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Reaction Mechanisms

Palladium-Catalyzed anti-Markovnikov Oxidation of Terminal Alkenes

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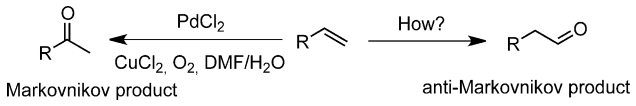
aldehydes · alkenes · palladium · reaction mechanisms · regioselectivity

The palladium-catalyzed oxidation of alkenes, the Wacker–Tsuji reaction, is undoubtedly a classic in organic synthesis and provides reliable access to methyl ketones from terminal alkenes under mild reaction conditions. Methods that switch the selectivity of the reaction to provide the aldehyde product are desirable because of the access they provide to a valuable functional group, however such methods are elusive. Herein we survey both the methods which have been developed recently in achieving such selectivity and discuss common features and mechanistic insight which offers promise in achieving the goal of a general method for anti-Markovnikov-selective olefin oxidations.

1. Introduction

The palladium(II)-catalyzed oxidation of olefins into carbonyl compounds, a reaction which is 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-catalyzed reactions over the last half century,[3] and is used widely in the preparation of carbonyl-containing compounds because of its tolerance of other functional groups and efficiency, particularly given that oxygen can often be used as terminal oxidant. Under the Wacker–Tsuji conditions, the palladium(II)-catalyzed oxidation of α-olefins usually follows Markovnikov selectivity to afford the methyl ketone products (Scheme 1).



Scheme 1. Wacker oxidation of α-olefins with Markovnikov and anti-Markovnikov (AM) regioselectivity. DMF = *N*,*N*-dimethylformamide.

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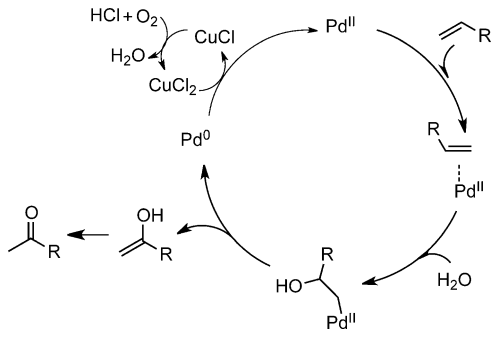
The mechanism(s) by which the Wacker reaction proceeds has been the subject of investigation for over 50 years with one of the earliest studies reported by Smidt et al.[2a] The generally accepted global mechanism is one in which an alkene coordinates to palladium(II) with subsequent nucleophilic attack by water and β-hydride elimination to afford the carbonyl product.[4] Conventionally, copper(II) chloride and molecular oxygen[5] are used as the oxidant to regenerate palladium(II) from the palladium(0) formed in the reductive elimination step, and this step was studied extensively by Goddard and co-workers[6] and by Stirling, Ujaque, and co-workers[7] using theoretical methods (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]

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

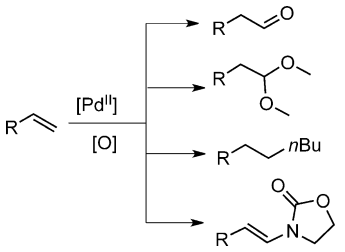


Scheme 2. General mechanism for Wacker–Tsuji oxidation of alkenes.

need for homologation, aldol condensation routes in the case of β-hydroxy-aldehyde synthesis,[11] and alkene bond cleavage through periodate oxidation or ozonolysis.[12]

Aldehyde selectivity, under Wacker–Tsuji reaction conditions (Scheme 1), was achieved as early as the mid 1980s,[21] albeit with high selectivity only for certain substrates in which various functional groups were present to direct the catalyst to provide the AM product. The substrates include α,β-unsaturated cyclic carbonates,[13] 2-vinyl furanoside derivatives,[14] and more recently, phthalimide-protected allylic amines.[15]

The 2007 review by Muzart et al. highlighted the challenge presented in achieving high selectivity in the oxidation of terminal alkenes to aldehydes.[16] In the present Minireview, we focus on those systems which 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, as AM amination,[17,18] alkylation,[19] and acetalization[20] of α-olefins has been achieved using essentially the same palladium catalysts (Scheme 3). These quite diverse



Scheme 3. Palladium-catalyzed AM oxidation of α-olefins to aldehydes, acetals, alkanes, and enamines.

reaction classes[16] can be considered to follow mechanisms similar 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,[21,22] and to employ ligands for the palladium(II) catalyst, including nitrite and HMPA,[23] the so-called catalyst-directed selectivity approach.[24] Indeed the use of even these simple ligands has provided more general access to AM oxidation of α-olefins (see below). Although DMF is used predominantly, the palladium-catalyzed 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 *tert*-butanol high AM regioselectivity was obtained in the oxidation of styrene and allyl acetate compared with the same reaction carried out in DMF.[21,25] Finally, although oxygen is the archetypal oxidant in the Wacker–Tsuji reactions, other terminal oxidants have been employed successfully (even as early as the 1960s)[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.

