme 6).[76] In this system ethyl diazoacetate (**17**) was generated by diazotisation of glycine ethyl ester (**20**), and used in a telescoped nucleophilic addition to provide a library of β-hydroxy-α-diazoesters (**21**). The substrate benzaldehyde (**22**) was processed on a 38 mmol scale to provide 6 g of α-diazoester (**21**) in two hours of continuous operation. Moreover, the authors then went on to add a third telescoped reaction step where a rhodium catalyst induced a 1,2-hydride shift in the α-diazoester (**21**) to provide the β-keto ester (**24**) in 73% yield. The Kim group have also recently developed a microfluidic procedure for continuously generating ethyl diazoacetate (**17**) and using it in coupling reactions with aldehydes.[77] Notably, their device incorporated continuous liquid-liquid extraction and separation stages to transfer ethyl diazoacetate (**17**) into toluene after it was generated in an aqueous phase.



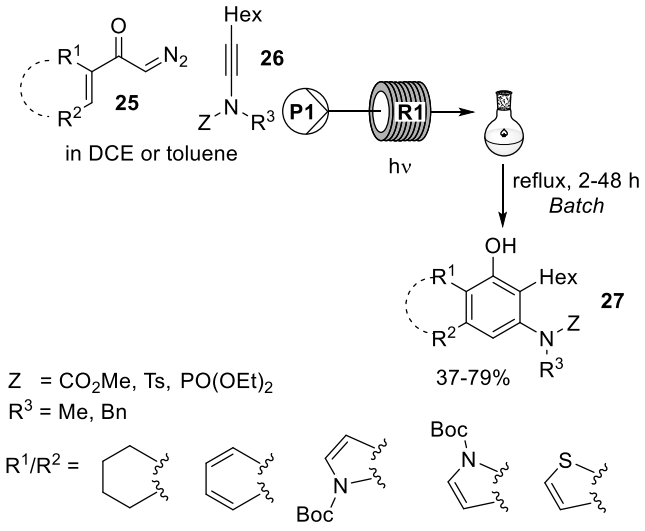
Scheme 6. Generation and use of ethyl diazoacetate (**17**) in a three step telescoped flow reaction.[76] **P** = pump, **R** = reactor coil.

The Danheiser group have recently described a new modification of their benzannulation reaction whereby batch prepared α,β-unsaturated diazoketones (**25**) are reacted with carboxymethyl, *N*-sulfonyl and *N*-phosphoryl ynamides (**26**) to form highly substituted polycyclic aromatic and heterocyclic systems (**27**).[78] The irradiation for the photo-Wolff reaction was

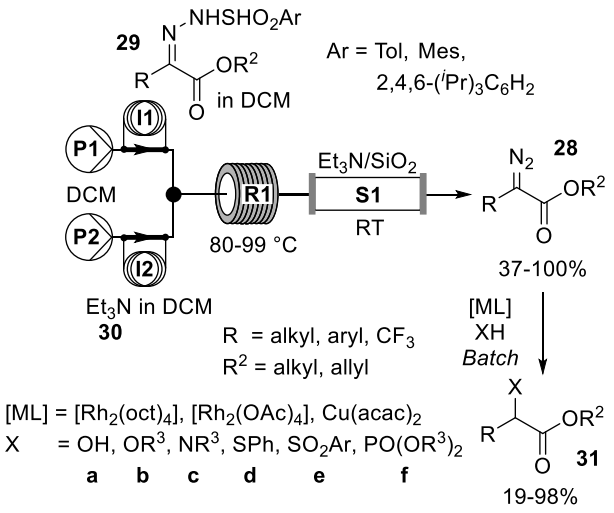
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provided by a single pass-through photochemical flow reactor based on the design of Booker-Milburn,[79] in comparable yields to the batch protocol (Scheme 7).[78] After formation of the ketene Wolff intermediate in the flow reactor, the output was collected and refluxed in batch for a period (2-48 h) in order to complete the benzannulation.[78] No attempt to accelerate the benzannulation in flow was reported although others have previously found success in performing benzannulations under superheated flow conditions.[80,81] Continuous photochemical reactors have also been applied to the Wolff rearrangement of α-diazo-β-ketoamides into trans-β-lactams.[82]

