Selective catalytic oxidations by palladium and manganese

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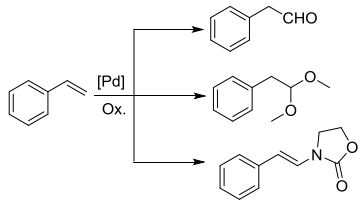
Summary

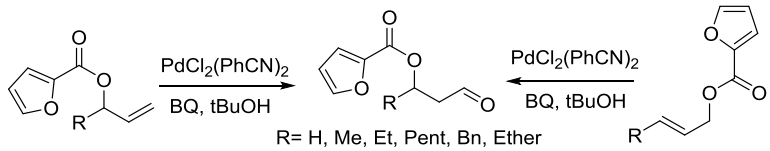
What is the difference between fire and life? Both are essentially oxidations with oxygen; the difference is selectivity and control. In this dissertation the goal was primarily achieving control over oxidation chemistry to gain selectivity using palladium and manganese based catalysts.

Palladium catalysed *anti*-Markovnikov (AM) selective oxidation of α-olefins, including the preparation of aldehydes, acetals is a challenge and highly desirable in modern chemistry, as these reactions provide direct access to aldehydes under neutral conditions and often at room temperature.[1] Overall, it is apparent that AM selectivity is largely substrate dependent, *i.e.* that specific substrates bearing certain functional groups need to be present *i.e.* styrene (Scheme 1).[2] Furthermore, it is apparent that, although a general method based on specific reaction conditions is unlikely to emerge, recent examples suggest that at least for certain substrate classes generally applicable methods can be developed (Chapter 1).



Scheme 1. Various AM oxidation reactions of styrene that can be achieved with palladium catalysis.

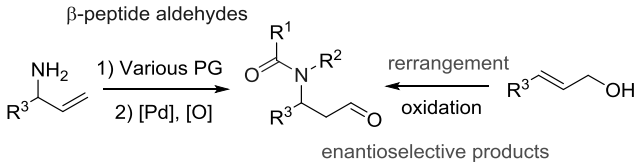
In chapter 2, the first highly selective catalytic *anti*-Markovnikov oxidation of allylic esters is described, which provides a facile route to the synthesis of protected β-hydroxy aldehydes from terminal alkenes with high selectivity, high yield and, importantly, with low Pd catalyst loadings. A key side reaction encountered was the palladium catalysed Overman rearrangement that eroded the enantiomeric excess of the substrates rapidly. However, this rearrangement is also an advantage in that the same aldehyde products can be obtained by using either the branched or linear protected allylic esters under the same reaction conditions. This aspect opens up new synthetic approaches to the preparation of β-hydroxy aldehydes from linear allylic esters or even the mixtures of terminal and internal alkenes (Scheme 2).



Scheme 2. Palladium AM oxidation of allylic esters to aldehydes.

In chapter 3, it was shown that the same catalytic system could be applied to the synthesis of protected β-amino aldehydes and again a palladium catalysed rearrangement allowed for the corresponding protected β-amino aldehydes to be prepared even from protected linear allylic alcohols under ambient conditions with a

wide range of protecting groups. Crucially, in contrast to allylic esters, the retention of enantioselectivity in chiral protected allylic amines and the applicability of this method to peptide synthesis presents considerable opportunities in synthesis and chemical biology (Scheme 3). These studies also enable us to identify the precise role played by alcohols and especially *t*-BuOH in the reaction, where it acts as a nucleophile and in the latter case provides the aldehyde product directly via elimination to isobutene (Chapter 3).



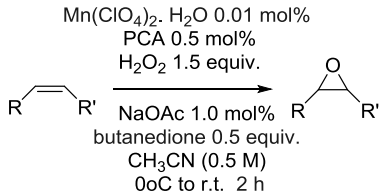
Scheme 3. AM oxidation of allylic amide catalysed by palladium.

From a mechanistic perspective the catalytic system, the development of which is described in chapters 2 and 3, and which consists of a Pd(II) catalyst, benzoquinone as oxidant and *t*-BuOH as solvent, is shown in chapter 4 to be distinct from the classic Wacker-Tsuji method in many aspects. The data reported indicate that although Pd(II) can bind to alkenes, such complexation may actually retard their oxidation rather than accelerate it and indeed leads to other isomerisation reactions not least enamine formation. Coordination of the oxidant prior to attack on the substrate is most likely to occur. These results hold important implications with regard to the standard mechanism proposed for the Wacker-Tsuji[3] reaction in that a redox neutral cycle (*i.e.* the Pd(II) oxidation state is not changed throughout the cycle) could be involved instead of generally accepted Pd(II)/Pd(0) cycle (Chapter 4). The coordination of the oxidant suggests that the use of other oxidants than benzoquinone such as *t*-BuOOH may offer additional opportunities in the AM oxidation of alkenes.

