Catalytic Conversions in Water. Part 22: Electronic Effects in the (Diimine)palladium(II)-Catalysed Aerobic Oxidation of Alcohols†

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Abstract: The electronic effects in the (diimine)Pd-(II)-catalysed aerobic oxidation of alcohols were investigated from the viewpoint of both the catalyst and the alcohol. A 'push–pull' mechanism is operative, where both electron-donating substituents on the benzyl alcohol ($\rho = -0.58$) and electron-withdrawing groups on the 4,4′-disubstituted-2,2′-bipyridine ligand ($\rho = +0.18$) increase the reaction rate. The results indicate partial reduction of the palladium centre in the transition state of the rate-limiting step.

Keywords: alcohols; electronic effects; N ligands; oxidation; palladium; water as solvent

Introduction

In recent years many groups have investigated palladium-catalysed aerobic oxidations of alcohols. The first successful system that did not require chlorinated solvents[1] or copper salts[2] for reoxidation of reduced palladium(0) was reported in 1977.[3] This method involved a simple $PdCl_2$-catalysed reaction in ethylene carbonate. The reaction was carried out at ambient temperature under 1 bar of dioxygen and with only 1 mol % of catalyst. Under these conditions full conversion was reached after circa 100 hours. Twenty years later the idea was rejuvenated by Peterson and Larock, who carried out the reaction with $Pd(OAc)_2$ in DMSO and reported comparable results.[4] In both cases, ethylene carbonate and DMSO acted both as the solvent as well as the ligand necessary for a smooth reoxidation.[5] Soon afterwards, better results were reported by Uemura et al. who carried out the reaction in toluene and obtained full conversion in 2 hours with 5 mol % catalyst.[6] In this non-coordinating solvent, however, the use of a ligand such as pyridine is imperative to maintain a proper catalytic cycle without concomitant precipitation of palladium black. In contrast, these monodentate pyridine ligands do not coordinate sufficiently tightly to palladium when the reaction is carried out in water.[7] For reactions in this solvent bidentate phenanthroline derivatives are preferred in combination with $Pd(OAc)_2$. These (phen)$Pd(OAc)_2$ complexes can be tuned to afford alcohol oxidation,[7] formation of hydrogen peroxide,[8] or Wacker-type reactions.[9]

Recently, we proposed a catalytic cycle for the (phenS*)$Pd(OAc)_2$-catalysed aerobic oxidation of alcohols in water (see Figure 1).[7b] The starting complex is believed to be a dihydroxo-bridged palladium dimer that is in equilibrium with two equivalents of a palladium monomer – $[(phenS^*)PdOH]^+$. After coordination of the alcohol, water is eliminated and a palladium alkoxide – $[(phenS^*)PdOR]^+$ – is formed. Under the reaction conditions, the rate-limiting step seems to be β-hydride elimination[10] of the palladium alkoxy intermediate, creating a carbonyl compound, palladium(0) and a proton.

Conversely, Stahl et al. have shown that starting from the reduced palladium species reoxidation of Pd(0) is first order in oxygen concentration. This reoxidation step may well be the slow step under certain reaction conditions.[11] For an excellent recent paper on mechanistic studies of the $Pd(OAc)_2$/pyridine system we refer to a recent contribution by Stahl.[12]

To obtain more detailed information about the nature of the rate-limiting step and to discover more active catalysts we synthesised a range of 4,4′-disubstituted-2,2′-bipyridines as ligands for the palladium-catalysed aerobic oxidation of 2-hexanol. Normally, phenanthrolines are the preferred ligands for palladium-catalysed aqueous oxidation. However, to study electronic effects on the *phenanthroline* ligand complicated multi-step syntheses of 4,7-disubstituted phenanthrolines starting