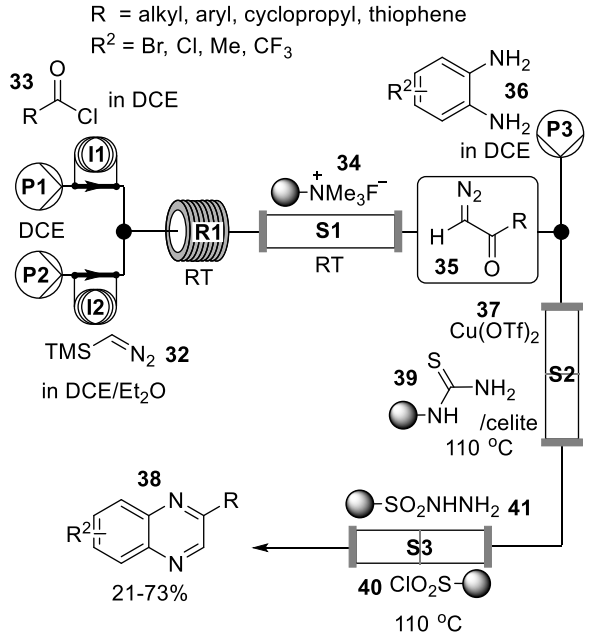


Scheme 7. Continuous photochemistry of α-diazoketones (**25**) in a Danheiser benzannulation.[78] **P** = pump, **R** = photo-reactor coil.



Scheme 8. Hybrid continuous/batch process for generating diazoesters (**28**) by a Bamford-Stevens reaction, and using them in metal catalysed X-H bond insertions.[83,84] **P** = pump, **I** = injection port, **R** = reactor coil, **S** = solid scavenger reactor.

α-Diazoesters (**28**) have been generated in a flow reactor by the base-induced decomposition of arylsulfonylhydrazones (**29**) in a Bamford-Stevens type reaction (Scheme 8).[83] Small plugs of the pre-prepared arylsulfonylhydrazones (**29**) were reacted with triethylamine (**30**) in a high temperature (80-99 °C) flow coil. Operating the system under 250 psi of back pressure allowed the dichloromethane (DCM) solution of reagents to be safely superheated to rapidly decompose the arylsulfonylhydrazones (**29**) to their respective α-diazoesters (**28**). The sulfinic acid by-product of this reaction was scavenged by passing the flow through a silica column which had been pre-treated with triethylamine. The utility of this process was further demonstrated by subjecting the resulting diazoester solutions to O-H and N-H insertion reactions in batch mode. A library of α-amino (**31c**) and α-alkoxy (**31b**) esters were produced with some automation but the authors did not capitalise on the increased safety of their process by performing a continuous scaled up example. In a follow-up paper they expanded the procedure to include S-H and P-H bond insertion reactions in a hybrid flow-batch procedure.[84] The aryl sulfinate by-product of the Bamford-Stevens reaction, when left in the flow stream (by removal of the triethylamine/silica scavenger column) participated in insertion reactions to provide α-sulfonyl esters (**31e**).



Scheme 9. Use of trimethylsilyldiazomethane (**32**) in the generation of α-diazoketones (**35**). The telescoped flow procedure converted the reactive diazo intermediates (**35**) into quinoxalines (**38**).[85] **P** = pump, **I** = injection port, **R** = reactor coil, **S** = solid scavenger reactor.

The telescoped generation and use of terminal α-diazoketones has been demonstrated by the Ley group and their collaborators at Novartis (Scheme 9).[85] In their system, trimethylsilyldiazomethane (**32**, $TMSCHN_2$) is used as a less explosive alternative to diazomethane (**1**). After the initial reaction between the acid chloride (**33**) and $TMSCHN_2$ (**32**) takes place at room temperature (**R1**) the TMS group is cleaved off by

