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Pd(II)-Catalyzed Deprotection of Acetals and Ketals Containing Acid Sensitive Functional Groups

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ABSTRACT

The pincer complex [Pd(C^1,O^1,N^1-L)(NCMe)]ClO_4 (L = monoanionic ligand resulting from deprotonation of the acetyl group of the dimethyl monoketal of 2,6-diacetylpyridine) is used for the high-yield and selective catalytic hydrolysis of aliphatic, aromatic, cyclic and acyclic dimethyl-acetals, -ketals and dioxolanes, even in the presence of large substituents. Other protecting groups, as THP or TBDMS, or very acid-sensitive alcohols were not affected. The catalyst is easily prepared in high yield from $Pd(AcO)_2$ and 2,6-diacetylpyridinium perchlorate stable to air and moisture, easily and fully recoverable and reusable.

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1. Introduction

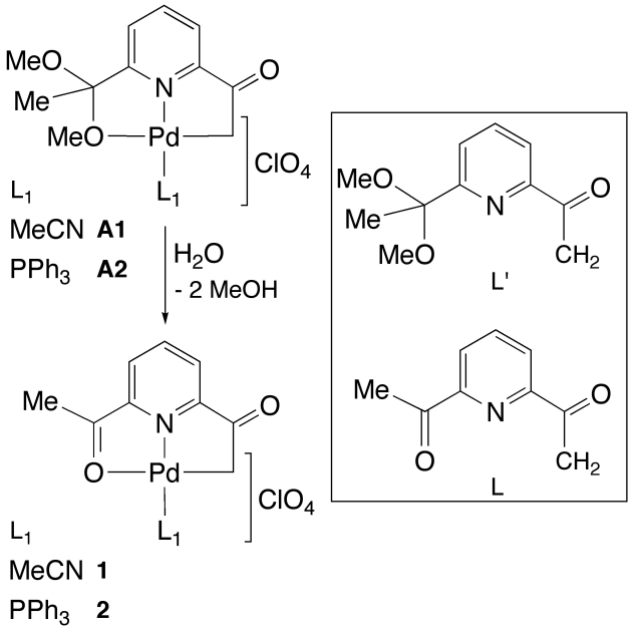
Protection and deprotection of functional groups are key in many multi-steps organic synthesis. Therefore, the development of new mild, efficient and selective reagents to remove established protecting groups is a valuable endeavor. In particular, the deprotection of acetals and ketals[1] to give the corresponding carbonyl compounds has a very important role in total synthesis.[2-4]

Many reagents have been developed for this purpose, for example, organic acids, metal chlorides, coordination complexes,[2] inorganic salts[2,3,5-9] and organic compounds.[2,10,11] While these reagents are useful towards functionally poor organic molecules they (1) are not efficient to all kind of acetals and ketals,[2,7,8,12] (2) use acidic medium unsuitable for compounds containing acid sensitive functional groups[2,5] or (3) give unwanted side-reactions with other protecting groups (tetrahydropyranyl (THP), methoxymethyl ether (MOM) or silyl ethers).[2,9,10] In the last decade, some methodologies have been highlighted over the rest, such as the use of triethylsilyl trifluoromethanesulfonate (TESOTf) + base,[11,13] that selectively unmasks acetals in the presence of ketals in good yields, Bi(III)[14] and In(III)[3,15] salts that deprotect acetals and ketals in the presence of THP and silyl ether protecting groups. Only one example of Pd-catalyzed deprotection of acetals and ketals has been reported by Lipshutz *et al.*[16] Low catalyst loading of $[PdCl_2(NCMe)_2]$ is able to afford the corresponding carbonyl groups in good yields but competitive reactions are given with THP alcohol protecting group.

2. Results and Discussion

We have recently isolated a family of Pd(II) pincer complexes $[Pd(C^1,O^1,N^1\text{-L})(L^1)]ClO_4$[17] (L = monoanionic ligand resulting from the cyclopalladation of 2,6-diacetylpyridine (Scheme 1), L^1 = MeCN (**1**), PPh_3 (**2**)) and other N-, P- and C-donor ligands obtained from the hydrolysis of the corresponding monoketal derivatives ($[Pd(C^1,O^1,N^1\text{-L}')(L^1)]ClO_4$ (L', see Scheme 1; L^1 = MeCN (**A1**), PPh_3 (**A2**)). Complex **1** can also be prepared from $Pd(OAc)_2$ and 2,6-diacetylpyridinium perchlorate.[17] The pincer ligands L and L' provide palladium complexes with interesting properties. Thus, L' is able to estabilize

complexes of Pd(IV), most of which are highly unstable, and Pd(II) and Pd(IV) derivatives of L or L' are catalysts.[17-19]



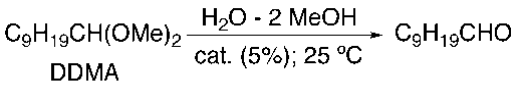
Scheme 1. Synthesis of complexes **1** and **2**.