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2. The Role of Solvent in anti-Markovnikov Oxidations

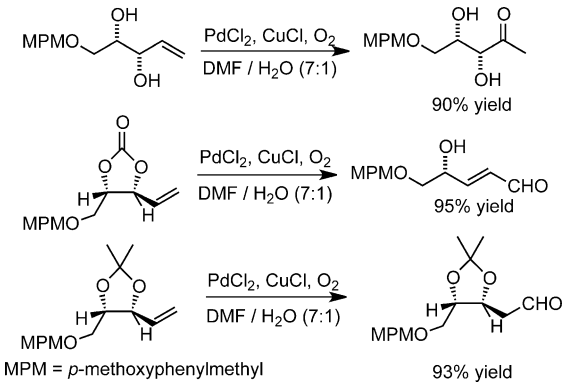
Although the Wacker process for the oxidation of ethylene is carried out using aqueous solutions at high temperature and pressures, the laboratory variant, the Wacker–Tsuji reaction, is conventionally carried out in DMF and less frequently in other solvents.[26–28] However, the challenges that AM oxidation of alkenes presents has driven the use of alternative solvents in the search for reaction conditions which give high AM selectivity, and reactions involving *tert*-butanol and acetonitrile are most notable (see below).

2.1. anti-Markovnikov Oxidations in DMF and Acetonitrile

The palladium(II)-catalyzed oxidation of terminal olefins with water usually proceeds in DMF and follows Markovnikov addition to give ketones as the primary products. Nevertheless under certain reaction 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 reference [16] 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.[13] Reaction of a terminal allylic diol under O_2 (1 atm), in DMF/H_2O with $PdCl_2$ and CuCl afforded the methyl ketone (Scheme 4). In contrast, the

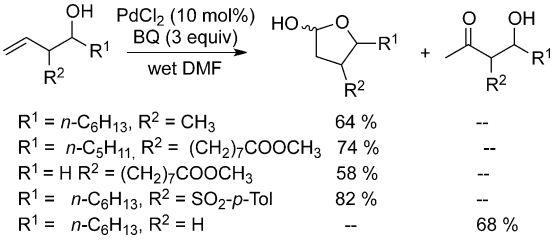


Scheme 4. Wacker oxidation of acetonides and cyclic carbonates of allylic diols.

corresponding acetonide was converted into the aldehyde product. An analogous cyclic allylic carbonate also underwent oxidation to the corresponding aldehyde product, albeit with decarboxylation to provide an γ-hydroxy-α,β-unsaturated aldehyde as the final product. The good AM selectivity obtained indicates that decarboxylation is either subsequent or concomitant with the alkene oxidation, because otherwise the ketone product would have been expected from the deprotected diol. The authors suggested that chelation of palladium(II) by two adjacent oxygen atoms may favor attack by water in an AM fashion. This mechanism was supported by the observation that the oxidation of α- or β-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.[29]

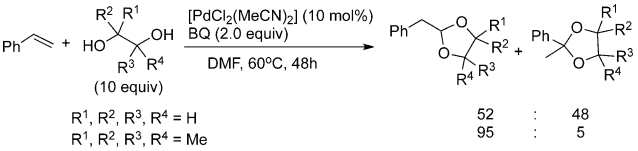
anti-Markovnikov Selectivity in the Oxidation of Allylic Alcohols: Steric Interactions or Hemiacetal Formation?

In a number of cases, homoallylic alcohols have shown a tendency towards formation of butyrolactols. Indeed, Nokami et al. reported that allylic alcohols bearing substituents α to the alkene and alcohol (at allylic position R^2; see Scheme 5) afforded γ-butyrolactols as the main products when using $PdCl_2$ as the catalyst and *p*-benzoquinone (BQ) as the oxidant in DMF with added water.[28] In contrast, methyl ketones were obtained as the main products when the hydroxy group was acetylated or in the absence of substituents at the allylic α-postion. 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 γ-butyrolactols with a set of substituents including alkyl, alkoxy, alkoxycarbonyl, and sulfonyl groups, thus indicating that steric effects dictate the product distribution (Scheme 5).



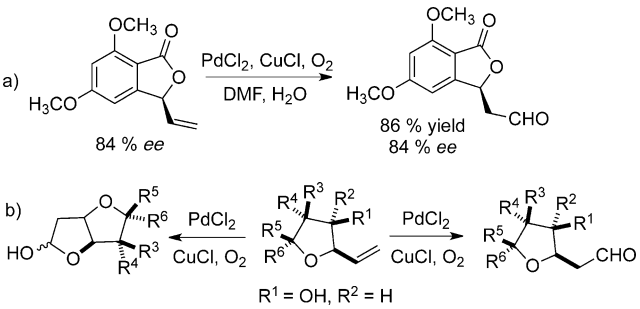
Scheme 5. Oxidation of 1-alkene-4-ol to γ-butyrolactols. Tol = tolyl.

