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Secondary Phosphine Oxides as Multitalented Preligands en Route to Chemoselective Pd-Catalyzed Oxidation of Alcohols

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Abstract: Secondary phosphine oxides $O=PHR_2$ (SPOs) have been identified as multitalented preligands for the chemoselective Pd-calatyzed oxidation reaction of alcohols via abstracting hydrogen methodology. SPOs promote the hydrogen abstraction step as well as the hydrogen transfer to a Michael acceptor by generating a putative active H-Pd species. The catalytic system operates in neutral conditions and was proved to be compatible with various electro- or nucleophilic functions within the substrates as well as water- and air-sensitive functional groups.

The surge in transition metal-based catalysis has unquestionably paved the way for the design of efficient catalytic systems in the field of oxidation of alcohols as evidenced by the numerous reports in this regard.^[1] In particular, the recent reemerging interest in using palladium(II)-based catalysts^[2] in combination with oxygen^[3] has conditioned the design of welldefined complexes for achieving highly selective transformations of primary or secondary alcohols into corresponding aldehydes or ketones respectively.^[4] Such a Pd(II)-based approach typically involves a putative Pd-hydride species as the crossroads through alcoholate formation and subsequent β -H elimination. Completion of the catalytic cycle then requires either the reoxidation of a Pd(0) species or direct reaction of HPdX with oxygen to regenerate the active catalyst (Scheme 1, pathway a).^[5] Despite obvious environmental benefit in the use of oxygen and great advances achieved hereof, many serious issues such as intolerance of sensitive functional groups and nature of ligands may emerge in maintaining catalytic activity and/or regio- and chemoselectivity.^[6] Alternatively, oxidizing alcohol in absence of any formal reoxidant necessarily implies metal-mediated hydrogen transfers from the substrate to a hydrogen acceptor such as electron-poor alkenes.^[7] This approach has recently been termed "abstracting hydrogen methodology"^[8] (AHM) (Scheme 1, pathway b). Surprisingly, the scarce precedent literature^[9] in which this combination has been convincingly performed proves that such a synergism remains to be harnessed. It should be noted that oxidation through hydrogen transfer is well-documented within the ruthenium chemistry.^[7] However, most of the involved substrates are devoid of other functional groups,^[10] probably owing to the high oxophilicity of the metal and the basic conditions which are usually required.

AHM-based approach is feasible if the H-Pd^{II} species generated by alcohol oxidation reacts with the H-acceptor faster

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Scheme 1. Catalytic pathways for the Pd(II)-catalyzed oxidation of alcohols

than it suffers from a reductive elimination or a degradation process and the quest for a multitalented preligand L is therefore of paramount importance. First, L should sufficiently provide electron-density towards the metal while maintaining a moderate steric hindrance.^[11] Second, it should not promote intramolecular deprotonation of the Pd-H bond, thus ruling out a good number of bidendate nitrogen ligands.^[12] Third, it should operate in neutral conditions to preserve the chemical integrity of both the Pd-H species and the substrate. Lastly, L would be synthetically useful only if it is both air and moisture stable and easy to handle. In this context, finding an alternative to ligands which are able to stabilize H-Pd species such as pincer-ligands is highly desirable.

Our solution to tackle this vexing issue lies in secondary phosphine oxides^[14] (SPOs, scheme 2) which are air-stable,^[15] unaffected by water,^[16] easy to handle.^[14a] and good electrodonating preligands.^[17] For instance, complex **A**, easily available from SPOs and Pd(OAc)₂,^[18] would be expected to generate a H-Pd species **B** through the oxidation of an alcohol.



Scheme 2. Proposed ligand-specific strategy to generate a H-Pd species

Moreover, the six membered hydrogen bonded chelate structure of **B** would enable to stabilize a 14 electron cationic Pd(II) complex from which a reductive elimination would be rather difficult. This peculiar structure would also allow to strongly minimize the steric hindrance since the edge between the P atom and the hydride could approach 120°.^[19]

In earlier studies, we noticed that the treatment of $Pd(dba)_2$ with *rac-tert*-Butyl(phenyl)phosphane oxide (L, 2 equiv) and acetic acid (2 equiv) in toluene resulted in the reduction of one C-C double bond of the dba ligand (scheme 3).^[20] This result could be attributed to the putative species **C** formed through

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ligand exchange. The loss of acetic acid would then afford the Pd^{II}-hydride complex **C** which upon loss of AcOH yields **D**. The latter would then react with dba and AcOH to deliver **E**. This observation clearly highlighted **L** as a Pd^{II}-H generator preligand class, all the more so given that oxidative addition of AcOH to Pd⁰ is known to proceed through an unfavorable equilibrium.^[21]



Scheme 3. Proposed mechanism for the double bond reduction of dba (dba = dibenzilideneacetone; H_2 dba = 1,5-diphenyl-pent-1-en-3-one).

