**Chapter 1**

**Introduction**

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# 1.1 Preparation of -diazocarbonyl compounds

## 1.1.1 Overview of diazo transfer reactions

α-Diazocarbonyl compounds are extremely useful in organic synthesis due to their ease of preparation and their diverse reactivity. Decomposition of these compounds under thermolysis, photolysis or transition metal catalysis generates a reactive carbene intermediate. Copper complexes were most commonly used prior to the discovery of the more efficient rhodium(II) carboxylate catalysts in the 1970’s.[1,2]

There have been many comprehensive reviews published on the preparation and synthetic uses of α-diazocarbonyl compounds.[3–9] They are a precursor to a series of reactive intermediates which can undergo a range of reactions (**Scheme 1.1**) including Wolff rearrangement, C-H insertion, X-Y insertion, ylide formation, and cyclopropanation. Our understanding of the full potential of the highly reactive diazo functional group is incomplete as the dangers associated with their production limit the frequency of their use in industry. These dangers arise from the reagents employed as diazo transfer reagents, which are often highly sensitive to shock and temperature.[10,11]



**Scheme 1.1**

There are numerous reported methods for synthesising diazo compounds, which are summarised in recent reviews.[4,5] Several of these routes are highlighted in **Scheme 1.2** below, and include; A) diazo transfer onto an activated methylene group, B) diazotization of α-acceptor-substituted primary aliphatic amines, C) dehydrogenation of hydrazones, D) base treatment of sulfonylhydrazones, E) alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonyl amides, carboxamides, ureas and urethanes, F) triazene fragmentation (rare), G) electrophilic substitution of diazomethyl compounds and H) substituent modification of an existing diazo compound (FG = functional group).



**Scheme 1.2**

While great progress has been made in the preparation of this class of compounds, they are not yet widely used in the pharmaceutical industry. The diazo functional group is present in many natural products, therefore development of a route to these compunds which has an increased safety profile would have a market within pharmaceutical development. Moody and Nawrat have compiled a comprehensive review of natural products that contain a diazo group.[12] A selection of these are outlined here.

Azaserine **1** is the most widely studied naturally occuring diazo compound. It was reported in 1954, after being isolated from *Streptomyces fragilis* as part of a screening program for new antitumour and antiobiotic agents.[13–15] **1** has been shown to be active against leukemia, however, following clinical trials it was found to be less active than other agents. It is used as a glutamine antagonist.



**Figure 1.1**

The kinamycins **2** and **3**, and related prekinamycins **4** and **5** shown in **Figure 1.2** are powerful antitumour antibioitcs. The kinamycins were isolated from *Streptomyces murayamaenis* in 1970 and a number of total syntheses have been published.[16–18]



**Figure 1.2**

The total synthesis of kinamycins C **6**, F **7** and J **8** were reported by Nicolaou and co-workers.[18] Starting from **9** kinamycin C is accessible in four synthetic steps. The diazo functionality is introduced in the last step by formation of the tosyl hydrazine, and subsequent oxidation to the diazo group by ceric ammonium nitrate (CAN). When formed as the TBS-ether **10**, kinamycins F and J can be accessed in just one additional synthetic step as illustrated below in **Scheme 1.3**.



**Scheme 1.3**

## 1.1.2 A brief history of diazo chemistry

The first reported synthesis of an -diazocarbonyl compound was in 1883, when Curtius synthesised ethyl diazoacetate **12** from glycine ethyl ester hydrochloride **11** (**Scheme 1.4**).[19,20] Since this early work, significant advances have been made in the field of diazo chemistry, many of which will be outlined in the following sections.



**Scheme 1.4**

### 1.1.2.1 Arndt-Eistert synthesis

Diazocarbonyl compounds with simple alkyl side chains became available through the work of Arndt and Eistert in 1927,[21–24] and Bradley and Robinson in 1928.[25] The authors reported the synthesis of diazoketones by addition of an acyl chloride to ethereal diazomethane **13** (at least 1-2 equiv excess) at or below 0 °C, illustrated below in **Scheme 1.5**.



**Scheme 1.5**

It was previously believed that this reaction was only capable of producing chloromethyl ketone. However the authors determined that by using an excess of diazomethane **13**, it was possible to trap the hydrogen chloride produced in the course of the reaction, therefore preventing its reaction with diazoketone.

### 1.1.2.2 Regitz diazo transfer method

The most common method for the transfer of a diazo group is the procedure described by Regitz.[26,27] This method involves deprotonation of the substrate by a base of sufficient strength, followed by transfer of the N2 group by a donor, invariably a sulfonyl azide (**Scheme 1.6**). Of the sulfonyl azides, *p*-toluenesulfonyl azide (tosyl azide) **14** is still the most widely used. Prior activation of the substrate may be necessary to achieve good conversion to the desired products.[28] Therefore substrates can be divided into two categories – those with sufficiently activated methylene protons such as -keto esters, malonic esters and -diketones will readily undergo diazo transfer.



**Scheme 1.6**

For the second category of substrates, where the methylene group is activated by only a single carbonyl group, the standard Regitz methodology is less successful. In these cases it is often necessary to first activate the substrate by a method called deformylating diazo transfer.[26,27] This is carried out by Claisen condensation of the ketone with ethyl formate as shown in **Scheme 1.7**. This introduces an additional electron withdrawing group in the form of the strongly activating formyl group, which is subsequently released as the sulfonyl amide in the course of the diazo transfer reaction. This allows the successful synthesis of most types of acyclic and cyclic -diazoketones.[29,30]



**Scheme 1.7**

Improvements on this method have been described by Danheiser *et al*.[31,32] Danheiser found that the harsh conditions required for the Claisen condensation could be replaced by use of trifluoroacetylation of kinetically generated lithium enolates. This improved the efficiency of the diazo transfer reactions, and is referred to as a trifluoroacetylation/detrifluoroacetylation diazo transfer (**Scheme 1.8**).



**Scheme 1.8**

Another modification of Regitz’s method was reported by Taber *et al*.[33] This method involves the TiCl4-mediated reaction of an ester with benzoyl chloride resulting in high yields of the -benzoylated ester, which can then undergo efficient diazo transfer. This method allows the easy preparation of gram quantities of -diazo esters, and is more accessible than the Danheiser acylation method, which requires the use of an expensive strong base and cryogenic conditions. This method is known as benzoylation/debenzoylation diazo transfer, and is illustrated below in **Scheme 1.9**.



**Scheme 1.9**

### 1.1.2.3 Other modifications to the Regitz method

There are two major concerns with the standard Regitz methodology that prevent it being used on an industrial scale. If these issues could be overcome, the potential of the diazo functionality could be unlocked and used to access a diverse range of chemistry and functionality for pharmaceutical processes. The first is the inherent instability of the diazo transfer reagents. Issues with their thermal and shock sensitivity must be addressed in order to use this method on an industrial scale, and this will be discussed in **Section 1.2.2**. The second issue is the difficulty associated with removing the sulfonyl amide by-product to give the pure diazo product. While this has been addressed with some of the newer diazo transfer reagents,[34–36] other approaches have also been developed.

Koskinen *et al*. reported diazo transfer under mildly basic conditions, using potassium carbonate in acetonitrile.[37] This method can be used to access a range of diazo-malonates and -diazo--ketoesters, using equimolar quantities of potassium carbonate as base, at room temperature. An added bonus of this method is that addition of a non-polar organic co-solvent precipitates the sulfonyl amide by-product, and so purification is by filtration only.



