Chapter 1
Selective catalytic oxidations

*From palladium-catalysed anti-Markovnikov oxidation of terminal alkenes to manganese catalysed oxidations with H₂O₂*

The palladium-catalysed oxidation of alkenes, the Wacker-Tsuji reaction, is undoubtedly a classic in organic synthesis providing reliable access to methyl-ketones from terminal alkenes often under mild reaction conditions. Methods that switch the selectivity of the reaction to provide the aldehyde product have been as elusive as they are desirable due to the access they provide to a valuable functional group. In this chapter, we survey both the methods which have been developed recently in achieving such selectivity and discuss common features and mechanistic insight that offers promise in achieving the goal of a general method for *anti*-Markovnikov selective olefin oxidations. Finally the scope of this thesis will be described briefly together with a short introduction to manganese catalyst systems that are investigated in chapters 5 and 6.

This chapter was published in part as a review:
Chapter 1

1.1 Introduction

The palladium(II)-catalysed oxidation of α-olefins to carbonyl compounds, reactions that are closely related to the industrial Wacker process for the oxidation of ethene to acetaldehyde,\(^1\) is generally referred to as the Wacker–Tsuji reaction.\(^2\) This transformation has become one of the best known palladium-catalysed reactions over the last half century,\(^3\) and is used widely in the preparation of carbonyl containing compounds due to its good tolerance to other functional groups and efficiency, in particular that oxygen can often be used as terminal oxidant. Under the Wacker–Tsuji conditions, the palladium(II) catalysed oxidation of α-olefins usually follows Markovnikov selectivity to afford the methyl ketone products (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Wacker oxidation of α-olefins with Markovnikov and anti-Markovnikov (AM) regioselectivity.

The mechanism(s) by which the Wacker reaction proceeds has been the subject of investigation for over 50 years with one of the earliest studies reported by Smidt et al.\(^2a\) The generally accepted global mechanism is one in which an alkene coordinates to the Pd(II) followed by nucleophilic attack by water and β-hydride elimination to afford the carbonyl product.\(^4\) Conventionally, copper(II) chloride and molecular oxygen\(^5\) are used as oxidant to regenerate palladium(II) from the palladium(0) formed in the reductive elimination step, which was studied extensively by Goddard and coworkers\(^6\) and by Stirling, Ujaque and coworkers\(^7\) by theoretical methods, recently (Scheme 2). The nucleophilic addition and other steps of the Wacker process have been studied in detail by Henry and co-workers and by other groups.\(^4,8\)

![Scheme 2](image)

**Scheme 2.** General mechanism for Wacker-Tsuji oxidation of alkenes.

Anti-Markovnikov (AM) selective oxidation of α-olefins is, however, highly desirable\(^9\) as these reactions provide direct access to aldehydes under neutral conditions and often at room temperature. As such it provides an alternative to, for example, hydroformylation,\(^10\) thereby circumventing the need for homologation, aldol condensation routes in the
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3 case of β-hydroxy-aldehyde synthesis\textsuperscript{[11]} and alkene bond cleavage through periodate oxidation or ozonolysis\textsuperscript{[12]}.

Aldehyde selectivity, under Wacker-Tsuji reaction conditions (Scheme 1), was achieved as early as the mid-1980s, albeit with high selectivity only for certain substrates in which various functional groups were present to direct the catalyst to provide the AM product, including α,β-unsaturated cyclic carbonates,\textsuperscript{[13]} 2-vinyl furanoside derivatives\textsuperscript{[14]} and more recently phthalimide protected allylic amines.\textsuperscript{[15]} An exception to this is the report by Feringa, in which AM selectivity was achieved with styrene under non-Wacker-Tsuji oxidation conditions \textit{(vide infra)}.

The 2007 review by Muzart et al. highlighted the challenge presented in achieving high selectivity in the oxidation of terminal alkenes to aldehydes\textsuperscript{[16]} in the present introduction, we focus on those systems that have shown the highest AM selectivity in the oxidation of terminal alkenes and on the exciting recent progress in this field.

It should be noted that AM oxidation of α-olefins is not limited to aldehyde formation but also AM amination,\textsuperscript{[17,18]} alkylation\textsuperscript{[19]} and acetalisation\textsuperscript{[20]} of α-olefins has been achieved using essentially the same palladium catalysts. (Scheme 3) These quite diverse reaction classes\textsuperscript{[21]} can be considered to follow broadly similar mechanisms to that of the Wacker-Tsuji oxidation and hence to broaden the mechanistic perspective, we will survey the various approaches taken in achieving AM selectivity in the oxidation of α-alkenes in general.

An obvious, albeit highly challenging, approach to achieving AM selectivity in the oxidation of alkenes is to modify the reaction conditions substantially,\textsuperscript{[21, 22]} and to employ ligands for the Pd(II) catalyst, including nitrite and HMPA – the so-called catalyst directed selectivity approach.\textsuperscript{[24]} Indeed the use of even these simple ligands has provided more general access to AM oxidation of α-olefins \textit{(vide infra)}. Although DMF is used predominantly, the palladium-catalysed oxidation of alkenes is remarkably tolerant to variations in solvent; indeed the reaction shows a distinct, albeit unpredictable, dependence of aldehyde/ketone selectivity on solvent. For example with t-butanol high AM regio-selectivity was obtained in the oxidation of styrene and allyl acetate compared with the same reaction carried out in DMF.\textsuperscript{[21, 25]} Finally, although oxygen is the archetypal oxidant in the Wacker-Tsuji reactions, other terminal oxidants have been employed successfully also (even as early as the 1960s)\textsuperscript{[26]} and in the latter part of this review a brief discussion of the various strategies employed in terms of palladium re-oxidants will be discussed.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_3.pdf}
\caption{Palladium-catalysed AM oxidation of α-olefins to aldehydes, acetics, alkanes and enamines.}
\end{figure}
1.2 The role of solvent in Anti-Markovnikov oxidations

Although the Wacker process for the oxidation of ethylene is carried out using aqueous solutions at high temperature and pressures, the laboratory variant, the Wacker-Tsuji reaction, is conventionally carried out in DMF and less frequently in other solvents.\cite{26,27,28} However, the challenges that AM oxidation of alkenes presents has driven the use of alternative solvents in the search for conditions that give high AM selectivity, most notably t-butanol and acetonitrile (\textit{vide infra}).

