

Oxidation Chemistry

Safety and quality on the pharmaceutical scale

Oxidations and reductions are one of the foundations of functionalization for pharmaceutical synthesis. Archimica is engaged in developing a wide range of new industrial approaches to oxidation-reduction that respond to the commercial environment.

Facilities and methodology are critical to progress

At Archimica, we are continually developing our expertise in the field of oxidation by finding answers to specific synthesis challenges and developing commercial applications of the latest research. Our goal is to offer the pharmaceutical industry the world's most comprehensive and functional toolbox for reduction and oxidation operations.

Chemistry is of course important in the development of the oxidation reaction in the service of the pharmaceutical industry. At the same time, not enough can be said about the infrastructure and practices that surround these chemistries in making the broad range of oxidation technology available for commercial scale pharmaceutical projects.

Catalyst separation is critical to product purity and the economics of a project. Precise process control is always an issue when treating organic compounds with oxidizers at elevated temperatures to avoid decomposition – but also to maintain safety surrounding a project.

A broad toolbox and commercial platform

Archimica has a great deal of experience with the entire spectrum of oxidations. Starting with air and oxygen, our oxidation toolbox includes inorganic and organic peracids and their salts, halogenation, reactions with organic oxidizers and more.

Because of our experience and the breadth of our technology, we start our work in oxidation with a library of thousands of reactions. Our process development expertise and engineering knowledge has solved the major issues for many general situations, requiring only adaptations to rapidly target and

- Air, oxygen oxidation
- Baeyer-Villiger oxidation
- Catalytic dehydrogenation
- Hydrogen peroxide
- N-oxides
- Oxa acids
- Peracids
- Permanganates
- Sharpless oxidation
- Swern oxidation
- Willgerodt-Kindler reaction
- And many more

then fine-tune the best approach to the functionalization, cleavage or carbon-carbon bond formation in question. We handle these types of reactions on the scales that will be required for commercial production, addressing issues of safety, efficiency, mildness and selectivity around the world, oxidation technology is run on a wide variety of equipment and in countless syntheses every day.

Air and oxygen

Archimica conducts catalyzed air oxidation employing sophisticated metal catalysts. Our work with oxygen applies in great depth to the oxidation of glycols to oxa acids (Figure 1). This technology required elaborate safety and process control systems to avoid decomposition due to the treatment of organic compounds with oxygen at elevated temperatures. A wide range of oxa acids, with varying chain-length and substitutions, are available on a commercial scale.

Oxidations with inorganic acids and salts

Archimica utilizes a broad range of inorganic acids – or peroxy-compounds – and their salts in oxidation reactions for the pharmaceutical industry. Chief among these is our work with hydrogen peroxide which Archimica employs on a large scale in a highly concentrated form (70%) at our commercial scale, pilot and lab facilities. Hydrogen peroxide is used for a broad variety of reactions including versatile heterocycle functionalizations such as N-oxides and synthesis of hydroxy-substituted heterocycles (Figure 2 and 3). From

hydroxy substituted heterocycles, halogenated heterocycles can be created, which can then allow C,C bond formation through coupling or substitution.

Hydrogen peroxide is the basis for other types of oxidation in conjunction with metal catalysts. An example of this is the Sharpless oxidation – the chiral form of the cis-dihydroxylation. This reaction uses hydrogen peroxide with chiral titanium salts as mediators and is a very elegant chiral method that allows for a high degree of functionalization (Figure 4). This approach allows the creation of two chiral centers plus two C,O bonds, out of a simple C=C double bond which is ideal for further functionalization.

Archimica employs the highly reactive potassium permanganate for oxidations in a mild and tailored fashion. These include, importantly, cis-dihydroxylations that convert olefins (C=C double bonds) to cis-diols, a very useful functionalization reaction with preferred regioselectivity. We have also developed permanganate-based chemistry to provide commercial scale replacements for some classical reagents – osmium tetroxide and lead tetraacetate – which though useful on the laboratory scale, present challenges on the commercial scale.