**Scheme 1.10**

Another successful method for purifying diazo compounds from the Regitz methodology without diminishing the yield was described by Presset and co-workers.[38] A range of diazo transfer reagents and purification techniques were tested, and *p*-tosyl azide **14** followed by purification on silica gel and/or alumina gave the highest yields and the most reproducible results. Use of both silica gel and alumina in the purification process allowed complete removal of the sulfonyl amide by-product (**Scheme 1.11**).



**Scheme 1.11**

# 1.2 Diazo transfer reagents

## 1.2.1 Comparison of classical and modern diazo transfer reagents

As no single reagent is suitable for all diazo transfer reactions, a number of factors must be considered when choosing an appropriate reagent. The reagent of choice will satisfy the following criteria:

* Have readily available starting materials
* These starting materials should be inexpensive
* The azide would preferably have a low explosive potential, and
* The resulting sulfonyl amide should be easily separable from the diazo product.

There are numerous reviews in the literature[7,26,27,39] on the wide range of diazo transfer reagents available[40–46] as well as their individual properties including hazards, stability and safety.[10,45] A review has been carried out by Bollinger *et al*.,[10] which found that methanesulfonyl azide (mesyl azide) **15** was the most dangerous of the reagents reviewed, with the highest impact sensitivity and the largest heat of decomposition. A close second to mesyl azide in impact sensitivity is *p*-toluenesulfonyl azide (tosyl azide) **14**, and although the authors strongly advise against the use of mesyl azide, they acknowledge tosyl azide as being widely used (**Figure 1.3**).



**Figure 1.3**

Bollinger *et al*. reported the *p*-dodecylbenzenesulfonyl azides **16** as having the smallest specific heat of decomposition, as well as second highest initiation temperature of the ten azides tested. *p*-Dodecylbenzenesulfonyl azide also displayed no impact sensitivity at the highest test levels making it the safest reagent reported. As can be seen in **Table 1.1**, the corresponding sulfonyl amide is a liquid, and therefore has the extra advantage of ease of separation from any crystalline diazo products. The relatively good safety profile of reagent **16** is reflected by their use for large scale diazo transfer reactions for over 9 years at Merck without incident.[45] The reagent **16** is stable for prolonged periods of storage without noticeable deterioration in the freezer (-20 °C).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Sulfonylazide** | **m.p.**  **(ºC)** | **Initiation**  **Temp. (ºC)** | **Rate of**  **Decomp.a** | **Impact Sensitivity**  **Kg cm-1** | **Sulfonylamide**  **m.p. (ºC)** |
| **14** | 19-20 | ~120 | 1.00 | 50 | 135.7-137 |
| **16** | Liquid | ~151 | 0.36 | -ve to 150 | Liquid |
| **17** | 41-43 | ~146 | 0.96 | 300 | 218.5 |
| **18** | 184-186 | ~163 | 2.29 | 300 | 295-296 |

**Table 1.1 *Properties of some common diazo transfer reagents***



**Table 1.1** shows that naphthalene-2-sulfonyl azide **17** has low impact sensitivity and a highly crystalline, poorly soluble by-product, which allows easy separation from liquid diazo products. Another diazo transfer regent found to have an improved safety profile over tosyl azide **14** is *p*-carboxybenzenesulfonyl azide **18**. This reagent has the advantage of being water soluble, but the disadvantage of requiring an excess of base for activation, making it unsuitable for base sensitive substrates. The trimethylamine salt of this acid is soluble in acetonitrile, while its by-product is insoluble – which can be used to facilitate purification of the diazo product.

## 1.2.2 Progress towards safer diazo transfer reactions/reagents

Various diazo transfer reagents have been developed in an attempt to demonstrate to the pharmaceutical industry that diazo compounds could be part of their chemical armoury if their synthesis could be scaled up safely. The risks associated with preparing and using traditional diazo transfer reagents have been well reported in the literature.[10,45] Consequently, interest in the development of safer alternatives has seen the development of a range of diazo transfer reagents with improved safety profiles, greater ease of handling, and easier isolation of the diazo-product. The following section shows a selection of the recent breakthroughs in safer alternatives to the traditional transfer reagents.

**Polystyrene-supported benzenesulfonyl azide**

Green and co-workers[36] developed a polymer-supported benzenesulfonyl azide **19** which has the following benefits compared to the standard unmodified reagent:

* Thermally stable
* Is not friction sensitive
* Easy preparation and handling
* Improved safety profile
* Ease of purification of the diazocarbonyl product – the resin containing sulfonyl amide by-product can be removed by filtration, with no need for an aqueous work-up.



**Scheme 1.12**

The polymer-supported benzenesulfonyl azide resin **19** is prepared in one step from commercially available polymer-supported benzenesulfonyl chloride **20** by reaction with sodium azide at room temperature, as illustrated above in **Scheme 1.12**.

The standard tosyl azide **14** needs to be stored in the freezer in an isolated container and then carefully warmed to room temperature before use. Extreme caution must be taken in its handling and care must be taken when pipetting the liquid that it doesn’t come into contact with any sharp edges. In contrast the polymer-supported benzenesulfonyl azide **19** can be stored on the bench and has much easier handling as it can be easily weighed out in the solid form.

Green and co-workers achieved successful diazo transfer to a range of substrates including β-ketoesters and diketones in good to excellent yields (**Scheme 1.13**). Once the reaction was complete, the polymer-supported benzenesulfonyl amide was removed by filtration to give pure -diazocarbonyl product on removal of solvent. This is in direct contrast to standard tosyl azide which requires an aqueous work-up to remove *p*-toluenesulfonyl amide by-product **21**, and sometimes column chromatography to remove any unreacted tosyl azide and residual sulfonyl amide.

Green used solution-phase reagent 4-carboxybenzenesulfonyl azide (*p*-CBSA)[30] **18** in direct comparison reactions, and found that yields in both cases were similar, although *p*-CBSA often required longer reaction times.



**Scheme 1.13**

**Oligomeric benzenesulfonyl azide**

Hanson *et al*. reported construction of a high loading, soluble oligomeric benzenesulfonyl azide **23** using cheap, readily available starting materials *via* ring-opening metathesis (ROM) polymerization.[35] High loading on the oligomer is ensured by functionalising the monomer, before forming the active polymer *via* (ROM) polymerization. In this case, monomeric benzenesulfonyl chloride was formed, polymerized and then treated with sodium azide in the presence of a phase transfer catalyst, Hex4NBr, to give oligomeric benzenesulfonyl azide, as shown in **Scheme 1.14**.



**Scheme 1.14**

A major benefit of this reagent is that it is soluble in organic solvents such as DCM, THF and DMF, while its sulfonyl amide by-product is not. Therefore, filtration through a silica gel solid-phase extraction (SPE) cartridge yields pure diazo product.

**Scheme 1.15**

The authors reported successful diazo transfer to a range of esters, ketones and phosphonate esters, as shown above in **Scheme 1.15.** The diazo compounds were formed in good to excellent yields (74-97%) and excellent purities following purification by filtration of the crude mixture.

**Imidazole-1-sulfonyl azide hydrochloride**

Goddard-Borger *et al*. reported imidazole-1-sulfonyl azide hydrochloride **25**.HCl as a crystalline, shelf-stable, and easily prepared alternative to trifyl azide (TfN3) **24** in diazo transfer reactions.[47] Trifyl azide **24** has a poor shelf and must therefore be prepared in solution before use.[48] The expense of trifluoromethanesulfonic anhydride, used in the preparation of **24**, prevents its use on a large scale. In addition to this, inconsistent yields in the synthesis of trifyl azide mean that the solution must either be standardised or used in a liberal excess.