1.2.1 AM oxidations in DMF and acetonitrile

The palladium(II) catalysed oxidation of terminal olefins with water usually proceeds in DMF and follows Markovnikov addition to give ketones as the primary products. Nevertheless under certain conditions, and in particular for specific classes of substrate, AM selectivity has been observed when the reaction has been carried out in DMF. From the point of view of application, most of the examples in the literature\cite{16} have involved relatively complex compounds as single examples or with highly restricted substrate scope.

The oxidation of acetonides and cyclic carbonates of allylic diols has been reported by Kang and co-workers to proceed with AM selectivity.\cite{13} Reaction of a terminal allylic diol under O$_2$ (1 atm), in DMF/H$_2$O with PdCl$_2$ and CuCl afforded the methyl ketone. By contrast the corresponding acetonide was converted to the aldehyde product (Scheme 4). An analogous cyclic allylic carbonate underwent oxidation to the corresponding aldehyde product also, albeit with decarboxylation to provide an \(\gamma\)-hydroxy-\(\alpha\),\(\beta\)-unsaturated aldehyde as the final product. The good AM selectivity obtained indicates that decarboxylation is either subsequent or concomitant with the alkene oxidation as otherwise the ketone product would have been expected from the deprotected diol. The authors suggested that chelation of Pd(II) by two adjacent oxygen atoms may favour attack by water in an \textit{anti}-Markovnikov fashion.

This mechanism was supported by the observation that the oxidation of \(\alpha\)- or \(\beta\)-alkoxy substituted olefins did not yield the corresponding aldehydes selectively. Furthermore, Jung and Nichols have shown that the same high selectivity for the aldehyde product is obtained in the oxidation of terminal allylic acetonides, albeit with the yield of aldehyde being, in the authors’ own words, low or irreproducible.\cite{29}

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\node[align=center] at (0,0) {Scheme 4. Wacker oxidation of acetonides and cyclic carbonates of allylic diols.};
\end{tikzpicture}
\end{center}
\end{scheme}

\textit{Anti-Markovnikov selectivity in the oxidation of allylic alcohols: Steric interactions or hemiacetal formation?}

In a number of cases, homo-allylic alcohols have shown a tendency towards formation of butyrolactols. Indeed, Nokami reported that allylic alcohols bearing substituents \(\alpha\) to the alkene and alcohol(at allylic position R) afforded \(\gamma\)-butyrolactols as the main products.
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when using PdCl$_2$ as catalyst and $p$-benzoquinone as oxidant in DMF with added water.$^{[28]}$ By contrast, methyl ketones were obtained as the main products when the hydroxyl group was acetylated or in the absence of substituents at the allylic $\alpha$-position.

Such an observation might suggest that the formation of the lactol is the underlying reason for the observed AM selectivity. However, similar regioselectivity was observed upon oxidation of $\gamma$-butyrolactols with a set of substituents including alkyl, alkoxy, alkoxy carbonyl and sulfonyl groups indicating that steric effects dictate the product distribution (Scheme 5).

Ura and coworkers have investigated the Pd(II) catalysed formation of the cyclic acetals of vinylearennes, allyl ethers, and 1,5-dienes using BQ as oxidant and DMF as solvent.$^{[30]}$

Under these conditions pinacol showed the highest regioselectivity in the attack on terminal carbon of styrene due to its steric bulkiness, with less sterically hindered diols providing only a 1:1 ratio of cyclic acetal and ketal. The best regioselectivity was achieved for vinylarenes (>95%) (Scheme 6), while allyl ethers and 1,5-dienes showed slightly less selectivity towards formation of acetals.

Brimble and coworkers reported that AM oxidation of vinylphthalide could be achieved under classic Wacker oxidation conditions and suggested also that the bridging oxygen of the lactone would chelate to palladium, i.e. would act as a directing group.$^{[31]}$ The stereochemical integrity in substrate was completely retained during the oxidation (Scheme 7a).

Wacker-Tsuji oxidation of 3-hydroxy-4-vinylfuranoside derivatives with exclusively AM selectivity was reported by Mereyala and co-workers (Scheme 7b)$^{[14]}$ It was found that when the 3-hydroxy group was cis to the vinyl group the products formed were lactols due to the trapping of the aldehydes formed. The aldehyde and methyl ketone products were obtained in equal amounts and without formation of lactols when the 3-hydroxy group was trans to the vinyl group. Notably protection of the 3-hydroxy group invariably led to the formation of aldehydes regardless of whether the 3-hydroxy group was cis or trans to the vinyl group.

Scheme 5. Oxidation of 1-alkene-4-ol to $\gamma$-butyrolactols.

Scheme 6. Oxidation of vinylarenes to acetals via nucleophilic attack of diols.

Scheme 7a. Oxidation of 3-hydroxy-4-vinylfuranoside.