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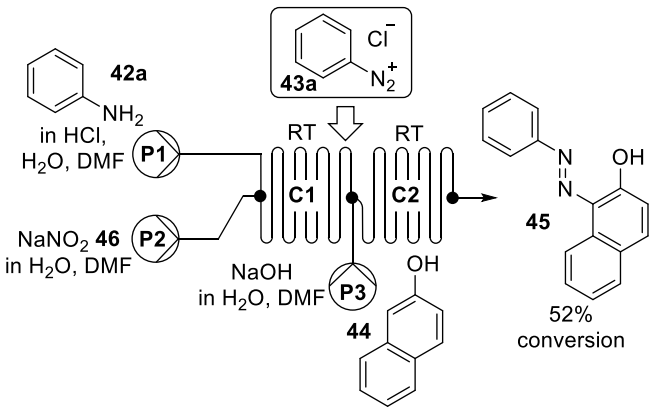
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passage through a column containing an immobilised fluoride source (**34**, **S1**) to reveal the α-diazoketone intermediates (**35**). The α-diazoketones (**35**) generated in flow were telescoped into a second flow process where they mix with *ortho*-diaminoaromatics (**36**) pumped (**P3**) into the system. Passage of the mixed stream through a heated column containing solid copper triflate (**37**, **S2**) resulted in formation of the desired quinoxalines (**38**) in yields of 21-73%. The research is particularly notable for its use of polystyrene-supported scavengers (**S2** and **S3**). Dissolved copper salts were removed by PS-thiourea (**39**), while PS-tosyl chloride (**40**) scavenged out the unreacted diamine and PS-tosylhydrazine (**41**) sequestered any remaining α-diazoketone (**35**). This scavenging strategy enabled the quinoxalines (**38**) to be obtained in pure form after simple removal of the reaction solvent.

Diazonium Ions

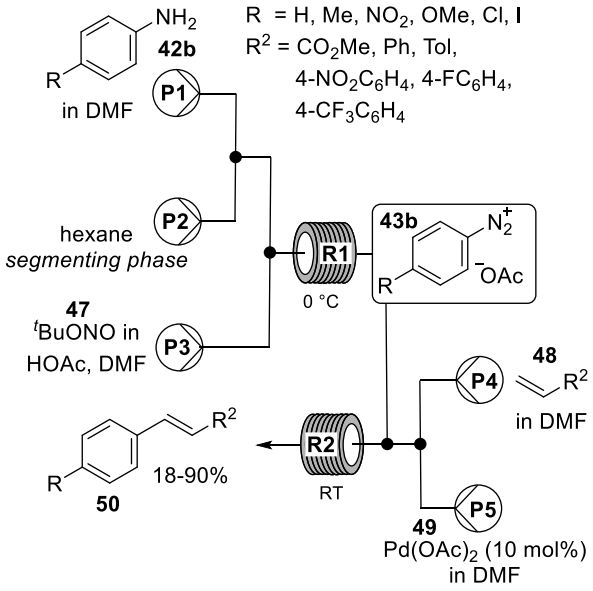
Diazonium salts are inherently unstable and present a serious explosion hazard. These reactive salts are typically generated and used *in situ* since many of them are too hazardous to isolate as the dry salt. The sensitivity of these ions can be moderated by the selection of appropriate counterions; the chlorides and acetates are unstable above 0 °C while the tetrafluoroborates, tosylates and disulfonimides are typically less sensitive.[86,87] Over the past 12 years there have been numerous attempts to use continuous processing to facilitate safe diazotisation reactions.

The earliest example of continuous diazotisation was demonstrated by the de Mello group in 2002.[88,89] Their simple system used sodium nitrite to generate the diazonium salt of aniline (**42a**) in a chip reactor (**S1**). The phenyldiazonium chloride (**43a**) was subsequently reacted with a third stream (**P3**) of β-napthol (**44**) to generate an azo dye, Sudan I (**45**), in 52% conversion (measured by on-chip UV/visible spectroscopy) (Scheme 10).[88] The use of sodium nitrite (**46**) as the diazotisation reagent necessitated a water and dimethylformamide (DMF) solvent mixture to prevent precipitation and subsequent blockage of the chip, or worse, the explosive decomposition of diazonium chloride (**43a**) deposits.



Scheme 10. Continuous generation of phenyldiazonium chloride (**43a**) in a microfluidic chip reactor with a telescoped azo-coupling to form Sudan I (**45**).[88,89] **P** = syringe pump, **C** = microreactor chip.