Due to the drawbacks associated with trifyl azide, the authors endeavoured to generate a diazo transfer reagent that was equally efficient but without the associated problems. This required finding an electron-withdrawing group capable of replacing the trifluoromethanesulfonyl moiety. Imidazylates exhibit similar reactivity while having the advantage of being relatively inexpensive to prepare, while enjoying a longer shelf life.



**Scheme 1.16**

One of the main aims had been to generate a convenient crystalline diazo transfer reagent and so the hydrochloride salt of **25** was formed as a colourless crystalline solid (**Scheme 1.16)**. This salt was successfully used to prepare a range of diazo compounds, as well as being used to convert a range of amines into the corresponding azides in excellent yields, as seen in **Scheme 1.17**.



**Scheme 1.17**

Ye and co-workers[49] later reported a safer synthesis of **25** in a bid to eliminate the explosion hazard associated with hydrazoic acid, which can form as a by-product in the Goddard-Borger synthesis from reaction of hydrochloride with sodium azide. This new synthesis, shown in **Scheme 1.18**, involves reaction of sulfuryl diimidazole **26** with methyl triflate, with subsequent addition of sodium azide in water-ethyl acetate (95:5).



**Scheme 1.18**

This synthesis can be scaled up considerably and is the first report of a safe preparation of a sulfonyl azide derivative at >100g scale. Some structural modifications of **25** such as **27**-**30**, have been investigated and reported to have improved chemical properties or an increased safety threshold (**Figure 1.4**).[49–52]



**Figure 1.4**

Since imidazole-1-sulfonyl azide was first reported, it has been widely used: Smith *et al*. used **25** to establish a one pot procedure for the synthesis of 1,2,3-triazoles from primary amines and terminal acetylenes *via* copper-catalysed click chemistry (**Scheme 1.19**).[53]



**Scheme 1.19**

Delville and co-workers used **25** for the optimization of a continuous flow system for the preparation of organic azides, as shown in **Scheme 1.20**.[54] Continuous flow microreactors are ideally suited to potentially explosive azide synthesis due to the intrinsically small volumes and highly controlled reaction conditions.



**Scheme 1.20**

**Benzotriazol-1-yl-sulfonyl azide**

The preparation of benzotriazol-1-yl-sulfonyl azide **31** was reported by Katritzky and co-workers.[50] They reported a new crystalline, stable and easily available diazo transfer reagent, which was intended for use forming azido-protected peptides, esters, ketones and thioesters. Chlorosulfonyl azide was prepared *in situ* from sodium azide and sulfuryl chloride, then reacted with benzotriazole and pyridine in acetonitrile to access benzotriazol-1-yl-sulfonyl azide **31** in good yields, as shown in **Scheme 1.21**. The reagent remained stable six weeks after its preparation and has high solubility in both organic and partially aqueous solvents. Benzotriazol-1-yl-sulfonyl azide **31** was successfully used by the authors to synthesise a wide range of azides and diazo compounds, an example of which is shown in **Scheme 1.21**.



**Scheme 1.21**

**Ionic liquid-supported sulfonyl azide**

A unique diazo transfer reagent was reported by Kumar *et al*. in the form of an ionic liquid-supported sulfonyl azide.[34] Ramachary and co-workers had achieved ionic liquid promoted diazo transfer reactions using traditional diazo transfer reagents.[55] Kumar extended this work and created an ionic liquid that acted as both reagent and solvent. The reagent **35** was successfully synthesised by reaction of 1-methylimidazole **32** with 1,3-propanesultone **33**, followed by reaction with trifluoromethanesulfonic acid (TfOH). The resulting ionic liquid **34** was then further functionalised by reaction with thionyl chloride, followed by sodium azide to give the ionic liquid-supported sulfonyl azide **35**, as seen below in **Scheme 1.22**.



**Scheme 1.22**

**35** is themally stable and shelf stable, and has been used successfully as a diazo transfer for a range of active methylene compounds, such as -ketoesters, ketones and sulfoxides, in excellent yields (83-94%) in less than 5 minutes. Extraction into hexane-ethyl acetate gives pure diazo compound without the need for chromatography.

# 1.3 Alternative solvents for diazo transfer

## 1.3.1 Water as solvent for diazo transfer

Since Anastas and Warner reported their 12 Principles of Green Chemistry in 1998,[56] there has been a surge in interest in water as a solvent for organic synthesis. In recent years, a number of reviews have been published examining the use of water as a viable solvent for organic reactions.[57–63] Water has many environmental and economic advantages over traditional organic solvents as it is a cheap, readily available solvent which is non-toxic and non-flammable. Although there are sometimes issues with low solubility of organic compounds in water, it has unique properties which are advantageous to many reactions. These include polarity, ability to form hydrogen bonds, and hydrophobic and hydrophilic interactions.

The emergence of water as a solvent for organic reactions can perhaps be credited to the work of Breslow.[64] The author reported a substantial increase in the rate of Diels-Alder reactions carried out on water versus a range if other organic solvents. The cycloaddition of butanone **37** and cyclopentadiene **36** in water was found to be 740 times faster than in isooctane, and had increased selectivity, illustrated in **Scheme 1.23**. The same reaction was carried out in the polar protic solvents methanol and ethanol, and these were found to have similar reaction rates to the other hydrocarbon solvents used. This result was rationalised by the hydrophobic effect[65] – which is the observed tendency of non-polar substances to aggregate in water and exclude water molecules.[66]



|  |  |
| --- | --- |
| Solvent | k (M-1s-1) |
| Isooctane | 5.94 x 105 |
| MeOH | 75.5 x 105 |
| H2O | 4400 x 105 |

**Scheme 1.23**

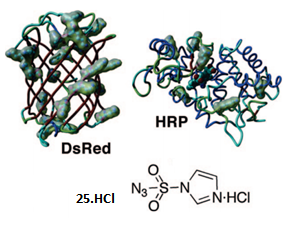
Novartis have used water as a solvent in their synthesis of 1-substituted-4-cyano-1,2,3-triazoles.[67] This synthesis involves the 1,3-dipolar cycloaddition of 2-chloroacrylonitrile **38** and the appropriate organic azide, which is followed by an aromatization which generates hydrogen chloride as a side-product. 2-Chloroacrylonitrile **38** polymerises under acidic or basic conditions. Therefore, by using water as a solvent, the reaction could take place in the organic phase while the by-product was solubilised in the water, thus giving higher yields of the product, as shown below in **Scheme 1.24**.



|  |  |
| --- | --- |
| Solvent | Yield (%) |
| *n*-Heptane | 46 |
| Toluene | 51 |
| Dimethylformamide | 78 |
| Ethanol | 40 |
| Neat | 72 |
| Water | 98 |

**Scheme 1.24**

Water has found widespread applications as a reaction medium, and has successfully been used to carry out Claisen rearrangements,[68] aldol reactions,[69] and allylation reactions.[70–72] The only example in the literature of diazo transfer in water was reported by van Heist *et al*.[73] The authors used imidazole-1-sulfonyl azide hydrochloride **25** in aqueous solution to carry out diazo transfer to amines, in order to directly introduce azides at the lysine positions or *N*-terminus of proteins and enzymes (**Figure 1.5**).