Scheme 7b. Wacker-Tsuji oxidation of 3-hydroxy-4-vinylfuranoside.
Similarly, Gelas and co-workers reported that the oxidation of \(\alpha,\beta\)-ethylenic acetal of mono- or di-saccharides resulted in oxidation of the double bond at the \(\alpha\)-position of the acetal group to afford the aldehyde product selectively.\(^{32}\)

The group of Pellissier and Santelli have reported the Wacker type oxidation of a range of steroid derivatives bearing a terminal vinyl group.\(^{33}\) Unsatisfactory selectivity was obtained with CuCl and \(O_2\) as oxidant, however, good AM selectivity was obtained with benzoquinone together with perchloric acid and \(\text{Pd(OAc)}_2\) as catalyst; a system reported earlier by Miller and Wayner.\(^{34}\) Aldehyde selective oxidation with palladium catalysts has been observed in the synthesis of steroid derivatives under these reaction conditions also. Again, ester and ether groups were proposed to coordinate to \(\text{Pd(II)}\), which facilitates the \textit{anti}-Markovnikov hydroxypalladation (Scheme 8).\(^{35}\) These data combined suggest that sterics or the presence of an oxygen bearing group (either from an alcohol, acetal or ester) in proximity to the alkene is key to AM selectivity.

Indeed substrate specific examples of AM oxidation under conventional Wacker-Tsuji conditions have been noted in the oxidation of allylic amines also. For example, Blechert and coworkers reported that oxidation of benzylloxycarbonyl protected allylic amines proceeded with full AM selectivity (76% yield), in their synthesis of tetraponerines (Scheme 9a).\(^{36}\)
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In 2009, Weiner et al. reported that phthalimide protected allylic amines underwent fully selective oxidation to the corresponding aldehyde under conventional Wacker-Tsuji conditions. These aldehyde products are key intermediates in the preparing of optically active β3-amino acids from allylic acetate using three consecutive catalytic steps.\(^\text{[15]}\)

The lack of AM selectivity with other protecting groups indicated that coordination via the carbonyl of the phthalimide group with the palladium catalyst is important. Indeed, the electron-withdrawing nature of the protecting group was unlikely to be a determining factor as the N-tosyl and N-nosyl protected substrates gave full conversion to the corresponding ketone products. Overall, however, the nature of the protecting group has been found to have a major impact on the selectivity of the oxidation – i.e. substrate control over selectivity rather than catalyst control, which holds consequences in regard to efforts to develop more general methods that would provide AM selectivity for a wider range of substrate classes. Again the role of solvent can appear to be less important with regard to selectivity as the same AM selectivity was observed with the use of t-butanol and [(\text{CH}_3\text{CN})\text{PdCl(NO}_2\)]\(^2\) as catalyst, however, for substrates bearing other protecting groups (e.g., Boc), a clear switching of selectivity was observed on changing solvent. Hence, the phthalimide protected allylic amines are more the exception than the rule in this regard (Scheme 9b).

Recently, Sigman and co-workers achieved high selectivity for the AM alkylation product with phthalimide protected allylic amines as substrates in the hydroalkylation using a combination of Pd(\text{MeCN})\(^2\)Cl, Zn(OTf)_2, BQ, 3Å MS, in DMA (Scheme 10).\(^\text{[19a]}\) In sharp contrast to the oxidation of protected allylic amines to aldehydes and ketones by Weiner et al.,\(^\text{[15]}\) where AM selectivity was observed only with phthalimide as a protecting group, Sigman and coworkers obtained good AM selectivity in hydroalkylation with a wide range of amine protecting groups in this study. Furthermore, Sigman and coworkers observed that protected allylic alcohols showed good AM selectivity also.\(^\text{[19b]}\) The absence of selectivity with dodecene, confirms that the allylic substituent is essential to achieve AM selectivity.

Scheme 9. Oxidation of alkenes bearing (a) protected diamines and (b) phthalimide protected allylic amines provide for high AM selectivity. Z = benzyloxytosylate or sulfonate.

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Perdeuteriated alkylzinc reagents were used to probe the selectivity of palladium hydride species, which form through trans-metallation with the organozinc reagent followed by β-hydride elimination.\[37\] Notably, though, the absence of deuterium incorporation at the allylic carbon (C\(^3\)) and the observation of stereoretention indicated that the palladium does not coordinate to that carbon, \textit{e.g.}, as a Pd(II) allyl species but instead results in deuterium incorporation in the C\(^1\) and C\(^2\) positions indicating that the palladium forms \(\sigma\)- and \(\eta^2\)- complexes only.

**Mechanistic studies**

In 2001, Spencer and co-workers reported that the regioselectivity in a palladium-catalysed alkene oxidation can be influenced substantially by the presence of an allylic hydrogen.\[38\] It was observed that when 1-phenyl-propene was used instead of styrene the regioselectivity changed towards the 1-phenylpropan-2-one product. Mechanistic studies indicated that an agostic C–H or enyl (\(\sigma+\pi\)) complex formed between the allylic hydrogen and the palladium catalyst, which may govern the regioselectivity observed (Scheme 11).

![Scheme 10. Alkylation of phthalimide protected allylic amine.](image_url)

![Scheme 11. Oxidation of \(\beta\)-(D\(_3\))methyl styrene.](image_url)

![Scheme 12. Rationalisation of observed AM regioselectivity.](image_url)

Notably, they also reported that with stoichiometric palladium(II) AM selective oxidation of styrenes took place in the absence of reoxidants.\[39\] The extent of \textit{anti}-Markovnikov selectivity for several substrates indicate the possible involvement of \(\eta^4\)-palladium–styrene complex (Scheme 12).