The Wirth group have applied segmented flow conditions to the Heck-Matsuda coupling in chip and coil based flow reactors. [90,91] Segmenting the reaction flow with an immiscible phase, in this case hydrocarbons, creates mixing vortexes within the reaction fluid packets and can enhance reaction rates.[90] In the coil reactor system a pumped (**P1**) flow of the aniline (**42b**) in DMF is segmented with hexane (**P2**) before a flow (**P3**) of *tert*-butylnitrite (**47**) and acetic acid was mixed into the reaction fluid packets (Scheme 11).[91] The arenediazonium acetate salt (**43b**) formed as the packets progressed through the first reaction coil (**R1**). After the introduction of the alkene (**48**) and $Pd(OAc)_2$ (**49**) flows (**P4** and **P5**) the Heck-Matsuda coupling takes place inside a coil reactor (**R2**) at ambient temperature to provide the styrenes (**50**) after a total residence time of just 27 min.



Scheme 11. Continuous generation and use of arenediazonium acetates (**43b**) in the Heck-Matsuda coupling.[91] **P** = syringe pump, **R** = reactor coil.

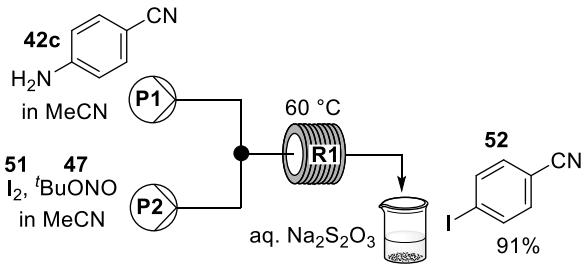
Following their earlier synthesis of the azo dye Sudan I (**45**) (Scheme 10), the de Mello group went on to investigate other reactions employing diazonium intermediates.[88] The absence of cross coupling by-products in their earlier work suggested that incomplete diazonium (**43a**) formation was limiting the overall reaction conversion. To remedy this they performed the reaction under anhydrous conditions, making use of isoamyl nitrite as an organic phase diazotisation reagent.[89] After optimisation of the substrate concentration and nitrite equivalents they proceeded to perform the Sandmeyer reaction in a microfluidic chip reactor. Under these conditions they were able to obtain three chloroarenes in yields ranging from 55% to 70%. These were notable for being 20% higher than the equivalent batch reactions. Furthermore, the reaction progress was monitored directly by on-chip Raman spectroscopy.

The use of copper in the Sandmeyer reaction necessitates the use of specific solvents like DMF to prevent the precipitation of salts inside flow reactors.[89] Alternatively, it is possible to generate aryl iodides under copper-free conditions and a continuous procedure for this reaction has been presented by

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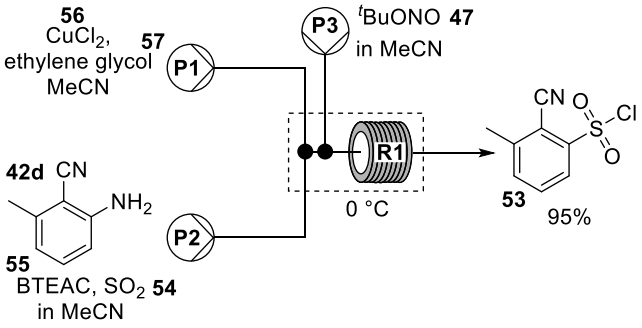
Pfizer scientists (Scheme 12).[92] It should be noted that this transformation is believed to proceed *via* a triazene intermediate rather than a diazonium ion, but regardless, the reaction still presents an explosion hazard on large scale. Using molecular iodine (**51**) as the iodide source enabled the authors to process a collection of 12 aromatic and heteroaromatic amines in moderate to good yields (43-91% yield). One substrate, 4-aminobenzonitrile (**42c**), was even scaled up from 1.5 mmol to 45 mmol in a continuous 7 h run, providing 8.8 g of 4-iodobenzonitrile (**52**) in 91% yield.



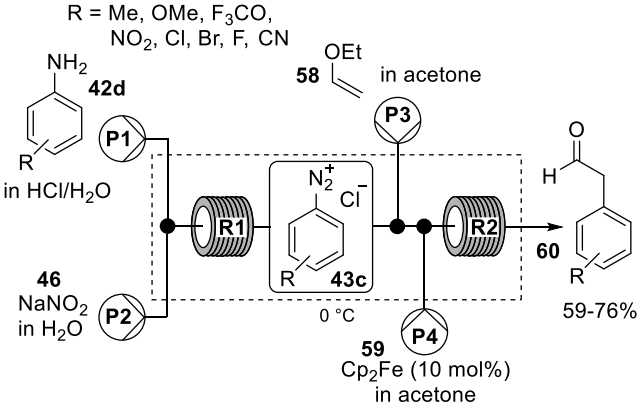
Scheme 12. Continuous metal-free coupling reaction to generate aryl iodides (**52**) from *in situ* generated triazene intermediates.[92] **P** = pump, **R** = reactor coil.