These observations led us to investigate the formation of D from alcohol instead of AcOH so as to perform their oxidation through AHM. The oxidation of benzyl alcohol (3a) has been first studied in toluene at 90-105 °C over 12 h, in the presence of the easily prepared well-defined complex **1** as catalyst, ^[18c] a series of hydrogen acceptors 2 and in the presence or absence of water as co-solvent (Table 1). While no reaction occurred in absence of hydrogen acceptor 2 and co-solvent, low yields were obtained when the reaction was performed with 2a and 1 (entries 1-2). Though yields were similar to those obtained with SPO, using PPh₃ as ligand led to the formation of Pd black, presumably due to the instability of the generated HPdOAc species or direct PPh₃-assisted reduction of Pd(OAc)₂^[22] (entry 3). Surprisingly, adding water as co-solvent slightly improved the yield (entry 4) and increasing the temperature to 105 °C provided 4a in 58% yield (entry 5). Whereas replacing 2a by 2b, 2c or 2d dramatically dropped the yield or did not impact the efficiency of the transformation (entries 6-8), we were pleased to find that the use of 2e allowed the formation of 4a in 88% yield. In contrast, 3a failed to react in similar conditions when Pd(OAc)₂ instead of **1** was used in absence of ligand (entry 10). Using bis(diphenylphosphino)-propane as ligand, that mimics the SPO-chelate structure, and Pd(OAc)₂ afforded 4a in only 4% yield and conversion of H-Pd into Pd(0).^[23] This highlights the role of SPOs in stabilizing palladium intermediates (entry 11). Lastly, 4a could also be obtained in 69% yield by using air as reoxidant, stressing the robustness of 1 (entry 12).

The scope of the process was then examined (Scheme 4). Thus, a wide range of secondary benzylic alcohols were successfully oxidized into corresponding ketones (**3b-h**). Aliphatic cyclic (**3i-n**) or acyclic secondary alcohols (**3o-s**) including sterically congested ones were also converted to their corresponding ketones in good to excellent yields. Interestingly, the reaction involving **3q** yielded **4q** in 93% yield without hydrolysis of the nitrile group.^[24] Whereas aerobic Pd(II)catalyzed oxidation of alcohols in the presence of highly airsensitive moieties are quite limited, **4r** could be obtained in a very good yield from **3r** without any alteration the phenylthio group. It should be stressed that despite well-known ligand properties, phenylthio group-, amine- and nitrile-containing

Table 1. Optimization of the Pd/L-catalyzed oxidation[a]



^[a]benzyl alcohol (1 mmol), **1** (0.05 mmol), **2** (1 mmol), toluene (8 mL).
 ^[b]determined by GC. ^[c](PPh₃)₂Pd(OAc)₂ (5 mol%) was used instead of **1**.
 ^[d]Reaction performed in toluene/H₂O (8/1, v/v). ^[e]Pd(OAc)₂ was used instead of **1**.
 ^[f]1,3-Bis(diphenylphosphino)-propane/Pd(OAc)₂ (5/5 mol%) was used instead of **1**.



Scheme 4. Scope of the process.^{[a] [a]}Reaction conditions: **3** (1 mmol), **1** (0.05 mmol), **2e** (5 mmol), toluene (8 mL), water (1 mL), 105 °C, 16 h; yields of isolated products are reported. ^[b]**3q** was quantitatively recovered. ^[c]**2d** (5 mmol) was used instead of **2e**. ^[d]Contaminated with 4% of citronellal.

substrates did not affect the structure of the catalyst, highlighting the high robustness of the $[(L)(L-H)Pd^{II}]$ species. Furthermore,

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both **3r** and **3s** have been identified as notorious difficult substrate classes in Pd-catalyzed oxidation reactions.^[25] The catalytic system operating in neutral conditions, base-sensitive

sulfonyl groups^[26] remained intact as in 4s while they were established to undergo elimination under Ru-catalyzed hydrogen transfer reaction conditions.^[27] Although they might lead to undesired products due to their potentially H-acceptor property, good yields were obtained for 4w, 4x and 4y from 3w, 3x and 3y respectively, for which the integrity of the double bonds was preserved. Changing 2e by 2d was however essential for the reaction involving 3y in order to minimize over reduction of the conjugated double bond. As the primary aliphatic alcohol substrate 3t was found to be reluctant to react, we examined the possibility to achieve chemoselective oxidation of diols featuring both primary and secondary alcohol functions. We were delighted to state that the method was highly selective towards secondary alcohols as illustrated by the obtaining of 4u-v. Although not mentioned in the Scheme 5, it should be pointed out that 4b. 4i. 4k. 4l and 4x were also obtained in vields similar to those reported using water as unique solvent.