The AM oxidation of 1,5-dienes has been reported by Ho and co-workers under Wacker oxidation conditions,\[40\] although sub-stoichiometric amounts of Pd(II) and \textit{gem}-disubstitution were required for AM selective oxidation of this substrate class.
1.2.2 AM oxidations in alcohols as solvent

As discussed above the effect of solvent on AM selectivity was noted by Feringa as early as 1986, in the aerobic oxidation of styrene using the catalyst \( \text{[PdCl(NO\textsubscript{2})\textsubscript{2}(MeCN)\textsubscript{2}] } \), with tert-butanol providing for selective conversion to the aldehyde product albeit with low overall conversions and 10% yield. Over and above the increased AM selectivity, the use of tert-butanol in place of DMF or THF resulted in an increase in reaction rate as noted later by Wenzel and coworkers. This increase in rate was ascribed to the protic nature of the solvent and indeed small amounts of water increased the reaction rate further albeit at the cost of a decrease in AM selectivity. Notably aldehyde selectivity increased in the order \( n\text{-butanol} < \text{sec-butanol} < \text{t-butanol} \), which taken together suggests that the tert-butanol acts as a nucleophile to attack the less hindered terminal carbon of the olefin to provide the aldehyde product, while other alcohols engaged in the competing attack at the more hindered carbon of the olefin to provide the ketone product. This latter study focused on the oxidation of allyl acetate, which was converted to aldehyde as the main product under optimized conditions (Scheme 13). It should be noted, however, that for 1-octene, the best selectivity (57%) was obtained only at low conversion (4%).

![Scheme 13. AM oxidation of allyl acetate.](image)

In 2005, Hosokawa’s group reported that, with modification of the reaction conditions, 5% decanal could be obtained from 1-decene in tert-butanol. Again the AM selectivity was attributed to the steric bulk of the alcohol, which acts as a nucleophile. Paired interacting orbitals (PIO) analysis was used to model the oxypalladation step in the reaction and indicated that the facile formation of a Pd–C and a C–OR bond at either C1 or C2 of olefin is responsible for the regioselectivity.

Grubbs’ and co-workers reported that a terminal alcohol could be prepared from terminal alkenes, e.g., styrene, via anti-Markovnikov oxidation catalysed by Pd(II) with Cu(II) present followed by \textit{in situ} reduction with isopropanol using Shvo’s catalyst. Primary alcohols were obtained with high selectivity in the case of styrene derivatives while secondary alcohols were the main product obtained in the case of aliphatic alkenes. The selectivity in regard to the final alcohol product was dependent on the regioselectivity of the initial oxidation. The authors noted that a tert-butyl vinyl ether was obtained in the absence of water, which was assigned as a key intermediate in the process of aldehyde formation, which supports the general model in which nucleophilic attack by solvent is the key step in determining selectivity.

![Scheme 14. AM oxidation of vinylarenes.](image)

Subsequently, the same group reported that the palladium-catalysed AM oxidation of styrene derivatives could be achieved in the absence of a Cu(II) salt and that the palladium(II) catalyst loading could be decreased from 10 mol% to 2.5 mol% when the reactions were carried out at 85°C (Scheme 14). These conditions were later applied.
to the preparation of linear amines via a two-step, one-pot reductive amination through sequential Pd(II)-catalysed oxidation and Ir(III)-catalysed reduction.\(^\text{[44]}\)

Murahashi and coworkers have reported that Pd(II) catalyses formation of cyclic acetals from terminal olefins (Scheme 15). Diols were used as nucleophile instead of water and good AM regioselectivity was observed with electron deficient olefins.\(^\text{[20]}\) It should be noted that in this system dimethoxyethane was used as solvent as the yields obtained in DMF were reported to be low. The formation of an acetal from CH\(_2\)=CHCOPh competed with the formation of significant amounts of Michael addition-type by-products, however, these side reactions could be suppressed by addition of Na\(_2\)HPO\(_4\). That the additive worked as a proton scavenger was confirmed by the observation that K\(_2\)CO\(_3\), inhibited these side reactions also. Based on a study of the 1,2-migration of deuterium in D\(_2\)C=CHCOPh, the authors proposed that the reaction pathway involved oxypalladation, Pd-H elimination, and subsequent ring closure to yield the enol ether. Oxygenation of Pd-H species with molecular oxygen was also proposed to be part of the catalytic cycle. Later studies provided further evidence (\(^{18}\)O incorporation from H\(_2\)\(^{18}\)O) for the involvement of a hydroperoxopalladium(II) species in the catalytic cycle in the oxidation of 1-decene.\(^\text{[45]}\)

Scheme 15. Oxidation of electron-poor \(\alpha\)-olefins to cyclic acetals.

Using methanol as nucleophile in the acetalisation of methacryloyl derivatives opened up a new route for synthesising both \((R)\)- and \((S)\)-3-hydroxy-2-methylpropanal dimethyl acetal. It was proposed that the stereochemistry in the acetal product was determined at the \(\text{trans}\)-oxypalladation and stereoselective 1,2-hydride migration steps.\(^\text{[46]}\) Again although alcohols were used as nucleophiles, instead of water, in the Pd(II) catalysed AM oxidation, dimethoxyethane was used as solvent.