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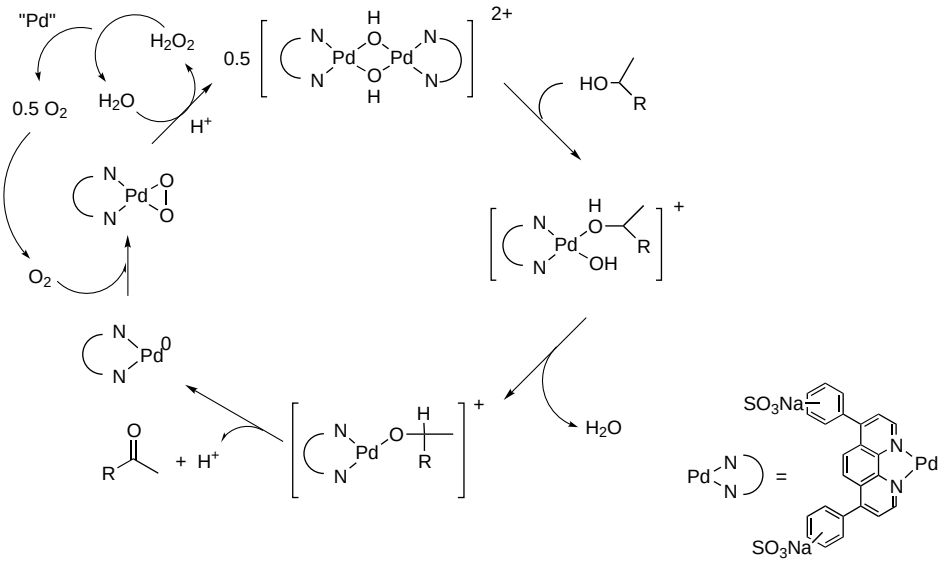


Figure 1. Mechanism for the Pd-bathophenanthroline-catalysed oxidation of alcohols.[7b]

from 1,2-diaminobenzene are required.[13] Therefore, we resorted to 4,4′-disubstituted-2,2′-bipyridines, which are considerably easier to synthesise starting from 2,2′-bipyridine.[14,15,16]

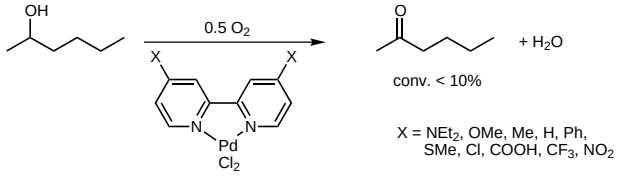
Variation of the electron density on the diimine ligand changes the redox properties of the catalyst as is indicated by the change in half-wave potentials.[17] Therefore, this variation should provide evidence for whether an oxidation step or a reduction step is rate-limiting. The reoxidation step of Pd(0) to Pd(II) should be facilitated by electron-donating substituents. On the other hand, if the reduction step is rate-limiting, then the reaction should be facilitated by electron-withdrawing substituents in the ligand.

In the second part of this paper investigations into the rate-limiting step will be described from the viewpoint of the alcohol. A series of *meta*- and *para*-substituted benzyl alcohols was oxidised by (neocuproine)$Pd(OAc)_2$. The results are ordered in a Hammett plot, which gives an indication of the nature of the reduction step. To our knowledge, a combined study on the electronic effects on both ligand and substrate has only been carried out for an oxoruthenium(IV) complex modified with *para*-substituted triphenylphosphine ligands.[18] In contrast, we could find no prior data on linear free energy relationships for palladium-catalysed (aerobic) oxidation of substituted benzyl alcohols.

To shorten the experimental time we advantageously made use of parallel experimentation methods: the catalytic experiments on the substituted benzylic alcohols were conducted in a reactor array of 24 mini-autoclaves. Selected experiments were also carried out in a conventional autoclave to ensure a proper outcome of the reactions. The parallel catalytic experiments allowed quick catalyst screening and optimisation of reaction conditions and also allowed for rapid generation of data for, e.g., Hammett plots.

Results and Discussion

A series of 4,4′-disubstituted-2,2′-bipyridines[14–16] and their complexes with palladium chloride[19] was synthesised according to literature procedures. As not all catalysts were soluble in neat water, reactions were carried out in a DMSO/H_2O (1:1) mixture. The substrate of choice was 2-hexanol (Equation 1).