This hydrolysis process did not occur in neutral homologous complexes of **A**, for example in [Pd(*O*[1],*C*[1],*N*[1]-L')Cl], suggesting that it could be caused by increasing the acidic character of the Pd(II) center in the cationic complexes **A**. To test if this hydrolysis could also occur with an 'external' acetal we attempted to use **A1** (L^1 = MeCN) or **A2** (L^1 = PPh_3) as catalyst for the hydrolysis of decanal dimethylacetal (DDMA). However, although it occurred, the process was very slow (Table 1) and curiously, the intramolecular hydrolysis did not take place while there was DDMA in solution. This suggested us that the intermolecular hydrolysis occurred by replacement of ketal group of the ligand by DDMA, preventing the intramolecular hydrolysis, and not by replacement of the ligand L^1, which, in addition, would be very improbable in the case of PPh_3 (**A2**). The greater reaction rate when **A1** was used as catalyst instead of **A2** could be attributable to a higher steric hindrance produced by the bigger phosphine ligand. Consequently, we thought that complex **1** could be better as catalyst than complexes **A** because the acetyl group is smaller than the ketal group, it is electron-withdrawing instead of

electron-donating, making the metal center more acidic, and the Pd–O bond in **1** is weaker than in the **A**-type complex with L^1 = 2,6-$Me_2C_6H_3NC$.[17] We selected DDMA for the test because the catalytic deprotection of some long chain aliphatic substrates have failed[8] and, particularly, the only reported catalytic hydrolysis of DDMA reached only 17% yield.[20]

Table 1

Deprotection of DDMA with various catalysts.



Cat.	Time (h)	Yield (%)[a]
1	8	95
A1	16	36
A2	16	6
$[PdCl_2(NCMe)_2]$[16]	16	30
$[Pd(AcO)_2]$	16	0
10 % AcOH	16	0

[a] Determined by ^{1}H NMR.

The deprotection of DDMA using **1** as catalyst was also compared with that of $[PdCl_2(NCMe)_2]$, which is the only palladium compound reported for this type of catalytic reactions,[16] as well as with $Pd(AcO)_2$ or 10% of AcOH. The reactions were performed at room temperature in wet acetonitrile with 5% mol amount of the catalyst. Complex **1** was by far the best catalyst for the reaction (Table 1). We have recently reported that **1** showed also to be a good precatalyst for some room temperature Pd(II)/Pd(IV) Heck-type reactions.[19]

In order to optimize the reaction conditions, we carried out some experiments at room temperature varying the amount of **1** added to the mixture (Table 2). Decanal was obtained in quantitative yields after 36 to 5.5 h depending on the concentration of the catalyst (1 to 10%, respectively). When the temperature of the reaction was increased to 50 ºC, 98% yield was obtained after 5 min using 1% mol of

1. Therefore, the latter reaction conditions can be used for hydrolyzing non-temperature sensitive substrates.

Table 2

Deprotection of DDMA at different concentrations of **1**, temperatures, and reaction times to reach >90% yield of decanal.

mol% of **1**	Temp (ºC)	Time	Yield (%)[a]
1	25	36 h	92
3	25	12 h	96
5	25	8 h	95
10	25	5.5 h	97
1	50	5 min	98

[a] Determined by ^{1}H NMR

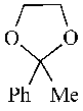
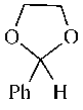
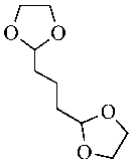
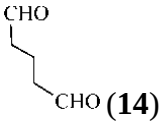
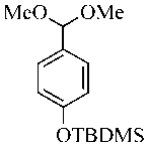
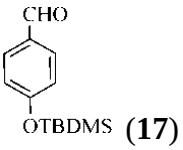
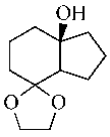
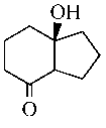
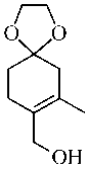
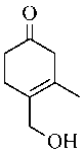
In order to know the potential of our methodology, a number of aliphatic, aromatic, cyclic and acyclic dimethylacetals, dimethylketals and dioxolanes were selected as substrates (Table 3). The reactions were performed in wet acetonitrile using 1% mol of **1** as catalyst.