**Figure 1.5** Reproduced from Ref 74.

## 1.3.2 Ionic liquids as solvent for diazo transfer

Ramachary and co-workers described the use of ionic liquids as reaction solvent for diazo transfer.[55] The ionic liquids chosen were 1-butyl-3-methylimidazolium (bmim) saltswhich can be reused for up to five runs without affecting reaction rates or yields (**Figure 1.6**).



**Figure 1.6**

A range of highly substituted symmetrical and unsymmetrical -diazoketones and -diazo esters were prepared using a variety reaction conditions. Multiple sulfonyl azides and various bases were used during optimisation, as well as two different ionic liquids: [bmim]BF4 **39** and [bmim]Br **41**. The authors reported that these reactions are successful in the absence of a base, but the presence of a catalytic amount of base serves to accelerate the reaction. The optimum reaction conditions were found to be as follows:

* 1 equivalent of methanesulfonyl (mesyl) azide **15**
* 5 mol% DMAP
* [bmim]Br **41** (1 mL)

Using these reaction conditions, diazo transfer to a wide range of substrates was achieved in very short reaction times (0.5 – 2h), as illustrated in **Scheme 1.25**.



**Scheme 1.25**

1.4 Diazo chemistry in continuous processing

## 1.4.1 Advantages and limitations of flow chemistry

Perhaps the greatest challenge in organic synthesis is to generate complex organic compounds from simple precursors. This is accomplished *via* multi-step synthesis, often with each step requiring purification and optimisation before being carried on to the next stage of the reaction. Although working in this manner is the foundation on which modern synthesis has been built, a new method which proposes to increase efficiency, decrease exposure to hazardous and toxic intermediates and offers new opportunities for easy scalability has emerged.

Flow chemistry has emerged in recent years as a safer, more economical route by which to carry out organic synthesis. Flow chemistry could be viewed as a better mirror to the single-cell multi-step biosynthetic pathways found in nature than traditional batch chemistry. Numerous reviews exist in the literature on the advantages of flow chemistry, which are outlined below.[74–84]

Reported advantages of flow chemistry include the following[80]:

* Controlled heat transfer
* Controlled mixing (both fast and slow)
* Increased photon-flux in photochemical reactions
* Increased electrode surface-to-reactor volume ratio (electrochemistry)
* Increased solution-solid phase interactions
* Controlled use of highly reactive/toxic materials
* Increased capacity to run serial reactions.

The tunability of flow reactors, and the fact that reactions take place in small diameter tubing or microchips allows reactions to be performed under a more extensive range of conditions than can be achieved with conventional reactors. The excellent heat/mass transfer capabilities that this affords in comparison to batch chemistry leads to faster reaction times, high reproducibility and superior overall yield when compared to the stepwise process.[81] In addition, continuous processing allows for rapid scale up of reactions without the significant redevelopment of the routes that are frequently required on scale-up of batch processes.[78] This is achieved by replication of the same microreactor conditions used in the laboratory, but on an industrial scale. This can shorten the development time from laboratory to final production levels by eliminating the need for redevelopment from laboratory to pilot plant, and from pilot plant to industrial scale.[77]

Jensen *et al*. reported an example of the effects of improved mixing in continuous flow processes.[79] In this example fast mixing eliminated the competitive formation of the dialkylated product, thus increasing yields of the desired monoalkylated product from 36% in batch to 92% in flow (**Scheme 1.26**).



**Scheme 1.26**

Perhaps one of the most significant advantages of continuous processing is the ease with which telescoped reactions can be carried out. To perform a telescoped reaction in batch, the chemist would typically be required to consecutively add reagents and/or catalysts to a reactor in order to initiate further transformations of intermediate products or to achieve *in situ* quenching of reactive species. This strategy is well suited to flow chemistry.[82]

In telescoped reactions in flow, intermediates can be generated in one reactor and then transferred to another reactor to react with additional reagents. Immobilized reagents are used to perform in-line quenching and scavenging of by-products that would traditionally be performed by aqueous work ups and/or column chromatography.[80] This allows the chemist to carry out “one-flow multi-step synthesis” that would previously have required isolation and purification between steps.[85] Bogdan *et al*. made use of this concept when developing a three-step telescoped synthesis of ibuprofen **42**, as shown in **Scheme 1.27**.[86] By designing a careful retrosynthetic analysis of ibuprofen the authors were able to design the synthesis such that any by-products and excess reagents from one reaction were compatible with downstream reactions. This meant that the three step synthesis could be carried out as one sequence without any breaks for purification.



**Scheme 1.27**

In a continuous process, reagents are pumped into a flow reactor separately, before meeting at a T-piece. This means that at any one time, a small volume of reagents are in contact with each other. This is especially important when the intermediates being formed are hazardous, toxic or volatile.[78] As the system is closed, the chemist is never in contact with any toxic reagents, and the potential for problems with highly reactive or explosive reagents is significantly reduced.[77] It also allows the chemist to isolate and use compounds sensitive to air and/or moisture.[81] Flow chemistry employs a ‘make and use’ concept,[77] which means that any unstable or dangerous intermediates are generated and then rapidly transferred to the next stage of the reactor to be consumed, before decomposition or other problems can occur. This further increases the safety profile of the flow process.

An application of this is seen in reports by Baxendale and co-workers.[77] Diethylamino sulfur trifluoride (DAST) is volatile, reacts violently with water and readily decomposes at temperatures above 90 °C; as such it is difficult to use in batch. However the authors successfully used it in a continuous flow process to carry out fluorination reactions – DAST provides rapid access to many chemical structures by replacement of alcohols or carbonyl groups with mono- or *gem* difluoro groups, as shown in **Scheme 1.28**.



**Scheme 1.28**

Continuous processing is not without its disadvantages. Homogenous solutions are extremely important when carrying out flow chemistry, as due to the nature of the small diameter tubing in the reactor, any precipitate reagents will quickly clog the lines and lead to system failure from pressure elevated above the operating limits.[79]

Reaction planning is key in the use of flow reactors. Understanding the chemistry being performed, and identification of all by-products is critical in effective experiment design, therefore downstream post reaction clean-up is essential.[82] Effective quenching mechanisms must be put in place for any hazardous or toxic intermediates, as well as a method of removing by-products if possible. An added challenge is ensuring downstream reagent compatibility. Solid supported reagents are extremely useful for these purposes, but they too have limitations regarding volume and scaling (pressure effects and reactor volumes).[77,82]

## 1.4.2 Generation of diazomethane using continuous flow technology

Diazomethane **44** is a powerful carcinogen and allergen and is highly toxic with a permissible exposure limit of 0.2 ppm averaged over an 8-h period. However, the biggest impediment to its use on an industrial scale is very high sensitivity to shock and heat. The explosive nature of **44** is such that its batch synthesis must be carried out in specialised vessels without ground glass joints. There have been several methods reported for generating diazomethane in small quantities at a laboratory scale using flow reactors,[87–90] however the real challenge lies in safely generating and using industrial scale quantities. Several reported methods are outlined below.

The first company to publish methods capable of generating truly large volumes of diazomethane is Aerojet General Corporation.[91] This process generated **44** in ethereal solution from decomposition of *N*-nitroso-*N*-methylurea **43** by addition of aqueous KOH reagent stream, illustrated below in **Scheme 1.29**. The process used a series of continuously stirred tank reactor (CSTR) stages, and was capable of providing a continuous supply of 61 mol h-1 of diazomethane in THF/ether.