Ura and co-workers have investigated the palladium(II) catalyzed formation of the cyclic acetals of vinylarenes, allyl ethers, and 1,5-dienes using BQ as an oxidant and DMF as the solvent.[30] Under these reaction conditions pinacol showed the highest regioselectivity in the attack on the terminal carbon of styrene because of its steric bulk, 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.



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

Brimble and co-workers reported that AM oxidation of vinylphthalide could be achieved under classic Wacker oxidation conditions and suggested also that the bridging oxygen atom of the lactone would chelate to palladium, i.e. would act as a directing group (Scheme 7a).[31] The stereo-

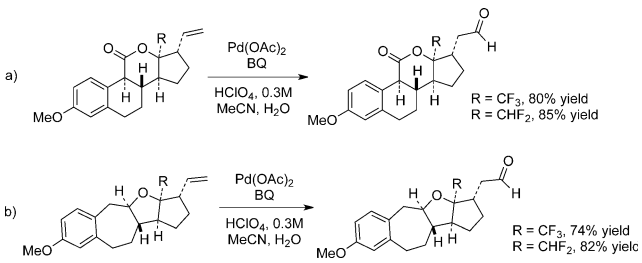


Scheme 7. Oxidation of a) vinylphthalide and b) 4-vinyl furanosides.

chemical integrity in substrate was completely retained during the oxidation. The 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, resulting from 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.

Similarly, Gelas and co-workers reported that the oxidation of α,β-ethylenic acetal of mono- or disaccharides resulted in oxidation of the double bond at the α-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 the oxidant, however, good AM selectivity was obtained with BQ together with perchloric acid and $Pd(OAc)_2$ as the catalyst, a system reported earlier by Miller and Wayner (Scheme 8).[34] Aldehyde-selective



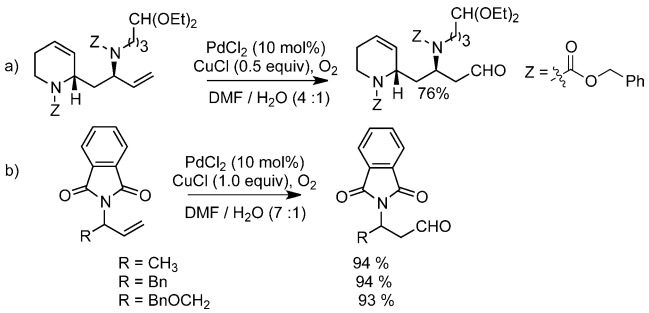
Scheme 8. Oxidation of terminal olefins in steroid derivatives.

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 palladium(II), which facilitates the AM hydroxypalladation.[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.

anti-Markovnikov Selectivity in the Oxidation of Allylic Amines

Indeed substrate-specific examples of AM oxidation under conventional Wacker–Tsuji conditions have also been noted in the oxidation of allylic amines. For example, Blechert and co-workers reported that oxidation of benzyloxycarbonyl-protected allylic amines proceeded with full AM selectivity (76% yield), in their synthesis of tetraponerines (Scheme 9a).[36]

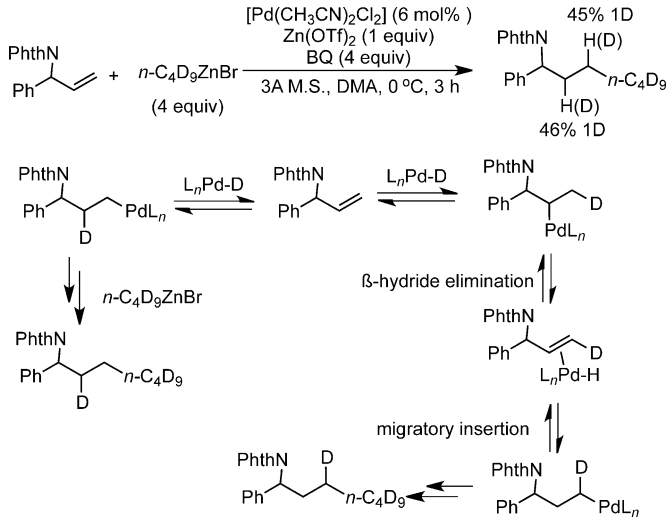
In 2009, Weiner et al. reported that phthalimide-protected allylic amines underwent fully selective oxidation to the corresponding aldehyde under conventional Wacker–Tsuji conditions (Scheme 9b). These aldehyde products are key



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

intermediates in the preparation of optically active β^3-amino acids from allylic acetate using three consecutive catalytic steps.[15] The lack of AM selectivity with other protecting groups indicated that coordination through 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 into 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, that is, substrate control over selectivity rather than catalyst control, which holds consequences in regard to efforts to develop more general methods which 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 *tert*-butanol and $[(CH_3CN)PdCl(NO_2)]$ as the catalyst. Hence, the phthalimide-protected allylic amines are more the exception than the rule in this regard.