All deprotection reactions led to the corresponding carbonyl compounds in more than 95% yield in the range of 1–120 min at room temperature or by heating at 50 ºC. As expected, ketals (entry 4, Table 3) were easier hydrolyzed than the corresponding acetals (entry 5). Moreover, dioxolane derivatives were somewhat more resistant than the corresponding dimethoxy compounds (entry 6). This methodology is compatible with the presence of other protecting groups such as *tert*-butyldimethylsilylether (TBDMS, entry 8) or acid-labile tetrahydropyranyl (THP, entry 7). However, in $[PdCl_2(NCMe)_2]$-catalyzed reactions of protected acetals compounds bearing THP groups, both hydrolytic processes are in competition.[16] We have also successfully deprotected two ketals containing really acid-sensitive hydroxy groups (entries 9 and 10) that could easily dehydrate, giving the corresponding α,β–unsaturated carbonyl compounds, if acid deprotecting reagents were used. Thus, it has been observed dehydration in attempts to deprotect **18**[21,22] and **20**.[23] These are very remarkable results because deprotection of compound **18** has only been accomplished with $(NH_4)_2[Ce(NO_3)_6]$ (CAN)[9,24] but the

hydrolysis of substrates similar to **20** has failed using $TiCl_4$ as catalyst or HCl in THF.[23,25] We have found that $[PdCl_2(NCMe)_2]$ (1%, 50 ºC, 1h) does not deprotect **20**. However, neither $(MeO)_2CH(CH_2)_3NH_2$, or its BOC-protected derivative, nor $(MeO)_2CHCH_2CN$ were hydrolyzed in the presence of **1**, probably because they N-coordinate to Pd preventing the coordination of the ketal group.

Table 3

Deprotection of selected acetals and ketals.[a]

Entry	Substrate	Product	Time (min)	Temp. (ºC)	Yield (%)[b]
1	$Me_2C(OMe)_2$ (**3**)	$Me_2C(O)$ (**4**)	10	25	99
2	$MeCH(OMe)_2$ (**5**)	MeCHO (**6**)	1	50	99
3	$C_9H_{19}CH(OMe)_2$ (**7**)	$C_9H_{19}CHO$ (**8**)	5	50	98
4	 (**9**)	PhC(O)Me (**10**)	7	50	98
5	 (**11**)	PhCHO (**12**)	12	50	98
6	 (**13**)	 (**14**)	120	50	95
7	$THPO(CH_2)_2OH$ (**15**)	No reaction	960	25	---
8	 (**16**)	 (**17**)	10	25	99
9	 (**18**)	 (**19**)	10	50	96
10	 (**20**)	 (**21**)	5	50	98

[a] Using 1% mol of **1** as catalyst. [b] Yields determined by ^1H NMR.

A large-scale deprotection of DDMA (40 mmol-scale) has been carried out obtaining 96% isolated yield of the desired aldehyde.

Complex **1** is stable during the hydrolysis reaction and can be easily recovered (95%) and reused. As complex **1** can also be obtained (and isolated in 94% yield) by reaction of $Pd(OAc)_2$ and 2,6-

diacetylpyridinium perchlorate,[17] we have also used complex **1** as catalyst for the deprotection of DDMA preparing it *in situ* by successive addition of equimolecular amounts of 2,6-diacetylpyridinium perchlorate and $Pd(OAc)_2$ to MeCN. We have proved that palladium acetate or the acetic acid by-product did not affect the catalytic hydrolysis of DDMA (Table 1). The ^1H NMR of CD_3CN solutions of reaction mixtures show that the formation of the catalyst is quantitative and instantaneous.

