Literature review

Kinetics:

The acid-catalyzed hydrolysis of amides has been extensively investigated and the subject thoroughly reviewed\(^6\). Although there has been general agreement for a long time on the predominant (A-2) mechanism\(^2\).

The acid-catalyzed hydrolysis of lactams has not been extensively studied, although various work withers\(^7,8\) have compared relative rates of hydrolysis for ring sizes from 4-7 atoms (\(n = 1-4\)).

\[
\begin{align*}
\text{C} & \quad \text{NH} \\
\text{CH}_2 & \\
\text{(CH}_2)_n & \\
\text{O} & \\
\end{align*}
\]

\(n = 1, \beta\)-lactam; \(n = 2, \gamma\)-lactam; 
\(n = 3, \delta\)-lactam; \(n = 4, \epsilon\)-lactam

Mhala and Jagdale\(^9\) have obtained the hydrolysis rate profile (as a function of acidity) for the \&-lactam at 97°C in sulfuric acid. Use of the Bunnett \(w\)-parameter treatment\(^10\) led to a curved relationship and hence somewhat inconclusive results.

Cyclization

The formation of 5-membered nitrogen heterocycles using radical cyclisation reactions has attracted the attention of synthetic chemists for many years. A wide range of N heterocycles have been prepared from unsaturated organohalides using a variety of radical cyclisation methods, the most popular of which involves reductive cyclisation using tributyltin hydride.\(^12\) The high toxicity of organotin derivatives and the difficulty of removing organotin halide derivatives from organic products has recently led to the development of alternative radical reagents to organotin derivatives. One particularly useful alternative method involves treatment of unsaturated organohalides with copper(I) or ruthenium(II) complexes in atom transfer radical cyclisation (ATRC) reactions.\(^2\) In these oxidative cyclisations, abstraction of a halogen atom by for example, CuCl is followed by scheme radical cyclisation

The resulting cyclic carboncentred radical can then abstract a halogen-atom from the CuCl\(_2\) to form the cyclic organohalide and CuCl, which can continue the chain reaction. There are a number of attractive features of this approach including the fact that
functionalized cyclic products are formed using catalytic amounts of easily recovered and inexpensive metal complexes.\textsuperscript{14}

\begin{center}
\begin{tikzpicture}
\node[draw,circle,minimum size=1cm] (a) at (0,0) {Cl};
\node[draw,circle,minimum size=1cm] (b) at (2,0) {CuCl};
\node[draw,circle,minimum size=1cm] (c) at (4,0) {CuCl\textsubscript{2}};
\node[draw,circle,minimum size=1cm] (d) at (0,-3) {Cl};
\node[draw,circle,minimum size=1cm] (e) at (2,-3) {CuCl};
\node[draw,circle,minimum size=1cm] (f) at (4,-3) {CuCl\textsubscript{2}};
\draw (a) to [bend right=45] (b);
\draw (b) to [bend right=45] (c);
\draw (d) to [bend right=45] (e);
\draw (e) to [bend right=45] (f);
\end{tikzpicture}
\end{center}

**Hydrolysis:**

Many authors have suggested that the mechanism of enzymatic hydrolysis is similar to that of alkaline hydrolysis\textsuperscript{15}. The knowledge of the stability of the former molecules in acidic medium is of great interest. As an example, acidic hydrolysis takes place in the human body when the antibiotic (amoxycillin, penicillin V, cloxacillin, ampicillin) is orally ingested\textsuperscript{16}. For these reasons is very important to have a good knowledge of the mechanisms of the action of $\beta$-lactam antibiotics, which in turn has facilitated the determination of new structures with a similar chemical reactivity in addition to resistance to bacterial defense mechanisms.

During the last ten years a great amount of theoretical studies on $\beta$-lactam antibiotics have been performed. *Ab initio* calculations were recently used to determine structural parameters for various $\beta$-lactam compounds\textsuperscript{17,18}. On the other hand, the chemical reactivity (basically alkaline hydrolysis) of $\beta$-lactam antibiotics has been studied by using semi-empirical methods preferentially\textsuperscript{19,20} with the exception of the early investigations of Petrongolo and coworkers\textsuperscript{21} and more recent studies with a high-quality basis set\textsuperscript{21}. A large number of kinetic studies regarding penicillin and cephalosporin degradation in acidic medium are found in the literature\textsuperscript{18} however, at present, there are still important doubts concerning the reaction pathway\textsuperscript{15}. Theoretical studies on neutral and acidic hydrolysis of amicid and similar systems have been carried out. Nevertheless, the reactivity of these molecules is essentially different to those of $\beta$-lactam antibiotics since oxygen-protonation is thermodynamically favored against nitrogen-protonation\textsuperscript{30,31} circumstances which, on the other hand, do not take place in $\beta$-lactam compounds\textsuperscript{12}. There are no theoretical studies on the acidic hydrolysis reaction of the structures selected as models of $\beta$-lactam compounds.
**Reduction**

The Birch reaction for the dearomatisation of aromatic substrates is an extremely practical and important tool for synthetic chemists and is used widely as a key step for the synthesis of natural products and molecules of biological interest. However, the partial reduction of pyrrole is difficult as the high electron density of these aromatic heterocycles inhibits the addition of an electron, the first step of a Birch reaction. Donohoe has shown that the partial reduction of pyrroles is possible but this process generally requires the presence of at least two electron withdrawing groups that reduce the electron density of the heterocycle such that reasonable yields of the 3-pyrrolines are obtained. This method was recently exploited for the elegant synthesis of the pyrrolidine alkaloid (±)-1-epiaustraline (Scheme 1).

**Catalysts**

Synthetic Organic Chemistry underpins a number of other important research areas including Synthetic Coordination Chemistry, Catalysis, Synthetic Supramolecular Chemistry, Chemical Biology and Biological Chemistry and Polymer Materials. It is also an area which has an important role contributing to solving problems in the Energy, Healthcare Technologies and Manufacturing the Future Challenge Themes and the Physical Sciences Grand Challenges, in particular Dial-a-Molecule. Examples of the impact that this area could have on these themes may include, but will not be limited to, new transformations and methodologies which will enable the use of non-petroleum, biomass based feedstocks in the manufacture of chemicals or new routes to synthetic analogues of biological molecules which will help us to better understand biological process or treat diseases.

**Oxidation**

Sulfonimidamides are derivatives of sulfonic acid and analogous of sulfonamides, in which one oxygen has been replaced by a nitrogen group. They are known since 1962, and a number of recent investigations focused on both their reactivity and application in organic synthesis, such as nitrogen sources for metal-catalyzed nitrene transfer reactions, and their biological activity, for instance as analogous of oncolytic sulfonylureas or mimics of intermediates in protease and amidase reactions. Only a few synthetic approaches for their preparation have been reported, the most direct and
common route being the nucleophilic substitution of a sulfonimidoyl chloride 2 with an amine (Scheme 1)

Various chlorinating reagents can be applied for the synthesis of the respective sulfonimidoyl intermediates. Among them, and despite its explosive nature, tert-butyl hypochlorite is the most widely used one.\textsuperscript{15} Other chlorinating agents present a rather limited substrate scope. For example, chlorine\textsuperscript{13} is preferred for N-alkyl sulfinamides, reacting very violently with N-aryl derivatives. N-chlorobenzotriazole is less efficient with bulky amines, and with chloramine-T or -N only N-tosyl or -nosyl sulfonimidamides can be obtained. In addition, an alternative route to the intermediate N-tosyl or -nosyl sulfonimidoyl chlorides involves the reaction of sulfinyl chlorides with chloramine-T or -N.