**Scheme 1.29**

Proctor and Warr of Phoenix Chemicals reported the synthesis of diazomethane on an industrial scale.[92] In this synthesis, diazomethane **44** is continuously generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonyl amide (**45**, Diazald®). A continuous stream of **45** is subjected to an aqueous KOH feed, generating diazomethane which is then extracted into the gas phase by subsurface and headspace flows of nitrogen gas. The nitrogen flow then carried the diazomethane into a solution containing substrate **46** to generate -chloroketone **47** (**Scheme 1.30**).



**Scheme 1.30**

The synthesis and the plant designed to run the process was capable of producing 60 metric tonnes of **44** per year, and operated safely for several years. A large number of safety features were incorporated into the plant such as in-line monitoring of **44**, secondary fail safe monitoring, automated shutdown, as well as a procedure for the worst case scenario – the reactor contents would be quenched automatically in the case of a reactor burst failure. Due to the need for decomposition by KOH, this synthesis is unsuitable for base-sensitive compounds.

## 1.4.3 Preparation of ethyl diazoacetate using continuous flow technology

Ethyl diazoacetate **48** is another important diazo-based reagent. It is used in the cyclopropanation of alkenes. **48** is a highly explosive reagent, and must be produced in a contained manner.

Rutjes *et al*. studied the formation of ethyl diazoacetate **48** from glycine ethyl ester hydrochloride **11** with sodium nitrite, as shown below in **Scheme 1.31**.[93] They effectively optimized the temperature, residence time and quantities of sodium nitrite being used to provide a process capable of delivering up to 175 mmol ethyl diazoacetate **48** per day using a microreactor with an internal volume of 100 μL. The authors postulated that with scale-up this method is viable for industrial application.



**Scheme 1.31**

Other laboratory-scale syntheses of ethyl diazoacetate **48** using continuous flow methods have been reported in the literature,[94,95] however there is little in the literature concerning industrial scale synthesis. Poechlauer and co-workers from DSM Pharmaceuticals have synthesised and applied both diazomethane and ethyl diazoacetate in continuous flow systems for plant-scale processes.[96]

## 1.4.4 Diazonium ions in flow

Diazonium salts can be very explosive: the stability of the salt is closely linked with the counter-ion. Diazonium halides are often dangerously explosive and have to be generated and used *in situ*. They are unstable above 0 °C and so must be used below this temperature. Diazonium salts with weakly coordinating counter-ions such as tetrafluoroborates, tosylates and disulfonyl amides are quite stable.[97,98] There are several examples in the literature of the generation and use of diazonium salts using continuous flow technology.[99–104]

Ley and collaborators at Pfizer have reported a variation of the Sandmeyer reaction which allows them to access sulfonyl chlorides from anilines *via* diazonium salts.[105] The classical reaction was first reported by Meerwein and co-workers.[106] This variation of the Sandmeyer reaction converted anilines to diazonium salts by reaction with sodium nitritein a mixture of conc. HCl and acetic acid (**Scheme 1.32**). The corresponding sulfonyl chlorides can then be prepared.



**Scheme 1.32**

Ley *et al*. aimed to generate diazonium ions in a continuous flow to form the sulfonyl chlorides. A number of adjustments to the original reaction conditions were necessary in order to make the process amenable to a flow process. Concentrated hydrochloric acid and acetic acid is not suitable for use in a flow reactor due to issues associated with corrosion of the stainless steel components in the pumps. The formation of precipitates was a major issue, causing blockages in the reactor. It was decided to use *t*-butyl nitrite **49** in place of sodium nitrite, which allowed use of benzyltriethylammonium chloride (BTEAC) **50** as an alternative source of chloride to hydrochloric acid. Ethylene glycol was used to solubilise CuCl2 in acetonitrile. By implementing these changes, illustrated in **Scheme 1.33**, the authors were able to design a successful flow synthesis for arylsulfonyl chlorides.



**Scheme 1.33**

Jacq *et al*. have reported the synthesis of diazonium salts as part of a telescoped synthesis of 2-substituted [1,2,3]-triazoles.[107] The diazonium salt **51** is formed by reaction of aniline **52** with *t*-butyl nitrite **49** in acetonitrile. The 2-arylhydrazonoomalononitrile intermediate **53** was then reacted with ammonia to produce 2-arylhydrazonoacetamidine **54** in good yields (>4g in 6.25h), as can be seen in **Scheme 1.34**.



**Scheme 1.34**

## 14.5-Diazocarbonyl compounds in flow

-Diazocarbonyl compounds are generally stable compounds, however the reagents used to generate them can be very shock and temperature sensitive, making them unsuitable for use on an industrial scale.[5,10] Various syntheses have been published making these versatile compounds in flow.[94,95,108–111]

Ley and collaborators at Novartis have reported generation and telescoped use of diazoketones from acyl chloride precursors.[109] The authors employed trimethylsilyldiazomethane (TMSCHN2) **56** as a safer alternative to diazomethane **44**. **56** is more thermally stable than **44**, but is still toxic and therefore requires care when handling. A range of aliphatic, aromatic and heteroaromatic diazoketones were generated by reaction of acyl halides and TMSCHN2 **56**in dichloroethane (DCE). PS-tetraalkylammonium fluoride salt **57** was found to work well as both base and impurity scavenger for this stage of the reaction.

Once the diazoketones had successfully been synthesised, it was decided to attempt to use them in the synthesis of interesting heterocycles, e.g. quinoxalines **58**. Diazoketone **59** was reacted with suitable 1,2-diaminobenzenes **60**. The authors chose to make use of PS-scavengers to purify the reaction stream in an attempt to carry out quinoxaline synthesis in a single telescoped flow sequence. PS-thiourea **61** was used to scavenge any dissolved metal salts. PS-tosylchloride **20** captured any unreacted diamine, and PS-tosylhydrazine (PS-TsNHNH2) **62** was used to scavenge residual diazoketone. In this manner an efficient, rapid and safe process for the generaton and use of diazoketones in a telescoped synthesis of quinoxalines **58** was developed, which is shown in **Scheme 1.35**.



**Scheme 1.35**

Bartrum and co-workers employed a Bamford-Stevens type reaction to synthesise -diazoesters as part of a two-step process to generate a range of different -alkoxy and -amino acid derivatives, illustrated below in **Scheme 1.36**.[110] This was achieved by decomposition of arylsulfonylhydrazones **63**, with the sulfinic acid by-product being trapped by a Et3N/silica gel scavenger column. Addition of a 250 psi back-pressure regulator (BPR) in line after the scavenger column allowed safe superheating of the hydrazones to their corresponding -diazoesters **64**.



**Scheme 1.36**

The -diazoesters were then collected and used in O-H and N-H insertion reactions in batch mode, to form a range of -alkoxy and -amino acid derivatives. The authors later reported S-H and P-H insertion reactions using the same hybrid flow-batch methodology.[111]

Wirth *et al*. reported the generation of -diazo--hydroxy esters using continuous processing.[95] This was achieved by *in situ* generation of ethyl diazoacetate and subsequent reaction with the appropriate aldehyde as shown in **Scheme 1.37**.