Another use of aryldiazonium salts is the Balz-Schiemann reaction.[38] The thermal decomposition of relatively stable aromatic diazonium tetrafluoroboronate salts provides aromatic fluorides but, like all processes employing diazonium intermediates, there are inherent risks associated with performing the reaction on a large scale.[93] Yu and co-workers have developed a continuous process for the Balz-Schiemann reaction whereby the aromatic amines were diazotised and then decomposed in two stages.[94,95] The diazotisation step proceeded in near quantitative yield for all substrates and demonstrated an improvement of about 10% over the equivalent batch procedures performed by the same group. After a workup procedure involving filtration, washing and drying, the diazonium tetrafluoroboronate salts were suspended in an aromatic halide solvent (choice of solvent depended on the substrate) and fed into a high temperature flow reactor by peristaltic pump. The product aryl fluorides were obtained in yields ranging from 72 to 95%.[94] In a separate publication they described the production of over 1 kg of difluorobenzene in a continuous reactor. [95] To remove the need for distillation of the product from the halogenated aromatic solvent they took the unusual step of using the target product as the solvent for the reaction. This was effective in their study but probably would not be suitable outside the academic research environment.

Ley and collaborators at Pfizer have demonstrated the continuous preparation of sulfonyl chlorides (**53**) in another variation of the Sandmeyer reaction employing sulfur dioxide gas (**54**) (Scheme 13).[96] The batch reaction is typically performed in concentrated hydrochloric acid and acetic acid with aqueous $NaNO_2$ (**46**).[33] This was considered too harsh for use in a flow reactor, potentially causing corrosion of stainless steel components in the pumps, so benzyltriethylammonium chloride (BTEAC, **55**) was used as a chloride source instead. Attempts were made to use $CuCl_2$ (**56**) immobilised on a solid support but, although the catalyst showed good initial activity, it was prone to leaching and the resulting precipitates of copper salts caused blockage of the system. To get around this they used ethylene glycol (**57**) to successfully solubilise $CuCl_2$ (**56**) in the organic phase. Problems were also encountered with the triazene intermediate precipitating in the reactor. Mechanistic studies using the ReactIR™ flow cell revealed that the triazene breaks down rapidly upon addition of the $CuCl_2$ (**56**). This information was used to rearrange the order in which the pumped flows were combined. Adding the $CuCl_2$ (**56**) stream (**P1**) to the aniline (**42d**), BTEAC (**55**) and sulfur dioxide (**54**) stream (**P2**) before the *tert*-butyl nitrite (**47**) stream (**P3**), reduced the precipitation of the triazene intermediate. The reactor coil and T-piece mixers were simply immersed in an ice bath to perform the reaction at 0 °C. The optimised flow system was used to prepare a library of sulfonamides (25-90% yield) after a quick addition of various amines to the flow reaction output.



Scheme 13. Continuous Sandmeyer reaction with sulfur dioxide (**54**) and a chloride source (**55**) to generate aryl sulfonyl chlorides (**53**) from *in situ* generated triazene intermediates.[96] **P** = pump, **R** = reactor coil.



Scheme 14. Continuous Meerwein arylation to produce monoarylatedacetaldehydes (**60**).[97] **P** = syringe pump, **R** = reactor coil.