Previously, Dai and coworkers reported acetalisation of terminal olefins with the nucleophile (i.e. an alcohol) as solvent, 10% Li\(_2\)PdCl\(_4\) as catalyst and 300 mol% CuCl\(_2\) as oxidant (Scheme 16). High selectivity in favour of the acetal (AM) product was obtained for tertiary allyl amine.\(^\text{[47]}\) Alkoxy chlorinated products were obtained with opposite regioselectivity, however, with a allyl sulfide or a secondary allyl amine.

Scheme 16. Acetalisation of allylic amines and allylic sulfides.
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With 4-pentenyl sulfide, the selective nucleophilic attack at the terminal carbon is ascribed to the direct influence of the S atom in the oxypalladation step. Presumably due to the fact that nitrogen is less suited to coordination to palladium than sulfur is, 4-pentenylamine afforded a 1:1 product ratio of acetal and ketal. It is of note that Cu(II) is essential in achieving acetal selectivity as when BQ was employed the product obtained with tertiary allyl amine was a mixture of the ketal and acetal products. Lempers and co-workers reported the Pd(II) catalysed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate using methanol both as nucleophile and solvent and oxygen as oxidant. Notably, addition of an Fe(III) salt as well as a Cu(II) salt was more efficient in reoxidation of the Pd(0) formed since Fe(III) can rapidly oxidize Cu(I) to Cu(II), and oxidation of Fe(II) to Fe(III) by oxygen is fast also.

The number of examples in which the regioselectivity of the palladium-catalysed oxidation of alkenes is reversed by the presence of functional groups that can engage in coordination to the catalyst is impressive and indicates that hydroxylpalladation is the key step that determines the outcome of the reaction under Wacker-Tsuji oxidation conditions (PdCl$_2$, DMF, H$_2$O, CuCl, O$_2$). Alcohols as solvent and nucleophile, in place of DMF / H$_2$O, provides a more general approach to achieving AM selectivity primarily due to the steric encumbrance imposed by the alcohol and the nature of substrates. Although the use of alcohols reduces the limitations in terms of allylic functional group, achieving a generally applicable method yielding AM selectivity consistently remains elusive.

1.3 Ligand-directed Pd(II) catalysed oxidations

A relatively straightforward approach to AM selective oxidation of $\alpha$-olefins is to use additives that can potentially act as ligands to palladium(II), providing, of course, steric and electronic perturbation of the catalysed reactions and, in the case of nitrite, mediating the oxygen transfer to the $\alpha$-olefin.

1.3.1 Palladium nitrite system

The oxidation of olefins to ketones in acetonitrile catalysed by bis(acetonitrile)chloronitro palladium(II) was reported by Andrews and Kelly in 1981. The proposed mechanism involves a palladium nitro-nitrosyl redox cycle involving oxygen. $^{18}$O-labeling indicated that the oxidation of olefins involves oxygen transfer from the nitro group to the olefin rather than from water as in the classical Wacker oxidation reaction. Furthermore [PdCl(NO)] was identified as a red-brown precipitate when the oxidation of 1-decene to 2-decanone was carried out in the absence of oxygen at room temperature. The precipitate was found to react with oxygen to regenerate the initial palladium-nitro complex. $^{18}$O-labelling, spectroscopic data and a crystal structure have confirmed that the formation of heterometallocycle is plausible as an intermediate step (Scheme 17).
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Scheme 17. Catalytic cycle for the oxidation of alkenes to ketones with [PdCl(NO\textsubscript{2})(MeCN)\textsubscript{2}].

Heumann reported that [PdCl(NO\textsubscript{2})(MeCN)\textsubscript{2}] catalysed the oxidation of 4-vinylcyclohex-1-ene with oxygen to the corresponding exocyclic-ketone as the sole product. In contrast, bicyclic olefins, such as 5-vinylnorbornene, underwent epoxidation of the internal alkene.\textsuperscript{[25]} Heumann and Andrews proposed that the cycloaddition of the nitropalladium complex to the olefin is likely to be followed by $\beta$-H elimination, which is consistent with heterocycles forming as intermediates in the catalytic cycle.

The application of a palladium-nitro/nitroso catalyst in the aerobic oxidation of terminal alkenes to aldehydes was reported by Feringa as early as 1986.\textsuperscript{[21]} The catalyst was prepared by heating a mixture of [PdCl(NO\textsubscript{2})(MeCN)\textsubscript{2}] and CuCl\textsubscript{2} in a molar ratio of 1:4 in $t$-butanol at 50$^\circ$C. In oxygen saturated $t$-butanol, 1-decene was oxidized to both aldehyde and ketone in a 3:2 ratio. Addition of KNO\textsubscript{2} improved the selectivity of aldehyde to 7:3. When carried out in propan-2-ol, the selectivity was reversed in favour of the ketone product, which is consistent with the later findings by Feringa and coworkers\textsuperscript{[15]} with regard to the solvent sensitivity towards regioselectivity in the case of protected allylic amines. Styrene was oxidized exclusively to phenylacetaldehyde albeit with only 10% conversion. An in situ formed heterobimetallic Pd(II)/Cu(II) catalyst coordinated to the substrate was considered to determine the selectivity of the cycloaddition step. The absence of activity with [PdCl\textsubscript{2}(MeCN)\textsubscript{2}] indicated that the nitro ligand was essential for the reactivity observed (Scheme 18).

Scheme 18. The catalytic pathway in the oxidation of a terminal alkene to an aldehyde with [PdCl(NO\textsubscript{2})(MeCN)\textsubscript{2}].