3. Conclusions

In conclusion, we have developed a new efficient and mild methodology for the deprotection of cyclic and acyclic acetals and ketals using [Pd(*O*^{1},*C*^{1},*N*^{1}-L)(NCMe)]ClO_4 as catalyst. We achieve quickly, with very good yields and under mild conditions the corresponding carbonyl compounds without side-reactions even in the presence of others protecting groups as THP or TBDMS and very acid sensitive alcohols. The hydrolysis (1) without dehydration of the alcohol **20** and (2) the high yield of the dehydration of DDMA are unprecedent. Viewed as a whole, and having in mind its hydrolytic properties, the catalyst offers unique properties: it is easily prepared in high yield from commercial products, $Pd(OAc)_2$, 2,6-diacetylpyridine and $HClO_4$, fully recoverable, reusable and stable in the solid state and in solution even in the presence of air and moisture.

4. Experimental Section

Unless otherwise stated, the reactions were carried out without precautions to exclude light, atmospheric oxygen or moisture. Melting points were determined on a Reicher apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer with Nujol mulls between polyethylene sheets. NMR spectra were recorded on a Brucker AC 200, or Avance 300 or 400 spectrometers. Chemical shifts were referred to TMS (^1H, ^{13}C). When needed, NMR assignments were performed with the help of APT, HMQC and HMBC techniques. High-resolution ESI mass spectra were recorded on an Agilent 6220 Accurate-Mass TOF LC/MS; the exact masses have been calculated for the combination of the most abundant isotopes. Complexes **A1**, **A2**, **1** and **2** were obtained following previously described procedures,[17] as well as compounds **18**[22] and **20**.[26]

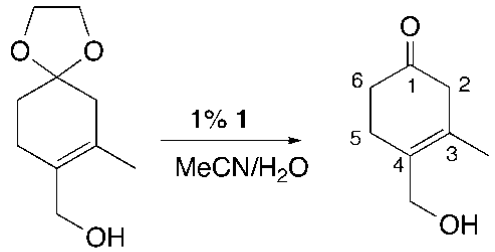
4.1. Typical procedure for the catalytic deprotection reaction

An NMR tube was charged with decanal dimethyl acetal (48.3 μL, 0.198 mmols), water (100 μL), catalyst **1** (8.07 mg, 0.002 mmols) and acetonitrile-*d*$_3$ (500 μL). The tube was shaken until complete dissolution. The sample was heated at 50 ºC and NMR spectra was recorded every 5 min. Conversion was calculated integrating the aldehyde proton and referenced with the solvent residual peaks.

4.2. Large-scale hydrolysis of decanal dimethyl acetal catalyzed by complex 1.

To a solution of decanal dimethyl acetal (10 mL, 41.02 mmols) and water (2 mL) in acetonitrile (50 mL), compound 1 was added (168.1 mg, 0.41 mmols). The resulting orange solution was heated at 50 ºC. After 20 min, the solution was concentrated (6 mL) and diethyl ether was added (15 mL) to precipitate an orange solid that was filtered off, washed with diethyl ether and dried in vacuo. Yield: 161.3 mg, 0.39 mmols (95%). The filtrate was washed with saturated aqueous solution of $MgSO_4$ and the solvent was removed in vacuo to obtain decanal of 98% of purity. Yield: 6.20 g, 39.42 mmols, 96%.

4.3. Experimental procedure for the synthesis of compound 21.



20 **21**

Scheme 2. Synthesis of **21** from **20**.

An NMR tube was charged with compound **20** (24.80 mg, 0.135 mmols), water (100 μL), catalyst **1** (0.53 mg, 0.0013 mmols) and acetonitrile-*d*$_3$ (500 μL). The tube was shaken until complete dissolution. The sample was heated at 50 ºC and NMR spectra was recorded after 5 min. Compound **21** was detected in 98% conversion. ^{1}H NMR (300 MHz, acetonitrile-*d*$_3$): δ 4.07 (s, 2 H, -CH_2OH), 2.78 (br, 2

H, H2), 2.48-2.37 (m, 4 H, H6+H5), 1.69 (s, 3 H, Me). $^{13}C\{1H\}$ NMR (75.45 MHz, acetonitrile-d_3) δ 212.9 (C1), 131.5 (C4), 128.3 (C3) 61.5 (CH_2OH), 46.0 (C2), 39.5 (C6), 28.0 (C5), 18.4 (Me). HRMS calc for $C_8H_{13}O_2$ [M+H]+ m/z 141.0910, found m/z 141.0915.

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Supplementary data

Supplementary data related to this article can be found at ……..

References and notes

(1) Although current IUPAC terminology classifies ketals as a subset of acetals, in this work we consider essential to maintain the use of both terms.

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Graphical Abstract