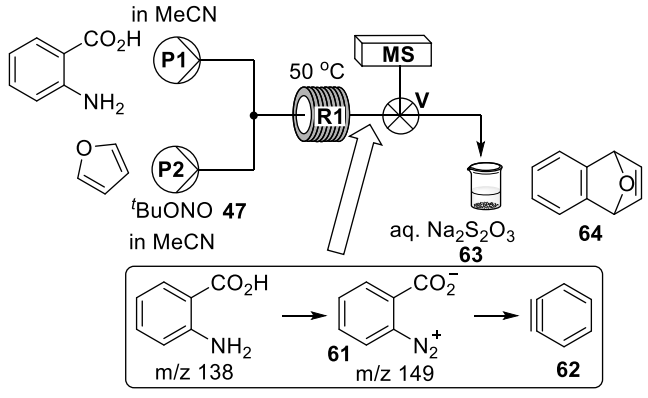
A common reaction pathway for aryl diazonium ions is the formation of aryl radical species by expulsion of nitrogen gas. The Meerwein arylation is the addition of such aryl radicals to alkenes under mild and non-basic conditions. Chernyak and Buchwald have developed a continuous process to formally arylate acetaldehyde at the α position (Scheme 14).[97] Syringe pumps (**P1** and **P2**) were used to combine a flow of an aniline

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(**42d**), in acidic water, with a solution of sodium nitrite (**46**). Aryl diazonium chloride (**43c**) was thus generated in the first reactor coil (**R1**) during the 2.5 min residence time. The ethyl vinyl ether (**58**) coupling partner was then introduced by another syringe pump (**P3**) before the final pump (**P4**) introduced a solution of ferrocene (**59**) to catalyse generation of an aryl radical in the second reactor coil (**R2**) by single electron transfer. Radical generation and the subsequent Meerwein arylation of the ethyl vinyl ether (**58**) occurred within an 8.5 min residence time inside the reactor coil (R2) to provide a continuous synthesis of monoarylacetaldehydes (**60**) in good yields (59-76%).

In another application employing diazonium species to generate aryl radicals in flow, Maggini and co-workers used an agitating cell reactor to functionalise single wall carbon nanotubes (CNT).[98] A dispersion of CNTs, 4-methoxyaniline and *iso*-pentylnitrite in 1-cyclohexylpyrrolid-2-one (CHP) was flowed through the agitating cell reactor at 70 °C resulting in the formation of the reactive aryl radical (*via* a diazonium intermediate) and its subsequent addition to the CNTs in a reduced reaction time compared to typical batch procedures for CNT functionalisation.

They Ley group have prepared the highly sensitive benzenediazonium-2-carboxylate (**61**) inside a flow reactor and thermally decomposed it to benzyne (**62**) for direct use in Diels-Alder reactions (Scheme 15).[99] Early results showed that the decomposition of the diazonium ion (**61**) was not complete at room temperature so in the interest of safety the reactor outlet was directed to a saturated sodium thiosulfate (**63**) quench solution to ensure reduction of any residual diazonium species (**61**). The reaction was optimised by on-line ESI-MS analysis using a miniature mass spectrometer and a large number of competing reaction pathways were proposed based on by-product ions observed in the mass spectra. After optimisation, the reactor outlet could be safely directed to a collecting vessel to safely provide the desired products (**64**). Continued monitoring by on-line MS ensured that no hazardous diazonium species (**61**) eluted with the product stream.



Scheme 15. Generation of benzyne by decomposition of benzenediazonium-2-carboxylate (**61**) inside a flow reactor. On-line mass spectrometry was used to elucidate competing reaction pathways.[99] **P** = pump, **R** = reactor coil, **V** = sampling valve, **MS** = mass spectrometer.

Alkyl diazonium salts have also been continuously prepared by the Ley group. Amino acids were converted to α-hydroxyacids by reaction with sodium nitrite (**46**) in the presence of sulfuric acid, and immediate substitution of the reactive diazonium group by water.[100] The process incorporated a continuous, three stage liquid-liquid extraction system to retrieve the product α-hydroxyacids from the aqueous reaction phase. Notably, the extraction system was constructed from readily available flow chemistry equipment, and a digital camera provided feedback to a computer controlling the pump flow rates. Using their system they produced eight chiral hydroxyacids in multigram quantities (1-20 g).

Summary and Outlook

Continuous processing of diazo and diazonium chemistry has been explored by many academic and industrial groups. Diazomethane (**1**) chemistry has been thoroughly investigated and there now exist procedures for the continuous generation and use of this versatile reagent at scales ranging from the laboratory (<5 mmol/hr) up to the process plant level (>50 mol/hr). Both of the common diazomethane precursors, *N*-nitroso-*N*-methylurea (MNU, **2**) and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®, **4**), have been prepared continuously and used to generate diazomethane (**1**) in telescoped flow procedures. Furthermore, recent advances in gas-permeable reactor technology have provided highly efficient and safe access to anhydrous diazomethane (**1**).