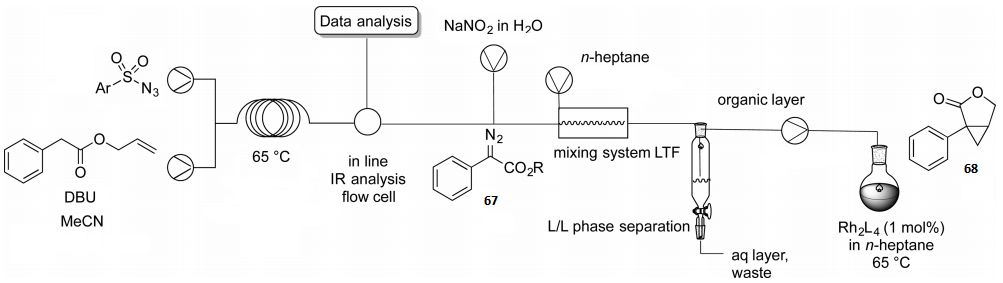
**Scheme 1.37**

Wirth and co-workers also published a telescoped synthesis of bicyclic lactones such as **68** *via* diazoesters.[112] The authors first optimized the rhodium(II) catalysed decomposition of diazoesters (**Scheme 1.38**), a range of which were also prepared in flow. The rhodium(II) catalysts were suspended in various solvents and combined with the diazoesters at a T-piece. A back-pressure regulator is required when using a solid reagent suspended in a solvent, due to the potential for clogging of the lines, as discussed in **Section 1.5.1**. Due to issues of solubility of the catalysts, it was decided that the intramolecular cyclopropanation under continuous flow conditions was not suitable for scale-up.



**Scheme 1.38**

The complete telescoped synthesis of the bicyclic lactone **68** is shown in **Scheme 1.39**. The authors used in-line IR analysis to confirm the formation of **67** before the continuous stream is directed into a unique in-line liquid-liquid extraction. A stream of the diazo compound in the organic layer was directed into a flask containing the rhodium catalyst in *n*-heptane to produce the desired product **68**. This method was successfully scaled-up to gram quantities, however a reduced yield was obtained. Although this is a semi-batch protocol, it avoids the need for column chromatography of the diazo reagent.



**Scheme 1.39** Reproduced from Ref 113.

# 1.5 Reactivity of -diazocarbonyl compounds

## 1.5.1 Mechanism of transition metal catalysed decomposition

The widely accepted mechanism for diazocarbonyl decomposition is shown in **Scheme 1.40**.[6,113,114] This has been confirmed using computational studies by Nakamura and co-workers.[115] The first step is electrophilic addition of the diazocarbonyl compound to the transition metal, followed by nitrogen extrusion. This results in the formation of a metal stabilised carbene, which is then transferred to an electron rich substrate (S:) to complete the catalytic cycle. The transition metal catalysts effective in the decomposition of α-diazocarbonyl compounds are essentially Lewis acids, which have an empty molecular orbital into which the electrophilic carbene can donate electrons.[3]



**Scheme 1.40**

Copper catalysts were the predominant catalyst for decomposition of -diazocarbonyl compounds for almost 70 years, until Teyssie introduced rhodium(II) acetate for the same purpose in 1973.[1,2] Rhodium(II) acetate **69** (**Figure 1.7**) is a binuclear compound, with four bridging acetate ligands and D4h symmetry.[116,117] It possesses one vacant axial coordination site per metal atom.



**Figure 1.7**

## 1.5.2 Wolff rearrangement

The Wolff rearrangement was first reported by Ludwig Wolff in 1902, and has since become a widely used synthetic pathway.[118] Many reviews have been published concerning this rearrangement,[119–122] the most comprehensive of which is a 100 year overview by Kirmse.[123] It is a 1,2-rearrangement of diazoketones, initiated by the loss of nitrogen, to form a ketene which may undergo further reactions with nucleophiles or cycloadditions to unsaturated systems (**Scheme 1.41**).



**Scheme 1.41**

The Wolff rearrangement can be initiated by thermolysis, photolysis, or metal ion catalysis. The widely accepted mechanism is viewed as concerted, although much evidence for a stepwise mechanism *via* formation of reactive carbonylcarbenes has been derived from various matrix-isolation studies and low-temperature time-resolved spectroscopy.[124–129]

The most common application of the Wolff rearrangement is the Arndt-Eistert synthesis, which is a one-carbon homolgation of carboxylic acids using diazomethane.[130] Hundreds of variations on the original paper have been published to date, including the example shown below in **Scheme 1.42**.[131] The reaction of a bis(acid chloride) with diazomethane failed to give reproducible results. By using (trimethylsilyl)-diazomethane instead, the authors were able to successfully produce diazoketone **70**, which could be converted to diester **71** in the presence of silver benzoate in ethanol.



**Scheme 1.42**

The Wolff rearrangement also has applications in natural product synthesis. Thommen *et al*. reported the use of a Wolff rearrangement to give ring contraction as a crucial step in the total syntheses of taiwaniaquinone F **73** and taiwaniaquinol A **74**.[132] This photolysis mediated rearrangement of the diazo derivative of sugiol methyl ether **72** yielded the unusual 6-5-6 ring system associated with taiwaniaquinoids.



**Scheme 1.43**

## 1.5.3 C-H insertion reactions

Carbene insertion into C-H bonds is an important synthetic reaction. Hundreds of examples of this extremely useful transformation can be found in the literature, and the reaction has been reviewed most recently by Maguire[133] and Doyle.[134] This section will examine the history of its discovery, along with some interesting applications in natural product synthesis.

The first report of C-H insertion was a photolysis reaction reported by Meerwein and co-workers.[135] Transition metal catalysed C-H insertion was first reported by Greuter *et al.* as illustrated in **Scheme 1.44**.[136] The authors reported copper mediated generation of a carbene from the corresponding diazoalkane **75**, which underwent C-H insertion to form the cyclopentanone **76**.



**Scheme 1.44**

The full potential of the C-H insertion reaction was only recognised after Teyssie and co-workers reported the first example of such a reaction catalysed by rhodium(II).[137] Since then, rhodium(II) acetate **69** has become one of the most widely used reagents in diazo chemistry, and is used in various syntheses of natural products. A complete synthesis of the alkaloid morphine **79**, a powerful analgesic, was published by White *et al*. in 1997 that employed an intramolecular carbenoid C-H insertion reaction.[138] Rhodium(II) acetate was used to achieve the transformation from the diazoketone **77** to **78**, establishing a bond from C13 to C15, as shown below in **Scheme 1.45**.



**Scheme 1.45**

Lloyd and co-workers employed another rhodium(II) catalyst, in their selective C-H insertion reactions for the synthesis of -methylene--butyrolactone natural products.[139] Dirhodium tetraoctanoate **80** is a rhodium(II) is a binuclear compound, with four bridging octanoate ligands whose structure is shown in **Figure 1.8**.



**Figure 1.8**

The authors synthesised a range of conformationally restricted cyclohexane derivatives by use of rhodium(II) catalysed decomposition of the corresponding diazophosphonates (**Scheme 1.46**). This method was then used in the synthesis of the natural product, -cyclocostunolides **81**.



**Scheme 1.46**

## 1.5.4 Dioxinones

Diketene **82** was first reported by Wilsmore in 1907,[140] but it was not until 1952 that Carroll and Bader reported the reaction of diketene with ketones to form 2,2-disubstituted-4-methyl-6-keto-1,3-dioxinones, as shown in **Scheme 1.47**.[141,142]



**Scheme 1.47**

The structure of 2,2,6-trimethyl-4H--1,3-dioxin-4-one **83**, the adduct formed by reaction of diketene with acetone, was confirmed using proton magnetic resonance in 1956.[143] Since their discovery, dioxinones have been widely used, and have been reviewed a number of times.[144–147] The following section will outline some uses of dioxinones.