$\alpha$-Alkoxytetrahydrofurans could be prepared by oxidation of homoallylic alcohols using $t$-butanol or isopropanol as solvent (Scheme 19).\textsuperscript{[28]} The method holds the advantage that a substituent at the allylic position is unnecessary, in contrast to where DMF, with water present also, was used.\textsuperscript{[28]} This method shows significantly higher selectivity of oxidative cyclisation to alkoxytetrahydrofurans, compared to the Wacker type oxidation to methylketones. Addition of a methylene unit to the carbon chain resulted in a loss in selectivity with both pyran and furan products formed, indicating that the five membered ring is formed more favourably than the six membered ring.
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Scheme 19. Oxidation of homoallylic alcohols to α-alkoxytetrahydrofurans. The same palladium-nitro/nitroso redox couple has recently been employed by Grubbs and coworkers in the aerobic oxidation of linear aliphatic α-olefins and linear α-olefins bearing functional groups, including carboxylic acid, halides, ester, ether, and aryl groups. The catalyst system was comprised of \([\text{PdCl}_2(\text{PhCN})_2], \text{CuCl}_2\), and AgNO\(_2\) in t-butanol/MeNO\(_2\) at 20-25°C. An aldehyde/ketone ratio of 4:1 was obtained in the oxidation of 1-dodecene, albeit that the yield of the aldehyde was reduced by the partially competitive formation of olefin isomerization products also. In the case of linear α-olefins selectivity towards the aldehyde product was found to depend on the functional groups present. The authors ascribed the increase in ketone formation to an intermolecular Markovnikov attack by these nucleophilic functionalities. This catalytic system, which uses \([\text{PdCl}_2(\text{PhCN})_2]\) with NaNO\(_2\), was applied in the AM oxidation of alkenes bearing oxygen groups at the allylic or homoallylic positions (Scheme 20).

Scheme 20. Oxidation of alkenes bearing oxygen groups at the allylic or homoallylic positions. 

18O labelling studies indicated that 81% of the oxygen incorporated into the aldehyde product originated from the nitrite salt used. It was noted that the remaining 12% could arise from water through a competing traditional Wacker-type nucleophilic attack. The combination of a Pd(II) salt and nitrite as catalyst afforded better selectivity and yield of aldehyde. It is possible that the catalyst facilitates formation of an NO\(_2\) radical \textit{in situ} and that radical-type addition of NO\(_2\) to the alkene occurs, which is selective for the terminal position as this would generate an intermediate secondary alkyl radical (Scheme 21a). It was proposed that the radical addition pathway was central to the formally \textit{anti}-Markovnikov selectivity observed. However, trapping of the intermediate radical has not been achieved yet.
1.3.2 Other ligands

In 1991, Hosokawa et al. reported that N-allylamides could be oxidized to aldehydes in high selectivity using [PdCl₂(MeCN)₂], CuCl and hexamethylphosphoric triamide (HMPA) under water free aerobic conditions, while methyl ketones were obtained under the conventional Wacker conditions (Scheme 22).[23] The AM selectivity with HMPA was observed only with N-allylamides and a ca. 1:1 ratio of aldehyde to ketone was obtained in the oxidation of allyl acetate. In contrast to the conventional Wacker conditions where water acts as the source of the oxygen atom, HMPA is key for aerobic oxidation under anhydrous conditions and it was proposed that it acted as a ligand for copper to suppress deallylation. In the presence of water, 95–100% regioselectivity towards the methyl ketone products was observed.

Phthalimide protected allyl amine was unusual as excellent AM selectivity was obtained under classic Wacker oxidation conditions (Scheme 1 and Scheme 21b).[15] Indeed > 90% selectivity in favour of the aldehyde product was obtained for phthalimide protected homoallylic amine also, which do not show AM selectivity under Wacker-Tsuji conditions.[15] Notably, a kinetic study showed that the selectivity remained constant after 5% conversion indicating that the formation of the catalyst that engages in the majority of the reaction is not immediate.

Scheme 21. a) Rationalisation of AM selectivity on the basis of radical stability and b) Oxidation of phthalimide protected allylic amines and homoallylic amines.
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Scheme 22. Oxidation of N-allylamides using HMPA as ligand.

The authors noted that the aldehyde selectivity maybe due to chelation of the hydroperoxo complex and amido carbonyl group to the palladium. In 1996, Hosokawa et al. isolated a proposed intermediate, a palladium-copper heterobimetallic complex with a μ₄-oxo atom derived from molecular oxygen (Scheme 23).[54] Freistad et al. reported, in 2007, the application of this system in the oxidation of trifluoroacetimide protected allylic amines bearing an adjacent acetonide functional group with good AM selectivity.[57]

Scheme 23. Formation of a palladium-copper heterobimetallic complex with a μ₄-oxo bridge.

Stahl and coworkers have reported the amination of styrene derivatives with palladium(II) as catalyst and deprotonated oxazolidinone as the nucleophile under aerobic conditions.[18] It was noted that the regioselectivity was controlled by the binding of the Brønsted base to the catalyst. When [(CH₃CN)₂PdCl₂] was used, the AM amination products predominate, while Markovnikov amination products were obtained in the presence of Brønsted bases such as NEt₃ and Bu₄NOAc (Scheme 24). The authors proposed that the kinetic and thermodynamic products of styrene aminopalladation exhibit opposite regiochemistry, and hence may be the reason for the reversal in regioselectivity observed upon changes in the Brønsted base used. The thermodynamic preference for AM amination of styrene with oxazolidinone reflects the stability of the η₃-benzyl adducts.

Scheme 24. Oxidative amination of styrene.