It is typical for the diazomethane (**1**) generated continuously to be used directly in a telescoped flow process. While most of the literature only demonstrate simple methylation reactions, there are examples where the Arndt-Eistert reaction has been used to continuously prepare synthetically useful terminal α-diazomethylketones (**10**).

The continuous chemistry of alternative diazoalkanes has been largely ignored. This is unsurprising since the use of such alternative diazoalkanes is currently limited to niche research areas. There is huge potential for flow processing technology to provide safe access to previously unexplored chemistry involving diazoalkanes beyond diazomethane. Realising this would enable broader use of diazoalkanes in synthesis.

The use of stabilised α-diazocarbonyl compounds has been demonstrated by several researchers but telescoped procedures where they are generated and subsequently used in flow are less common. Several research groups have used ethyl diazoacetate (**17**), a commercially available reagent, as a starting material but it can also be generated in flow by diazotisation of glycine (**20**). Other α-diazocarbonyl substrates have typically been prepared using traditional batch procedures before investigating the subsequent reactivity of the diazo group in a flow reactor. Where α-diazocarbonyl compounds have been generated in continuous processes it has been by the Bamford-Stevens reaction of arylsulfonylhydrazones precursor compounds or the Arndt-Eistert reaction of activated carboxylic acids with diazomethane (**1**) [or the equivalent trimethylsilyldiazomethane (**32**)] to produce terminal α-diazomethylketones (**10**, **35**).

α-Diazocarbonyl compounds are versatile intermediates. They have been used in continuous cyclopropanation reactions, carbonyl additions, photochemical Wolff reactions, and also in heterocycle synthesis. The continuous preparation and reaction of reactive aryl diazonium ions has also been widely researched. The synthesis of azo dyes, the Sandmeyer reaction and its

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modifications, the Meerwein arylation and aryne chemistry are just some of the continuous applications involving diazonium ions and associated intermediates.

Reactions of diazo and diazonium intermediates have been a popular testing ground for many continuous processing technologies. The examples featured in this minireview illustrate important developments in flow chemistry, including telescoped processing, in-line analysis, tube-in-tube gas/liquid reactors, inductive heating, solid supported catalysis, flow through photochemical reactors, and immobilised scavengers for work-up free synthesis.

The diazo and diazonium moieties are certainly important and synthetically versatile functional groups although their use on scale is widely feared and avoided. In the future we can expect to see many more applications exploiting the synthetic potential of these moieties as we gain confidence in safely handling them using the continuous processing technologies demonstrated in this minireview.

Acknowledgements

This work was undertaken as part of the Synthesis and Solid State Pharmaceutical Centre supported by the Science Foundation Ireland (grant: SFI SSPC2 12/RC/2275).

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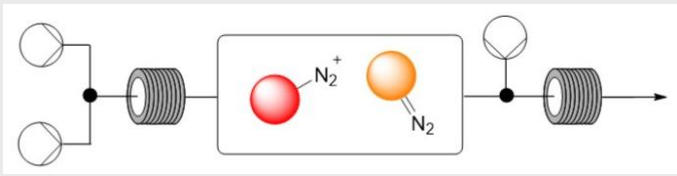
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Received: ((will be filled in by the editorial staff))
Revised: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

This is the pre-peer reviewed version of the following article: Deadman, B. J., Collins, S. G. and Maguire, A. R. (2014), Taming Hazardous Chemistry in Flow: The Continuous Processing of Diazo and Diazonium Compounds. Chem. Eur. J. which has been published in final form at http://dx.doi.org/10.1002/chem.201404348
DOI: 10.1002/chem.201404348

CHEMISTRY
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The synthetic utilities of the diazo and diazonium groups are matched only by their reputation for explosive decomposition. Continuous processing technology offers new opportunities to make and use these versatile intermediates with improved safety. This minireview discusses the state of the art in flow chemistry involving these reactive species.

Flow Chemistry

*Benjamin J. Deadman, Stuart G. Collins and Anita R. Maguire**

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Taming Hazardous Chemistry in Flow: The Continuous Processing of Diazo and Diazonium Compounds