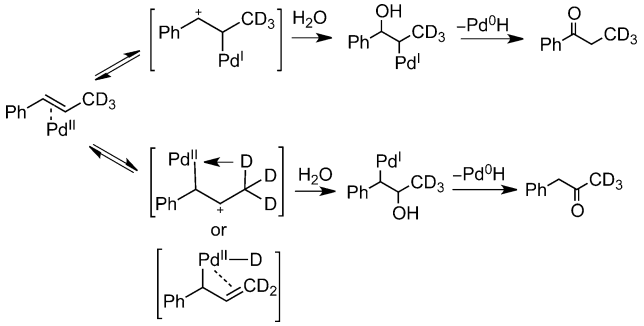
Recently, Sigman and co-workers achieved high selectivity for the AM alkylation product with phthalimide-protected allylic amines as substrates in hydroalkylation using a combination of $[Pd(MeCN)_2Cl_2]$, $Zn(OTf)_2$, BQ, and 3 Å M.S. in DMA (Scheme 10).[19a] In sharp contrast to the oxidation of protected allylic amines to aldehydes and ketones by Weiner et al.,[15] where AM selectivity was observed only with phthalimide as a protecting group, Sigman and co-workers obtained good AM selectivity in hydroalkylation with a wide range of amine protecting groups in this study. Furthermore, Sigman and co-workers observed that protected allylic alcohols showed good AM selectivity also.[19b] The absence of selectivity with dodecene, confirms that the allylic substituent is essential to achieving AM selectivity. Perdeuterated alkyzinc 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 atom (C3) and the observation of stereoretention indicated that the palladium does not coordinate to that carbon atom, for example, as a palladium(II) allyl species. Instead deuterium incorporation at the C1 and C2 positions indicates that the palladium forms σ- and η^2-complexes only.



Scheme 10. Alkylation of a phthalimide-protected allylic amine. Tf = trifluoromethanesulfonyl.

Mechanistic Studies

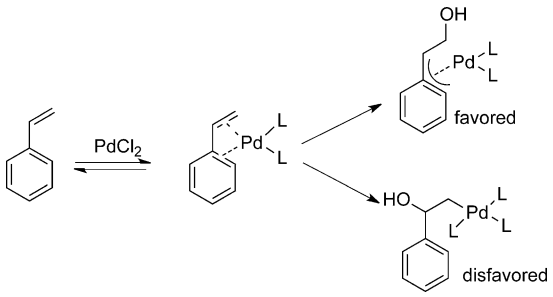
In 2001, Spencer and co-workers reported that the regioselectivity in a palladium-catalyzed alkene oxidation can be influenced substantially by the presence of an allylic hydrogen atom.[38] It was observed that when 1-phenylpropene was used instead of styrene the regioselectivity changed towards the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



Scheme 11. Oxidation of β-[D_3]methyl styrene.

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

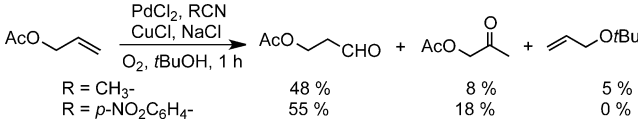
The AM oxidation of 1,5-dienes has been reported by Ho and co-workers under Wacker oxidation conditions,[40] although substoichiometric amounts of palladium(II) and *gem* disubstitution were required for AM-selective oxidation of this substrate class.



Scheme 12. Rationalization of observed AM regioselectivity.

2.2. anti-Markovnikov Oxidations in Alcohols as the Solvent

As discussed above the effect of solvent on AM selectivity was noted by Feringa[21] as early as 1986 in the aerobic oxidation of styrene using the catalyst [$PdCl(NO_2)(MeCN)_2$], with *tert*-butanol providing selective conversion into 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 co-workers.[25] 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*-butanol < sec-butanol < *t*-butanol, and taken together suggests that the *tert*-butanol acts as a nucleophile to attack the less hindered terminal carbon atom of the olefin to provide the aldehyde product, while other alcohols engage in the competing attack at the more hindered carbon atom of the olefin to provide the ketone product. This latter study focused on the oxidation of allyl acetate, which was converted into the aldehyde as the main product under the optimized reaction conditions (Scheme 13). It should be noted, however, that for 1-octene,



Scheme 13. AM oxidation of allyl acetate.

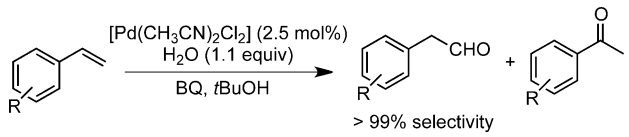
the best selectivity (57%) was obtained only at low conversion (4%).

In 2005, the group of Hosokawa reported that with modification of the reaction conditions 5% decanal could be obtained from 1-decene in *tert*-butanol.[41] 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 the olefin is responsible for the regioselectivity.

Grubbs' and co-workers reported that a terminal alcohol could be prepared from terminal alkenes (e.g., styrene) by

AM oxidation, catalyzed by palladium(II) in the presence of copper(II), with subsequent in situ reduction with isopropanol using Shvo's catalyst.[42] 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, and was assigned as a key intermediate in the process of aldehyde formation, thus supporting the general model in which nucleophilic attack by solvent is the key step in determining selectivity.