At the same time, Atwood and coworkers reported a stoichiometric amine addition to Pt(II)-coordinated alkyl olefins.[58] In this case, regiochemical distinction between the kinetic and thermodynamic products was observed also, however, the AM aminoplatination adduct was favoured kinetically, presumably for steric reasons, and it isomerized to the Markovnikov adduct at elevated temperatures.
1.4 Oxidants

Although molecular oxygen is the ideal terminal oxidant in terms of atom economy, the value of AM-oxidation products often makes the use of other oxidants attractive where higher reaction rates and selectivity can be achieved. In general, it is considered that the reoxidation of the Pd(0) intermediate formed in the reaction is the key step to achieving high turnover numbers and therefore, in principle, any electron sink would suffice. The only exception to this are cases where palladium reacts directly with molecular oxygen to form palladium-peroxy species as proposed by Murahashi and coworkers.\cite{murahashi1, murahashi2}

Several alternative reoxidants have been shown to be useful in the AM selective oxidation of terminal alkenes already including copper/oxygen combinations and benzoquinone.\cite{copper_oxygen, benzoquinone}

In several cases the use of oxidants other than molecular oxygen have been found to increase the rate of reaction substantially and on occasion have led to improved AM selectivity also, indicating that the oxidant has a direct role in at least controlling the position of the rate determining step or even in leading to alternative reaction mechanisms.

Indeed Spencer and coworkers (vide supra) have demonstrated that the regeneration of the Pd(II) species is not necessarily only a peripheral part of the catalytic cycle in regard to selectivity. They noted that with stoichiometric palladium(II) the oxidation of terminal alkenes proceeded with high AM selectivity.

However, under catalytic conditions the ketone product was obtained with oxidants such as benzoquinone and MnO₂ and decreased moderately with oxidants such as a H₂O₂ and t-BuOOH, which can be considered as dioxygen-like species. The only exception to this was a non-coordinating oxidant the heteropoly-acid H₄[PMo₁₁VO₄₀][HPA], which provided high AM selectivity (Scheme 25).\cite{spencer}

Overall, as can be seen in the discussion above, a strong correlation between the terminal oxidant used and the extent of AM selectivity obtained cannot be drawn, since it is the combination of solvent, oxidant, catalyst, ligand and substrate which determines the selectivity together, with no single factor dominating the outcome of the reactions. Nevertheless, the use of alternate reoxidants such as DDQ, as shown by Chen et al.\cite{chen} recently for palladium catalysed C-H activation to form α,β-unsaturated aromatic aldehydes, does present an obvious path towards achieving catalyst control over selectivity.

1.5 Conclusion and outlook for anti-Markovnikov oxidation of terminal alkenes

The aim of this introduction is to provide an overview of the successful efforts to achieve anti-Markovnikov selective oxidation, including the preparation of aldehydes, acetals, in amination and alkylation (Scheme 3). Overall, it is apparent that AM selectivity is largely
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substrate dependent, *i.e.* that specific substrates bearing certain functional groups need to be present. Nevertheless, some hints that catalyst control over selectivity can be achieved have appeared in the literature. It should be noted that AM selectivity observed for a specific substrate for one reaction class does not necessarily imply that similar selectivity will be observed for other conversions. For example, in the case of AM hydroalkylation of allylic amines,[19a] the nature of the protecting group is of less relevance than for the corresponding AM oxidations of the substrates.[15]

From a mechanistic perspective, two key aspects are apparent. The first is that the formation of an $\eta^2$-palladium complex followed by nucleophilic attack of either water or alcohol is likely to determine the selectivity observed. The second is that the mechanism in its detail is not only dependent on the solvent composition used but also on the substrate and terminal oxidant. Despite considerable efforts, in particular in the 1980 and 1990s, there remains an increasing need to explore the mechanism of the known AM reactions to establish commonalities that can be used to develop more robust general approaches to achieve AM selective oxidations of alkenes. Whether such a goal of generally applicable conditions can be reached is, however, placed in doubt by the observation that even with the same catalyst, apparently similar reactions can proceed by quite different mechanisms as in the case of $[\text{Pd}(\text{CH}_3\text{CN})_2\text{ClNO}_2]$. Of particular note is that in certain cases, stoichiometric reactions (in terms of Pd(II)) have provided high AM selectivity whereas catalytic variants show a considerable decrease in selectivity. This observation indicates that achieving AM selectivity may be a kinetic problem rather than a thermodynamic one and efforts to accelerate the reoxidation of the palladium(II) catalyst may be of most impact in terms of selectivity.

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

1.6 Goals and outline of thesis

The overall aim of the studies described in this thesis is to achieve highly selective catalytic oxidation of organic substrates. In the chapters 2 and 3 the highly challenging goal of selective *anti*-Markovnikov oxidation of terminal alkenes, specifically allylic esters and amides is tackled. The aldehydes obtained are highly valuable intermediates especially in the synthesis of unnatural $\beta$-amino acids. In chapter 4 a preliminary exploration of the mechanisms by which these reactions proceed will be described. The aim of this study was to understand the key factors that determine selectivity and the mechanism by which oxidation proceeds in terms of the role of oxidant.

In the second part of this thesis, an alternative approach to the oxidation of alkenes is explored in chapter 5, using a recently discovered[60] manganese catalyst system is described. In chapter 6 this catalytic system is applied further in the oxidation of alcohols and alkanes. Here a brief introduction to earlier work with this catalytic systems is given.
Chapter 1

Developing catalytic systems for the oxidation of alkenes to epoxides or cis-diols has attracted an increasing attention in recent decades. In particular, the use of atom economic and environmentally friendly terminal oxidants, especially oxygen and hydrogen peroxide. Manganese, a relatively non-toxic 1st row transition metal, has shown advantages in oxidation catalysis in both cost and reactivity. The development of new methods for selective oxidative transformations based on manganese catalysts is a major part of the work described in this thesis. Although the topic has been reviewed in detail recently, here, a brief introduction to the background of the in-situ prepared homogeneous manganese based catalyst system used in the oxidation of alkenes with \( \text{H}_2\text{O}_2 \) by our group will be given.