Finally, recent progress made in achieving AM selectivity under relatively mild reaction conditions and with ever shorter reaction times indicates that further efforts towards AM selective methods will simultaneously lead to improvements with regard to catalyst loading also. The prospect of direct catalytic AM functionalisation at the terminal position of α-olefins with full catalyst control makes these efforts highly attractive and worthwhile to pursue.

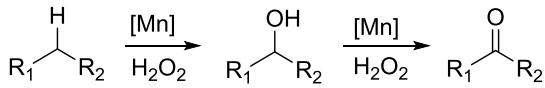
In chapters 5 and 6, a manganese/pyridine-2-carboxylic acid based catalyst developed by our group recently[4] for the *cis*-dihydroxylation of electron deficient alkenes was explored. This catalytic system is highly attractive since stoichiometric amounts of an environmentally friendly terminal oxidant H_2O_2 provided good activity in the oxidation of alkenes. Furthermore, pre-prepared ligands were not needed, which saves energy and cost. However, at the outset of this thesis project, there was still a limitation that needed to be overcome, including safety concerns in regard to the use of acetone as solvent together with H_2O_2 as oxidant – with the potential for explosions in large scale reactions. The use of other ketones as co-solvents could remove this risk, however, although CF_3COCH_3 was found to be effective, it is volatile and corrosive and hence far from being an ideal solution.

In chapter 5, we show that a safer system can be employed where sub-stoichiometric amount of butandione was used as additive and wide solvent scope has been successfully tested for this method. Applying this method in the *cis*-dihydroxylation of electron deficient alkenes shows the same exceptional selectivity and activity observed with acetone. Furthermore, selective epoxidation of electron rich alkenes with H_2O_2 was achieved with high turnover numbers (up to 300,000) and turnover frequency (up to 40 s^{-1}). Importantly, the tolerance to other oxidation sensitive functional groups, the mild conditions (*i.e.* between 0 ^oC and r.t.) and solvent scope make this system highly competitive with stoichiometric oxidants such as *m*CPBA (Scheme 4). The system shows good to excellent selectivity in the epoxidation of dienes and bifunctional substrates. Mechanistic studies focused on the role of butanedione in the reaction and highlighted the key role that the formation of butanedione-hydrogen peroxide adducts play in the reaction. A key challenge, however, that became clear in the study is to overcome the competing oxidation of the ketone that ultimately limits turnover number (Chapter 5).



Scheme 4. Epoxidation of alkenes with manganese/pyridine-2-carboxylic acid.

In chapter 6, selective oxidation of secondary alcohols can be achieved at room temperature with this *in situ* prepared manganese catalyst with high turnover numbers (up to 10,000) and with near stoichiometric H_2O_2. The reaction is scalable from 100 mg to 4 g and in many examples with high selectivity. Although we have demonstrated previously that this catalyst system is tolerant of several common protecting groups(Chapter 5), the selectivity of the catalyst towards secondary alcohols over primary alcohols is demonstrated also, which reduces the need for the introduction prior to oxidation and subsequent removal of protecting groups and is complimentary to catalytic methods for selective primary alcohol oxidation based on copper and Tempo catalysts.[5] For benzylic alcohol oxidation and in particular for cyclic systems, selective oxidation to the mono-ketone product can be achieved under mild conditions and with good efficiency in terms of the oxidant H_2O_2. With higher catalyst loadings (0.1 mol%) selective C-H activation at benzylic positions can be achieved as well as C-H activation of alkanes (Scheme 5, Chapter 6).



Scheme 5. C-H bond activation oxidation and alcohol oxidation catalysed by manganese.

In this dissertation, the original goal – to achieve selectivity and control over the oxidation of alkenes, alcohols and alkanes – has to, a large extent, been achieved. The key challenge remaining in the palladium catalysed AM oxidation of alkenes is to move further and use oxygen as a terminal oxidant, most probably through regeneration of the benzoquinone used. With respect to oxidation with the manganese/picolinic acid catalyst system, key questions remain regarding the mechanism by which these

reactions take place and equally to apply this system in multistep catalytic oxidations to access other functionalities, not least α-hydroxy-ketones, and alternatives to ozonolysis.

Bibliography

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