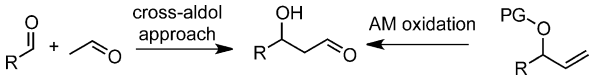
Subsequently, the same group reported that the palladium-catalyzed AM oxidation of styrene derivatives could be achieved in the absence of a copper(II) salt and that the palladium(II) catalyst loading could be decreased from 10 mol% to 2.5 mol% when the reactions were carried out at 85 °C (Scheme 14).[43] These reaction conditions were later



Scheme 14. AM oxidation of vinylarenes.

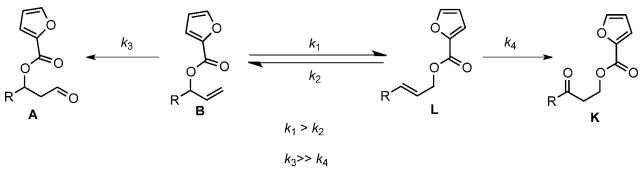
applied to the preparation of linear amines by a two-step, one-pot reductive amination through sequential palladium(II)-catalyzed oxidation and iridium(III)-catalyzed reduction.[44]

The AM oxidation of allylic alcohols presents opportunities as an alternative to aldol condensations in the synthesis of protected β-hydroxy aldehydes (Scheme 15). Our group



Scheme 15. Routes to the synthesis of β-hydroxy aldehydes.

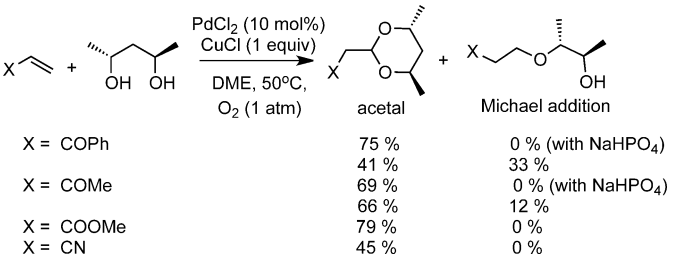
reported recently that such regioselectivity could be achieved through the palladium(II)-catalyzed oxidation of ester-protected allylic alcohols using BQ as an oxidant in *tert*-butanol.[45] Furthermore, catalyst loading could be decreased to 0.5 mol% and relatively mild reaction conditions (i.e., neutral conditions and at ambient temperature) could be employed. Again, a key strength of palladium(II)-catalyzed oxidations is the simultaneous occurrence of orthogonal reactions as demonstrated in this study. A palladium-catalyzed rearrangement of ester-protected linear allylic esters to the corresponding branched isomers was found to proceed under the reaction conditions employed,[45,46] and enabled isolation of protected β-hydroxy aldehydes (Scheme 16). Hence both linear and branched allylic esters can be used as starting materials to obtain the same protected β-hydroxy aldehydes. Reaction monitoring by ^{1}H NMR spectroscopy indicated that the Curtin–Hammett principle[47] applied in this case. The selectivity towards the branched aldehyde product



Scheme 16. Palladium(II)-catalyzed equilibrium between linear and branched allylic esters and competing oxidation reactions.

resulted from the low rate at which the thermodynamically more stable linear allylic alcohol underwent oxidation and the relatively rapid palladium(II)-catalyzed interconversion between the branched and linear allylic alcohols. The absence of substitution of the acetyl-protecting group with CD_3CO (i.e., originating from CD_3CO_2H added to the reaction mixture) and the partial retention of enantiomeric excess at the allylic position when starting from a single enantiomer of the branched allylic ester suggests that, at least in the oxidation step (k_3 and k_4 in Scheme 16), a palladium(II) allyl species is not formed as an intermediate.

Murahashi and co-workers have reported that palladium(II) catalyzes formation of cyclic acetals from terminal olefins (Scheme 17). Diols were used as nucleophiles instead



Scheme 17. Oxidation of electron-poor α-olefins to cyclic acetals.

of water and good AM regioselectivity was observed with electron-deficient olefins.[20] It should be noted that in this system dimethoxyethane was used as the solvent because 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 byproducts, however, these side reactions could be suppressed by addition of Na_2HPO_4. That the additive worked as a proton scavenger was confirmed by the observation that K_2CO_3 also inhibited these side reactions. Based on a study of the 1,2-migration of deuterium in D_2C=CHOPh, the authors proposed that the reaction pathway involved oxypalladation, Pd-H elimination to yield the enol ether, and subsequent ring closure to form the cyclic acetal. 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.[48]

Using methanol as nucleophile in the acetalization of methacryloyl derivatives opened up a new route for synthesizing both (*R*)- and (*S*)-3-hydroxy-2-methylpropanal dimeth-

yl acetal. It was proposed that the stereochemistry in the acetal product was determined at the *trans*-oxypalladation and stereoselective 1,2-hydride migration steps.[49] Again although alcohols were used as nucleophiles, instead of water, in the palladium(II)-catalyzed AM oxidation, dimethoxyethane was used as solvent.