Sato *et al*. reported that dioxinones could be used to form the corresponding acylketenes **84**, which could either react with nucleophiles to give -keto acid derivatives **85**, or react with dipolarophiles to give six-membered heterocyclic compounds **86**, such as lactones and lactams (**Scheme 1.48**).[144,145,148]



**Scheme 1.48**

Dioxinones have been used as a key intermediate in the biomimetic total synthesis of resorcylates.[149] Resorcylates are a large group of bioactive natural products, whose bioactivities include anticancer, antimalarial, mycotoxicity, antifungal and antibiotic properties.

Key steps in the synthesis of resorcylate Creuntaren A **87** are shown below in **Scheme 1.49**. Creuntaren A **87** is an antifungal agent that also inhibits the proliferation of different cancer cell lines, including a multidrug-resistant KB carcinoma cell line.[150] This is just one of the resorcylates whose total synthesis was achieved using dioxinones as key intermediates by Barrett and co-workers.[149]



**Scheme 1.49**

# 1.6 Lanthanides in organic synthesis

## 1.6.1 Background

In the 1980s, lanthanide reagents experienced a surge in popularity, with several reviews published on their use in organic synthesis in the intervening years.[152–164] The following is a brief summary of some of the many uses of lanthanide reagents.

## 1.6.2 Oxidation reactions

Cerium(IV) compounds are powerful one-electron oxidising agents.[164] Ceric ammonium nitrate (NH4)2Ce(NO3)6 **88**, abbreviated as CAN, is perhaps the most widely used reagent in this class. Cerium(IV) oxidants have been used to oxidise aromatic systems,[165] arenes,[166] alcohols,[167,168] and even -hydroxy ketones.[169–171]

CAN has been used in the total synthesis of (±) Lantalucratin A **89**,[172] a natural product with a naphthoquinone skeleton which has shown cytotoxic activity against various human tumour cell lines.[173] CAN was used to mediate an intramolecular oxidative cyclisation under mild conditions in an excellent yield as the key step in this complete synthesis, as shown in **Scheme 1.50**.



**Scheme 1.50**

## 1.6.3 Reduction reactions

The first practical use of lanthanide reducing agents was in the use of ytterbium in liquid ammonia for dissolving metal reductions (**Scheme 1.51**).[174] This is similar to a Birch reduction with alkali metals but has advantages in ease of handling of the metal, and in avoiding the strongly basic hydroxide work up.



**Scheme 1.51**

Possibly the most well-known use for lanthanide reagents in organic synthesis is the Luche procedure for the selective reduction of conjugated aldehydes and ketones to allylic alcohols.[175–177] The selective 1,2 reduction of enones was first detailed by Luche in 1978, and used sodium borohydride in conjunction with CeCl3, as seen in **Scheme 1.52**. This transformation was not achievable, or proceeded much less efficiently when traditional reducing reagents such as DIBAL, LAH or NaBH4 alone were used.



|  |  |  |
| --- | --- | --- |
|  | A | B |
| With CeCl3 | 97% | 3% |
| Without CeCl3 | 0% | 100% |

**Scheme 1.52**

The Luche procedure has been exploited in the total synthesis of isocladosporin **91** and 3-*epi*-isocladosporin **92**, as seen below in **Scheme 1.53**.[178] In this synthesis the authors used sodium borohydride and cerium trichloride at -78 °C to diastereoselectively reduce the ketone in **90** to afford the *in situ* lactone, and isocladosporin **91** and 3-*epi*-isocladosporin **92**. All other reduction conditions resulted in loss of diastereoselectivity and/or deprotection of the methoxymethyl acetal (MOM) protecting groups.



**Scheme 1.53**

Samarium(II) iodide’s role as a one-electron reducing agent has been recently reviewed.[179] Samarium(II) iodide may be used to reduce α-functionalized carbonyl compounds,[180] arenes,[181] ketones and aldehydes,[182] carboxylic acids,[183] organic halides[182] and nitro compounds.[184] The reactivity of SmI2 is strongly dependent on the choice of reaction solvent. The use of hexamethylphosphoramide **93** (HMPA) as a co-solvent in samarium iodide reductions has been shown to allow the reductions to proceed under much milder conditions than in its absence.[185] More recently, hydroxylated HMPA[186] **94** and dipyrrolidinomethylaminophosphoric acid triamide (DPMPA)[187] **95** have also been reported as activators of samarium(II) iodide reductions (**Figure 1.9**).



**Figure 1.9**

## 1.6.4 Carbon-carbon bond forming reactions using lanthanide catalysis

Lanthanide reagents have found many uses in carbon-carbon bond forming reactions. Organocerium reagents have proved to be very efficient alternatives to Grignard and organolithium reagents, and have been recently reviewed by Sambri.[188] Other organolanthanides have also been shown to be effective alternatives, but the low cost and proven success of organoceriums has led to their preferential use.

Organoceriums are prepared *in situ* by transmetalation reactions from organolithium or organomagnesium reagents.[189–193] The structure of the active species remains undetermined. These reagents have been used to react with aldehydes and ketones to give the corresponding alcohol, often in higher yields than those reported when using traditional reagents. This was exploited in a key step in the total synthesis of (+)-dihydro-epi-deoxyarteannuin B **96**, a key intermediate in the synthesis of (-)-Artemisin **97**, as shown in **Scheme 1.54**.[194]



**Scheme 1.54**

Scandium (III) triflate was found to be an effective catalyst for the aldol reaction of silyl enol ethers with aldehydes.[157,195] Kobayashi and co-workers examined the effect of typical lanthanide triflates in this reaction, and found Sc(OTf)3 **98** to be more effective than either the ytterium or ytterbium triflates (**Scheme 1.55)**.[196]



|  |  |  |  |
| --- | --- | --- | --- |
| **Entry** | **Catalyst** |  | **Yield (%)** |
| **1** | Sc(OTf)3 | **98** | 81 |
| **2** | Y(OTf)3 | **99** | Trace |
| **3** | Yb(OTf)3 | **100** | Trace |

**Scheme 1.55**

Kobayashi and co-workers also investigated the recovery and re-use of the scandium triflate catalysts for these aldol reactions.[195] The scandium triflate **98** was recovered almost quantitatively after the reaction was complete. The recovered catalyst’s activity was seemingly undiminished as it performed comparably in the subsequent run (**Scheme 1.56**).



**Scheme 1.56**

As scandium(III) triflate is more soluble in water than in organic solvents it can be recovered from the aqueous layer as shown in **Figure 1.10**.



**Figure 1.10**

More recently, Allen *et al*. reported the development of chiral lanthanide-containing complexes that produce Mukaiyama aldol products with excellent enantioselectivities.[197] Mukaiyama aldol reactions are used to synthesise -hydroxy carbonyls, and requires a catalyst to induce stereochemistry. When the pre-catalyst L shown in **Scheme 1.57** is used in conjunction with neodymium triflate **101** for aromatic aldehydes, excellent yields and good enantioselectivities were obtained. However when the same conditions were employed with alkyl aldehydes, the efficacy of the reaction significantly decreased.



|  |  |  |
| --- | --- | --- |
| **Aldehyde** | **Yield** | ***syn:anti*** |
| *p*-Chlorobenzaldehyde | 93% | 36:1 |
| *p*-Methylbenzaldehyde | 90% | 12:1 |
| Formaldehyde | 56% | 1:3 |

**Scheme 1.57**

## 1.6.5 Lanthanide triflates as Lewis acid catalysts

Kobayashi first reported the use of lanthanide triflates as water compatible Lewis acids.[198–200] Use of these lanthanide triflates as water compatible Lewis acids has several benefits.[201] These include the ability to use water as reaction solvent in place of organic solvent, and no necessity to use anhydrous solvents and substrates. In addition to this, aqueous solution allows for the use of the Ln(OTf)3 hydrates, which are less costly than the anhydrous forms.[202]