Over the last three decades many novel ligand systems have been developed for iron or manganese oxidation catalysts. Typical examples of such ligands included \( N,N',N''-\)trimethyl-1,4,7-triazacyclononane and pyridyl based ligand families (e.g., TPEN, TPTN). These ligands showed varying efficiency together with iron or manganese in catalysing epoxidation and cis-dihydroxylation of alkenes and C-H activation in the presence of peracetic acid or \( \text{H}_2\text{O}_2 \). A key drawback of many of the pyridyl based catalysts was that they required 8-10 equiv. of \( \text{H}_2\text{O}_2 \) and engaged in substantial catalase type activity prior to the onset of oxidation of substrates. For example, full conversion in the oxidation of cyclooctene required 8 equivalents \( \text{H}_2\text{O}_2 \). With 4 equivalents of \( \text{H}_2\text{O}_2 \) less than 20% conversion was obtained, however addition of a further 4 equivalents of \( \text{H}_2\text{O}_2 \) resulted in full conversion. It was considered that the excess of oxidant was used to degrade pyridine based ligand. Indeed, Pijper et al. confirmed that degradation of the pyridyl based ligands (TPTN, 1, 2, 3, 4) to picolinic acid occurred during manganese catalysed oxidations, i.e., \( ^1\text{H} \) NMR spectra showed the formation of pyridine-2-carboxylic acid after catalysed epoxidation of 2,3-dimethylbut-2-ene in acetone-d6.

These results prompted the authors to replace ligand 1 by an equivalent amount of pyridine-2-carboxylic acid, which showed the same activity and selectivity with a range of substrates for epoxidation or cis-dihydroxylation of alkenes. Importantly much less \( \text{H}_2\text{O}_2 \) was needed when pyridine-2-carboxylic acid was used compared with that required with the pyridyl based ligands.

Understanding the role of ligands, i.e. as a source of pyridine-2-carboxylic acid, led to the development of a new catalytic system for the oxidation of alkenes, which consisted of \( \text{Mn(ClO}_4)_2 \), pyridine-2-carboxylic acid, NaOAc, \( \text{H}_2\text{O}_2 \) in acetone. Only near stoichiometric amounts of oxidant were needed for the reaction, which provided high reactivity and selectivity on oxidation of electron deficient alkenes to diols.

Scheme 26. Ligands discussed in the text.
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Scheme 27. Oxidation of electron deficient alkenes.

This catalytic system is relatively insensitive to the nature of the base, where 1 mol% of NaOAc, Na₂CO₃, NaHCO₃, NaOH or NH₄OAc provided comparable results. The base is essential for the reactivity as no conversion was observed using acids such as acetic acid instead. However, surprisingly, addition of acetic acid after the reaction started did not inhibit the reaction as long as base was added initially.

Ketone based solvents were found to be essential for this system. Acetone and butanone were used successfully as solvents for oxidations with this catalyst system. A ketone co-solvent was tested to understand the role of ketone in the reaction when acetonitrile was used as 'innocent solvent'. There was 20% conversion obtained with 10 vol% acetone while an electron deficient ketone showed higher activity. More than 95% conversion has been observed using 10 vol% CF₃COCH₃. ¹⁹F NMR spectroscopy for this reaction indicated intermediate formation of a ketone peroxide. However, conversion was not obtained with CCl₃COCCl₃.

In conclusion, the in situ prepared catalyst system was shown to be highly active in the cis-dihydroxylation of electron deficient alkenes. A number of electron rich alkenes were found to form epoxide as main product under the same reaction condition. This catalytic system is highly attractive since stoichiometric amounts of an environmentally friendly terminal oxidant H₂O₂ provided good activity in the oxidation of alkenes. Furthermore, pre-prepared ligands were not needed, which saves energy and cost.

However, there was still a limitation that needed to be overcome, including safety concerns in regard to the use of ketones as solvent together with H₂O₂ as oxidant – with the potential for explosions in large scale reactions. The use of ketones as co-solvents could remove this risk, however, CF₃COCH₃ is volatile and corrosive and hence not an ideal choice.

In chapter 5, this catalyst system, manganese / pyridine-2-carboxylic acid, is developed into a versatile method for the epoxidation of a broad scope of alkenes using a wide range of solvents. Multigram scale selective oxidations of electron rich alkenes using near-stoichiometric H₂O₂ under ambient conditions is described. It will be shown that high T.O.N. (up to 300,000) and T.O.F. (up to 40 s⁻¹) can be achieved with good to excellent selectivity, remarkable functional group tolerance and a wide solvent scope. Furthermore, the role of ketone co-solvent is explored through the use of spectroscopy.

In chapter 6, the oxidation of alcohols and C-H activation is reported with high turnover numbers and mild reaction conditions. Again the in situ prepared catalyst based on manganese(II) salts, pyridine-2-carboxylic acid and butanedione, is employed, which provides good to excellent conversions and yields with H₂O₂ as oxidant. Regio-selectivity in the oxidation of alcohols and C-H bond oxidation is described. Secondary alcohols are showed to react faster than primary alcohols and benzyl C-H oxidation proceeds in preference to aliphatic C-H oxidation.
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1.7 Bibliography


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Chapter 1