Previously, Dai and co-workers reported acetalization of the terminal olefins with the nucleophile (i.e., an alcohol) as the solvent, 10% Li_2PdCl_4 as the catalyst, and 300 mol% $CuCl_2$ as the oxidant (Scheme 18). High selectivity in favor of the acetal (AM) product was obtained for tertiary allyl amines.[50] Alkoxy chlorinated products were obtained with opposite regioselectivity, however, with an allyl sulfide or a secondary allyl amine.

With 4-pentenyl sulfide, the selective nucleophilic attack at the terminal carbon atom is ascribed to the direct influence of the S atom in the oxypalladation step. Presumably as a result of 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 copper(II) is essential in achieving acetal selectivity because 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 palladium(II)-catalyzed oxidation of methylacrylate to 3,3-dimethoxy methyl propionate using methanol both as nucleophile and solvent and oxygen as the oxidant.[51] Notably, addition of an iron(III) salt as well as a copper(II) salt was more efficient in reoxidation of the palladium(0) formed since iron(III) can rapidly oxidize copper(I) to copper(II), and oxidation of iron(II) to iron(III) by oxygen is also fast.

The number of examples in which the regioselectivity of the palladium-catalyzed oxidation of alkenes is reversed by the presence of functional groups which can engage in coordination to the catalyst is impressive, and indicates that hydroxypalladation is the key step that determines the outcome of the reaction under Wacker–Tsuji oxidation conditions ($PdCl_2$, DMF, H_2O, CuCl, O_2). Alcohols as solvent and nucleophile, in place of DMF/H_2O, provides a more general approach to achieving AM selectivity primarily as a result of 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.

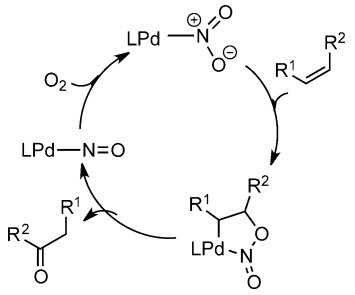
3. Ligand-Directed Palladium(II)-Catalyzed Oxidations

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

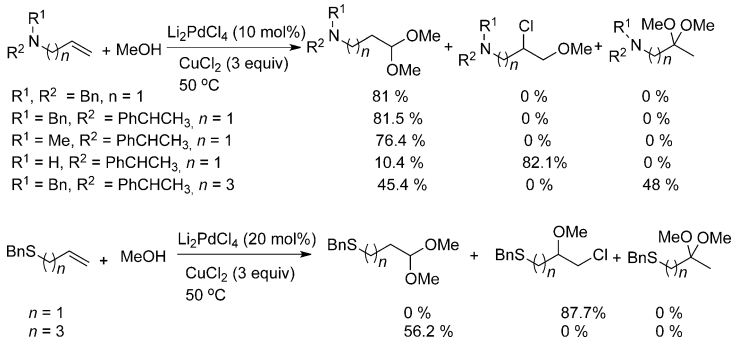
3.1. Palladium Nitrite System

The oxidation of olefins to ketones in acetonitrile catalyzed by bis(acetonitrile)chloronitro palladium(II) was reported by Andrews and Kelly in 1981.[52] The proposed mechanism involves a palladium nitro/nitrosyl redox cycle involving oxygen (Scheme 19). ^{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.[53–55] ^{18}O-labelling, spectroscopic data, and a crystal structure have confirmed that the formation of heterometallocycle is plausible as an intermediate step.

Heumann reported that $[PdCl(NO_2)(MeCN)_2]$ catalyzed the oxidation of 4-vinylcyclohex-1-ene with oxygen to the corresponding exocylic ketone as the sole product. In contrast



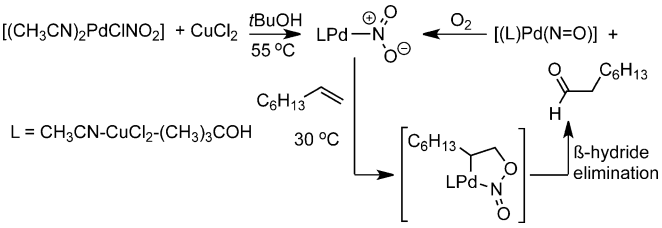
Scheme 19. Catalytic cycle for the oxidiation of alkenes to ketones with $[PdCl(NO_2)(MeCN)_2]$.



Scheme 18. Acetalization of allylic amines and allylic sulfides.

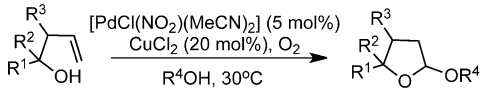
bicyclic olefins, such as 5-vinylnorbornene, underwent epoxidation of the internal alkene.[56] Andrews and co-workers[55] and Heumann and co-workers[56] proposed that the cycloaddition of the nitropalladium complex to the olefin is likely to be followed by β-hydride elimination, which is consistent with 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.[21] The catalyst was prepared by heating a mixture of $[PdCl(NO_2)(MeCN)_2]$ and $CuCl_2$ in a molar ratio of 1:4 in *tert*-butanol at 50 °C. In oxygen-saturated *tert*-butanol, 1-decene was oxidized to both the aldehyde and ketone in a 3:2 ratio. Addition of KNO_2 improved the selectivity for the aldehyde to 7:3. When carried out in propan-2-ol, the selectivity was reversed in favor of the ketone product. 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 $[PdCl_2(MeCN)_2]$ indicated that the nitro ligand was essential for the reactivity observed (Scheme 20).