The behavior of **1** in a toluene/H₂O (8/1) mixture at 105 °C was then studied using ESI(+)-MS (see Supporting info). After 15 min of stirring, a species at *m*/z 999 was intercepted and identified as the complex $[(L_2-2H+H)PdOH]^+$ in a dimeric form with $[L_2PdOH]^+$. This species was also intercepted in the presence of substrates **3b** and **2a** and could rationally originate from the dihydroxybridged palladium dimer **F** (figure 2). Trimeric Pd(II) acetate complex is known to be easily converted into $[Pd_3(\mu^2-OH)(OAc)_5]$ in the presence of water^[28] and a large number of dimeric bidentate diphosphine Pd(II) complexes were also proved to suffer from similar transformations when dissolved in water.^[9d,29] It should be noted that monomeric analogous species was reported to be active in aerobic Pd(II)-catalyzed oxidation reactions of alcohols in aqueous media.^[9d,25]



Figure 2. Detected cationic hydroxybispalladium(II) species

We lastly studied the hydrogen transfer step (Scheme 5). The reaction involving d_{1} -3b as deuterium source and 2a as H-acceptor afforded the corresponding oxidized product 4b and the monodeurerated product d_{1} -2a in which deuterium is exclusively placed at C-4, highlighting a highly regioselective D-transfer (Scheme 5, a). The partial deuterium incorporation can be rationalized by a possible D/H exchange between the formed deuteridopalladium species and the water cosolvent.^[30] In contrast, the similar reaction conducted with 3b in a mixture of toluene/D₂O (8:1) instead of d_{1} -3b in a mixture of toluene/H₂O led to d_{2} -2a in which a 100% deuterium incorporation was observed at the C-3 (Scheme 5, b). This result clearly suggests that once the double bond of 2a is inserted into the H-Pd bond, the formed C-bound Pd(II) enolate (I) is more prone to undergo

a hydrolytic cleavage than a β -H elimination despite its potentially available coordination site and the absence of anionic ligand X⁻ excess.^[31] The reaction performed with d_1 -3b in a toluene/D₂O mixture afforded d₂-2a with a quantitative deuterium incorporation at C-3 and C-4 (Scheme 5, c). Lastly, heating H₂-2a at 105 °C for 16 h in a toluene/D2O mixture as solvent and in the absence of 1 resulted in no D-incorporation at C3 (see Supporting info). It appeared clear that our reaction conditions did not allow to envisage a direct C α -Pd bond heterolytic cleavage and subsequent protonation of the organic moiety at first sight, such a chemical event usually requiring a reduction involving both tertiary amines and formic acid.^[32] A plausible alternative to this mechanism would be the presence of a Lpromoted equilibrium between G and the species H via the oxa- π -allylpalladium, **H** being susceptible to suffer from an heterolytic fission due to the ionic character of Pd-O structures (Scheme 5, d).^[33]



Scheme 5. Deuterium labelling experiments

In view of the above results, we propose the following mechanism (Scheme 6). The catalyst **1** would be converted into the inactive precatalyst **F** in the presence of water, namely a dihydroxybridged Pd dimer, which is in equilibrium with the active monomer **I**. The reaction of **I** with *d*_{*r*}-**3** would provide the deuteridopalladium species **J**, **4** and water either through a hydroxyPd(II)-alcohol^[34] or an alkoxypalladium intermediate.^[35] The double bond insertion of **2e** into the H-Pd bond would then yield the C-bounded Pd(II) enolate **M** in equilibrium with **N** as suggested by deuterium-labelling experiments. Subsequent protolysis of the latter would finally restore the active catalyst **I** and deliver the deutero-hydrogenated compound *d*_{*r*}-**2e**.

In conclusion, we have developed a novel Pd(II)-catalyzed oxidation of alcohol through AHM using SPOs as multitalented preligands. Scope and mechanistic investigations showed that SPOs enabled the generation of H-Pd(II) species as well as

subsequent hydrolysis of the generated organopalladium species resulting from the hydrogen transfer step to the acceptor. Unlike most of reported aerobic Pd- or Ru-catalyzed reactions, this method is compatible with a wide range of functional groups, including amines, sulfones, and water- or air-sensitive ones such as nitriles and sulfides. The catalytic system chemoselectively operates in neutral conditions leaving primary aliphatic alcohols intact. Studies of this *in situ* generated H-Pd species for C-C bond formation are currently underway.



Scheme 6. Proposed mechanistic cycle

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