(1)

Because the electronic properties of otherwise identical compounds are being compared in the same reaction, it is allowed to make use of the Hammett equation[20] $\log(k_X/k_H) = \rho^*\sigma$, where $\log(k_X/k_H)$ is measured as the ratio of the reaction rate constants of a substituted reactant (or in this case: catalyst) over an unsubstituted reactant (catalyst) and the value for the σ-constant is a measure of the electron donating or -withdrawing properties of the substituent 'X'.

The substituents investigated range from the strongly electron-donating diethylamino group ($\sigma \sim -0.53$) to the strongly electron-withdrawing nitro group ($\sigma = +0.81$).[21] Figure 2 shows a good correlation between the $\log(k_X/k_H)$ *vs.* the σ-value of the respective substitu-

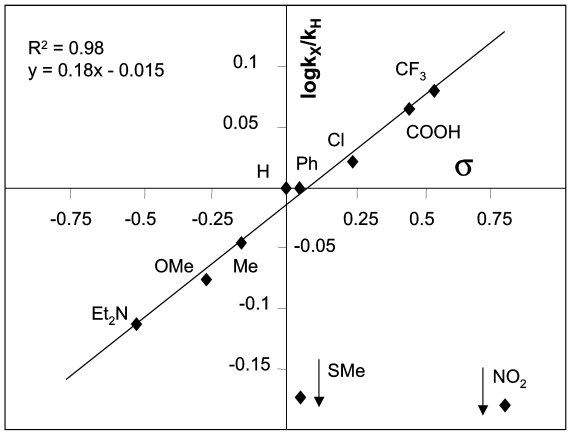
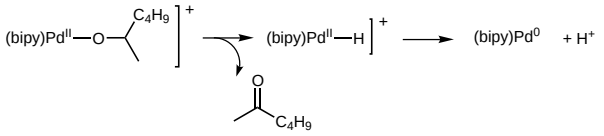


Figure 2. Hammett plot for palladium-bipyridine-catalysed oxidation of 2-hexanol.[23] Conditions: 0.05 mmol (0.5 mol %) catalyst, 10 mmol 2-hexanol, 1 mmol NaOAc, 50 mL DMSO/H_2O (1:1), 5–15 h, 100 °C, 30 bar 8% O_2/N_2.

ents. From the slope a positive ρ-value of 0.18 is obtained. In other words, the reaction rate increases with electron-withdrawing substituents on the ligand, suggesting that there is a build-up of negative (less positive) charge in the transition state. This is consistent with the reduction of (bipy)Pd(II) to (bipy)Pd(0) or $[(bipy)PdH]^+$ being rate-limiting (Equation 2).[22]

The small ρ-value of $+0.18$ indicates that only partial charge transfer to palladium has occurred. It would be too premature to conclude that the reaction proceeds *via* an early transition state.[24] The value is a net result of the different steps in the catalytic cycle. Furthermore, we cannot rule out that the palladium alkoxide complex is reduced *via* a palladium hydride species (Equation 2). As a (formal) result, palladium does not undergo a full two-electron reduction (Equation 2), because electron density is shared with the hydride.



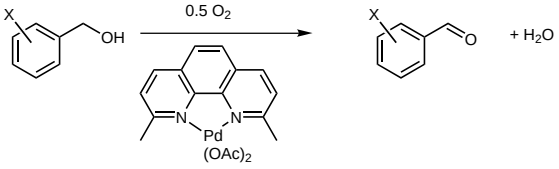
(2)

The observation that electron-withdrawing substituents on the ligand increase the reaction rate in alcohol oxidation is a strong indication that the reduction step is slow and that under these conditions reoxidation of (diimine)Pd^0 is facile. This conclusion is further substantiated by the observation that under the reaction conditions the oxygen pressure has little influence on the reaction rate.[7b,8d,12]

Based on these results we can rationally design ligands that would ensure higher reaction rates in the palladium-catalysed aerobic oxidation of alcohols. Examples may include polychlorinated[25] or polynitrated[26] phenanthrolines. We are currently pursuing electron-poor catalysts. The promoting effect of electron-withdrawing substituents on the ligand also has consequences for ligands suitable for fluorous biphasic catalysis.[6e,27] There would be no need to use spacer groups between the aromatic ring and the fluorous ponytails to neutralise their electron-withdrawing effect ($\sigma \sim +0.5$).