Scheme 20. The catalytic pathway in the oxidation of a terminal alkene to an aldehyde with $[PdCl(NO_2)(MeCN)_2]$.

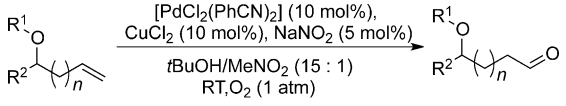
α-Alkoxytetrahydrofurans could be prepared by oxidation of homoallylic alcohols using *tert*-butanol or isopropanol as the solvent (Scheme 21).[57] The method holds the advantage that a substituent at the allylic position is unnecessary, is in contrast to where DMF is used in the presence of water.[28] This method shows significantly higher selectivity of oxidative cyclization 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, thus indicating that the five-membered ring is formed more favorably than the six-membered ring.



$R^1 = R^2 = R^3 = H$, $R^4 = t$Bu, 94%; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = t$Bu, 80%
$R^1 = R^2 = Me$, $R^3 = H$, $R^4 = i$Pr, 100%; $R^1 = R^2 = R^3 = Me$, $R^4 = t$Bu, 96%
$R^1 =$ Me, $R^2 =$ COOEt, $R^3 = H$, $R^4 = t$Bu, 63%;
$R^1 =$ Ph, $R^2 =$ COOEt, $R^3 = H$, $R^4 = t$Bu, >90%

Scheme 21. Oxidation of homoallylic alcohols to α-alkoxytetrahydrofurans.

The same palladium nitro/nitroso redox couple has recently been employed by Grubbs and co-workers 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.[22] The catalyst system comprised $[PdCl_2(PhCN)_2]$, $CuCl_2$, and $AgNO_2$ in *tert*-butanol/$MeNO_2$ at 20–25 °C. An aldehyde/ketone ratio of 4:1 was obtained in the oxidation of 1-dodecene, however the yield of the aldehyde was reduced by the partly competitive formation of olefin isomerization products. In the case of linear α-olefins the selectivity towards formation of 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 $[PdCl_2(PhCN)_2]$ with $NaNO_2$, was applied in the AM oxidation of alkenes bearing oxygen groups at the allylic or homoallylic positions (Scheme 22). High selectivity towards the aldehyde products were obtained (> 9:1).[58]

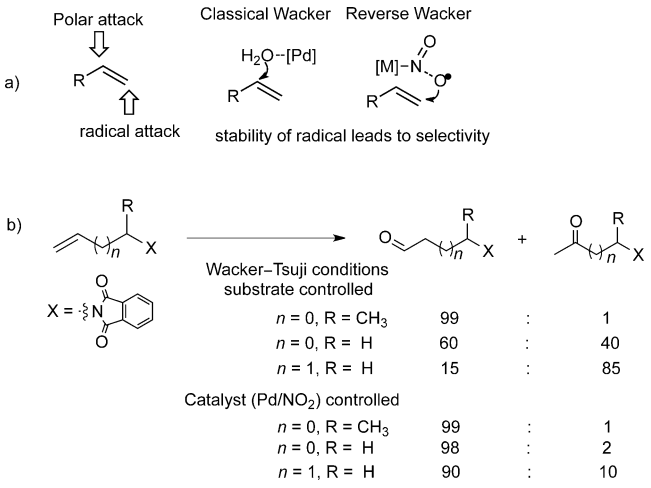


$n = 1$, $R^1 =$ TBS, $R^2 =$ butyl	76 %
$n = 1$, $R^1 =$ Me, $R^2 =$ butyl	71 %
$n = 1$, $R^1 =$ Ph, $R^2 = H$	88 %
$n = 0$, $R^1 =$ acetyl, $R^2 =$ hexanyl	75 %

Scheme 22. Oxidation of alkenes bearing oxygen groups at the allylic or homoallylic positions.

^{18}O-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 palladium(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 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 23a). It was proposed that the radical addition pathway was central to the formal AM selectivity observed. However, trapping of the intermediate radical has not been achieved yet.

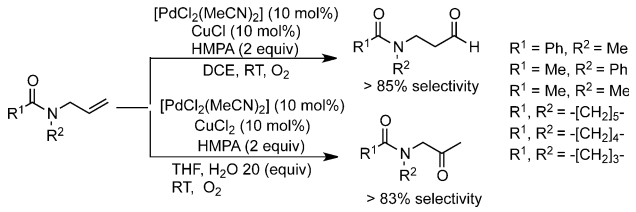
Phthalimide-protected allyl amines are unusual substrates since excellent AM selectivity was obtained under classic Wacker oxidation conditions (Scheme 1 and Scheme 23b).[15] Indeed greater than 90% selectivity in favor of the aldehyde product was also obtained for phthalimide-protected homoallylic amines, which do not show AM selectivity under Wacker–Tsuji conditions.[15] Notably, a kinetic study showed that the selectivity remained constant after 5% conversion, thus indicating that the formation of the catalyst which engages in the majority of the reaction is not immediate.