Nitric acid oxidation sees use as an alternative to air oxidation when air oxidation does not prove possible

Figure 1

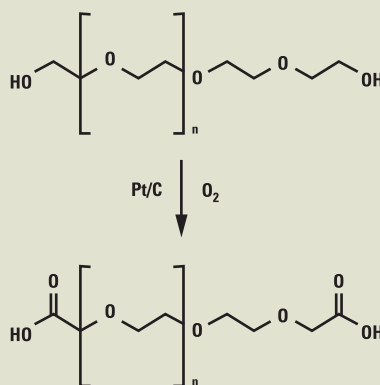


Figure 2

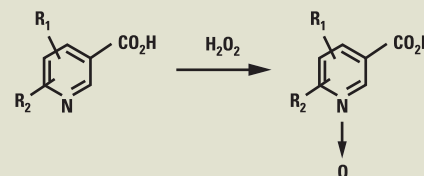


Figure 3

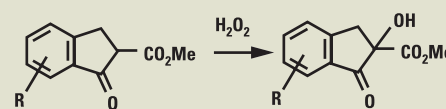


Figure 4



because substituents are sensitive, or when air will deactivate the catalyst in question. This reaction requires extremely fine process control. If done so, not only are acids available, but also 1,2-diketones from 2-hydroxyketones (Figure 5).

In a highly tailored reaction, framed within a technical process-control environment, selective nitrosations or nitrations to nitrogen or oxygen are possible in pharmaceutical ingredients' syntheses, using e.g. acetyl nitrate in a selective manner (Figure 6 and 7).

Manganese dioxide and its activated surface form are used for selective oxidations of secondary alcohols or benzylic, allylic and propargylic alcohols in the presence of simple primary alcohols. These approaches yield ketones or aldehydes and are an industrially viable alternative to the textbook reagent selenium dioxide, which is highly toxic and problematic for the pharmaceutical industry because of residual selenium compounds.

Peroxosulfates for transformations from methyl groups to aldehydes and percarbonates for mild functional oxidations in the presence of acid-sensitive groups are also part of the Archimica oxidation toolbox.

Oxidizing organic acids and salts

In many cases due to solubility, reactivity requirements and the need to reach specific targets, the use of organic peracids is advised (Figure 8). Examples include peracetic acid or perbenzoic acid and derivatives. These peracids can be generated also in situ

Figure 5

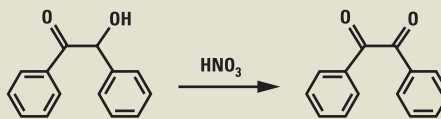


Figure 6

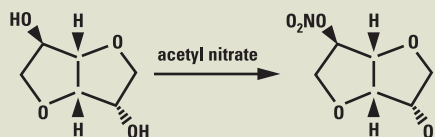


Figure 7

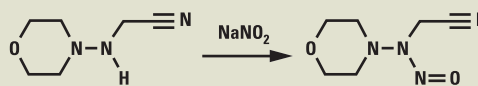


Figure 8



which allows further fine tuning of conditions. Peracid oxidations are also useful for heterocycle oxidation, Baeyer-Villiger oxidation or epoxidations which after hydrolysis leads to trans diols. All of these are extremely valuable for further transformations in both functionalization and C,C bond formation. In certain cases, Baeyer-Villiger oxidation, which offers esters or lactones from ketones, acids, alcohols and hydroxyacids, is done by Archimica at the commercial scale using hydrogen peroxide.

Special selective oxidations

Archimica's work in oxidation includes a variety of specialized approaches that improve efficiency while at the same time optimizing cost, safety and environmental factors.

The Swern oxidation has been widely used because it allows a targeted oxidation of primary alcohols to aldehydes under mildest conditions while tolerating most other functional groups. Archimica has developed variations of the Swern oxidation based on its clean $^{\circ}\text{T3P}$ technology,

which avoid the activation of dimethylsulfoxide by DCC or oxalylchloride – reagents which are both hazardous and can cause severe problems in scale-up and product isolation (Figure 9). This variation improves processability, environmental and process safety and improves selectivity at the commercial scale.

The Willgerodt-Kindler reaction (Figure 10) is an oxidation from acetophenones to phenylacetic acids, useful because acetophenones are easily accessible and phenylacetic acids are widely used in pharmaceutical synthesis or APIs. We have developed industrially and environmentally acceptable solutions for the special challenges posed by this technology and its low time/space yield as well as use of sulfides as a reagent.

Catalytic dehydrogenation is a special method that can be applied very efficiently in some cases and uses our large catalyst libraries to find an optimum solution (Figure 11).