The Diels-Alder reaction is a widely used synthetic transformation to yield cyclic compounds. These reactions are reversible, and are generally carried out at the lowest possible temperature. Lewis acid catalysts allow Diels-Alder reactions to proceed at room temperature or below, but can be accompanied by diene polymerization.[203]

Lanthanide triflates have been shown to successfully catalyse Diels-Alder reactions.[204] A recent example of this in the literature was reported by Tiseni when investigating tertiary-amine-catalyzed enantioselective [4+2] cycloadditions of ,-unsaturated acid chlorides and the electron-poor aldehyde chloral.[205] The authors found the use of erbium triflate catalyst **102** improved the scope of the reactions considerably, allowing the use of a wide range of aromatic and aliphatic aldehydes. Some examples of the transformations achieved are shown in **Scheme 1.58**.



|  |  |  |  |
| --- | --- | --- | --- |
| **R1** | **R2** | **Yield [%]** | ***ee* [%]** |
| Et | Ph | 62 | 95 |
| Ph | Ph | 64 | 94 |
| Ph | *m*-ClC6H4 | 78 | 93 |

**Scheme 1.58**

## 1.6.6 Lanthanides and diazo compounds

Aziridines are traditionally prepared using transition metal catalysis, either through addition of a nitrene moiety to an olefin, or the addition of a carbene moiety to an imine.[206–210] Wang and co-workers have reported lanthanide triflate catalysed aziridine synthesis from imines and diazo compounds.[211] This follows on from a publication by Templeton *et al*. of Lewis-acid catalysed synthesis of aziridines from ethyl diazoacetate **48** and imines.[212]

The authors used a variety of imines with ethyl diazoacetate **48** in the presence of 10 mol% of lanthanum triflate hydrate **103**. The reaction was found to proceed smoothly, even in protic solvents like ethanol. Ethanol was therefore used as the solvent of choice, as it allowed the use of the lanthanide triflates in their hydrated form, which are much less expensive than the anhydrous salts. Using these conditions, the reaction was found to be selective, affording predominately *cis* aziridines. A range of arylimines were reacted with ethyl diazoacetate **48** in ethanol to produce the corresponding aziridines as shown in **Scheme 1.59**.



|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Imine** | **R1** | **R2** | **Yield 104** | **Yield 105** | **Yield 106** | **Yield 107** |
| 1a | C6H5 | C6H5 | 53% | - | 13% | 17% |
| 1b | *p*-Cl-C6H4 | C6H5 | 55% | - | - | - |
| 1c | *p*-Me-C6H4 | *p*-Cl-C6H4 | 57% | - | 10% | 13% |

**Scheme 1.59**

Wang and co-workers investigated a range of lanthanide triflate catalysts and loadings. It was found that a 10-15 mol % catalyst loading gave the optimum results, and that neodymium triflate **101** gave the highest yield and *cis* selectivities were obtained in all cases. The heavier lanthanides resulted in reduced selectivities.

Curini *et al*. reported the use of lanthanide triflates to form ,-epoxy esters from the reaction of aldehydes with ethyl diazoacetate **48**, as illustrated in **Scheme** **1.60**.[213] The authors tested a variety of reaction conditions but found that the best results were obtained in solvent-free conditions. A range of aliphatic and aromatic aldehydes were tested, and were found to be very reactive in all cases, with reactions times of only 10 minutes.



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **R1** | **Ratio *cis*:*trans*** | **Yield with La(OTf)3** | **Yield with Eu(OTf)3** | **Yield with Yb(OTf)3** |
| CH3 | 1:1 | 92% | 35% | 29% |
| C5H11 | 1:1 | 85% | 41% | 40% |
| C6H5 | 4:6 | 73% | 19% | 18% |

**Scheme 1.60**

The same reaction was attempted using ketones as substrates in an attempt to form glycidic esters. Ketones were found to be much less reactive than aldehydes, with no reaction occuring in several cases, and a significantly longer reaction time (72h) for those that did react (**Scheme 1.61**). It was determined that -unsubstituted and -monosubstituted cyclohexanones were the only substrates for which the process is effective.



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **R1** | **R1** | **Yield with La(OTf)3** | **Yield with Eu(OTf)3** | **Yield with Yb(OTf)3** |
| H | H | 87% | 56% | 46% |
| H | CH3 | 83% | 34% | 32% |
| CH3 | H | 81% | 39% | 34% |

**Scheme 1.61**

## 1.6.7 X-H insertion reactions

X-H insertion reactions of diazocarbonyl compounds have been comprehensively reviewed,[3,8,90,214,215] most recently by Gillingham[216] and McKervey.[4] X-H insertion is the insertion of a carbene into the X-H bond, as can be seen in **Scheme 1.62**.



**Scheme 1.62**

O-H, S-H and N-H insertion reactions have been the most studied reactions in this class. The most popular transition metal catalysts used in the literature to achieve these transformations have been rhodium(II) and copper(I). Rhodium(II) acetate catalysed X-H insertion has even been used commercially by Merck in the preparation of (+)-thienamycin **108**, a powerful antibiotic (**Scheme 1.63**).[217]



**Scheme 1.63**

To date there has been only one report in the literature using lanthanide catalysts to achieve X-H insertion from diazocarbonyl compounds. Pansare and co-workers[218] were looking for a route to -alkoxy aryl ketones using mild conditions. They investigated a range of diazocarbonyl insertion reactions into the oxygen-hydrogen bonds in various alcohols, using scandium triflate **98** (2-10 mol%) as catalyst, and achieved successful O-H insertion (**Scheme 1.64**).



**Scheme 1.64**

The reactions were found to work well in either benzene or dichloromethane at room temperature, and was found to be faster for primary alcohols than secondary. Pansare also investigated O-H insertion using amino acid and hydroxy acid derived diazocarbonyl substrates. Diazoketone derived from *O*-acetyl mandelic acid were used as a substrate, and, underwent successful methanol insertion, showing the scope of the methodology (**Scheme 1.65**).



**Scheme 1.65**

The corresponding intermolecular N-H insertion reaction was also attempted with an amine, a carbamate and morpholine, but proved to be unsuccessful, as can be seen in **Scheme 1.66**.



**Scheme 1.66**

When the intramolecular reaction was attempted however, the reaction was successful yielding 3-phenyl-4-benzyloxycarbonyl morpholine-2-one **109** (**Scheme 1.67**).



**Scheme 1.67**

# 1.7 Objectives of current research

Following on from the above literature review, the objectives of this project are as follows:

* To synthesise a range of -ketoesters with varying ester side-chains by transesterification of the corresponding alcohol, as shown in **Scheme 1.68**.



**Scheme 1.68**

* To prepare a range of novel -diazo--ketoesters from -ketoesters *via* diazo transfer (**Scheme 1.69**).



**Scheme 1.69**

* To examine the effect of varying different parameters of the diazo transfer reaction on the efficacy of the reaction in an attempt to make it more environmentally benign by employing some of the 12 Principles of Green Chemistry,[56] and more appealing to industry.
* To apply this improved methodology to continuous processing.
* To synthesise a range of dioxinones *via* rhodium(II) catalysed decomposition of -diazo--ketoesters.



**Scheme 1.70**

* To investigate lanthanide catalysed decomposition reactions of -diazo--ketoesters.

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