Scheme 23. a) Rationalization of AM selectivity on the basis of radical stability. b) Oxidation of phthalimide-protected allylic amines and homoallylic amines.

3.2. Other Ligands

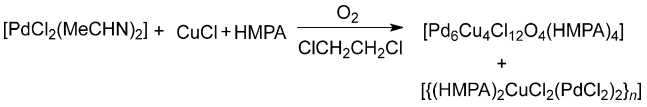
In 1991, Hosokawa et al. reported that N-allylamides could be oxidized into aldehydes in high selectivity using $[PdCl_2(MeCN)_2]$, CuCl, and hexamethylphosphoric triamide (HMPA) under water-free aerobic conditions, while methyl ketones were obtained under the conventional Wacker conditions (Scheme 24).[23] The AM selectivity with HPMA



Scheme 24. Oxidation of N-allylamides using hexamethylphosphoramide (HMPA) as ligand. DCE = 1,2-dichloroethane.

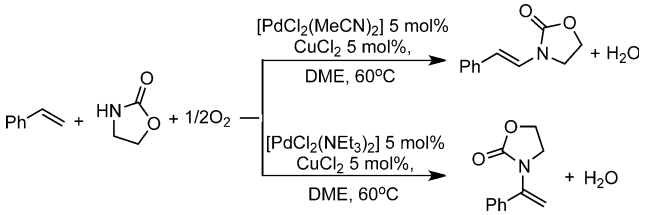
was observed only with N-allylamides and an approximate 1:1 ratio of aldehyde to ketone was obtained in the oxidation of allyl acetate. In contrast to the conventional Wacker conditions where water acts as the source of the oxygen atom, HMPA is key for aerobic oxidation under anhydrous conditions, and 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.

The authors noted that the aldehyde selectivity may be 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 μ_4-oxo atom derived from molecular oxygen (Scheme 25).[59] 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.[60]



Scheme 25. Formation of a palladium-copper heterobimetallic complex with a μ_4-oxo bridge.

Stahl and co-workers 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 $[(CH_3CN)_2PdCl_2]$ was used, the AM amination products predominate, while Markovnikov amination products were obtained in the presence of Brønsted bases such as NEt_3 and Bu_4NOAc (Scheme 26). The authors proposed that the



Scheme 26. Oxidative amination of styrene.

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 η^3-benzyl adducts.

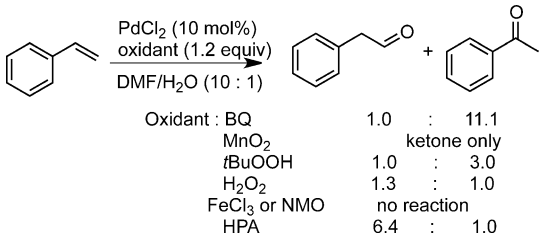
At the same time, Atwood and co-workers reported a stoichiometric amine addition to platinum(II)-coordinated alkyl olefins.[61] In this case, regiochemical distinction between the kinetic and thermodynamic products was observed also, however, the AM aminoplatination adduct was favored kinetically, presumably for steric reasons, and is isomerized to the Markovnikov adduct at elevated temperatures.

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 palladium(0) intermediate formed in the reaction is the key step to achieve 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 co-workers.[48,49] Several alternative reoxidants have been shown to be useful in the AM-selective oxidation of terminal alkenes, including copper/oxygen combinations and

BQ.[33,42,45] 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, thus 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 co-workers (see above) have demonstrated that the regeneration of the palladium(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 BQ and MnO_2, and decreased moderately with oxidants such as a H_2O_2 and *t*BuOOH, which can be considered to be dioxygen-like species. The only exception to this was a non-coordinating oxidant, the hetero-polyacid $H_4[PMo_{11}VO_{40}]$ (HPA), which provided high AM selectivity (Scheme 27).[39]



Scheme 27. Oxidation of styrene using different oxidants. NMO = *N*-methylmorpholine *N*-oxide.

Overall, as discussed 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, 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.[62] recently for palladium-catalyzed C–H activation to form α,β-unsaturated aromatic aldehydes, does present an obvious path towards achieving catalyst control over selectivity.

5. Conclusion and Outlook

The aim of this Minireview is to provide an overview of the successful efforts to achieve AM-selective oxidation, including the preparation of aldehydes, acetals, amino compounds, and alkylation (Scheme 3). Overall, it is apparent that AM selectivity is largely substrate-dependent, i.e. 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 η_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 which 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 $[Pd(CH_3CN)_2ClNO_2]$. 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. The prospect of direct catalytic AM functionalization of α-olefins under full catalyst control makes these efforts highly attractive and a worthwhile pursuit.

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