Oxidation of Substituted Benzyl Alcohols

The oxidation of the substrates (benzyl alcohols) was advantageously carried out in a high throughput fashion.[28] The reactions were carried out in an array of 24 mini-autoclaves of 3 mL working volume under 30 bar air. The oxidation of *meta*- and *para*-substituted benzyl alcohols was catalysed by a different palladium complex: (neocuproine)$Pd(OAc)_2$ (Equation 3). This complex is more active than (bipy)$PdCl_2$ derivatives and therefore reactions could be carried out at 70 °C. In this way the substituted benzyl alcohols were oxidised under truly identical reaction conditions and a Hammett plot (see Figure 3) could be obtained in 24 hours! Again, reactions were carried out in a water/DMSO mixture rather than in neat water. In this way all substrates were dissolved completely and equal concentrations were obtained at t_0.



(3)

As noted before, we could find no previous data on linear free energy relationships for palladium-catalysed alcohol oxidation reactions. The linear correlation of the

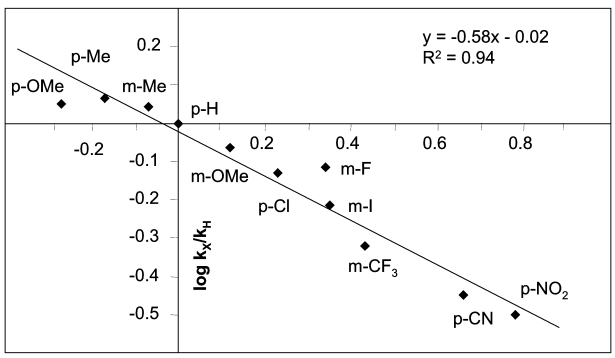


Figure 3. Hammett plot for the (neocuproine)$Pd(OAc)_2$-catalysed oxidation of substituted benzyl alcohols. Conditions: 0.002 mmol (0.5 mol %) (neocuproine)$Pd(OAc)_2$, 0.4 mmol benzyl alcohol, 0.1 mmol NaOAc, 1.5 mL solvent (water/DMSO = 40:60), 30 bar air, 1 h, 70 °C, 200 rpm.

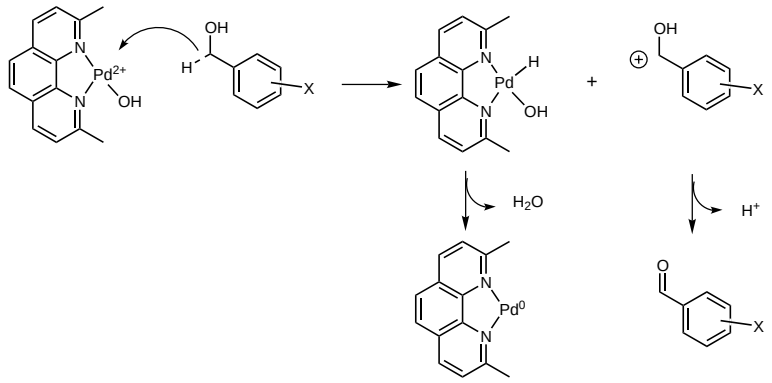
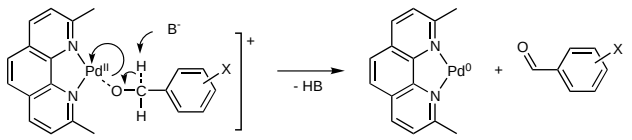


Figure 4. Cationic mechanism[31] inconsistent with small ρ-value (see Fig. 2).

$\log(k_X/k_H)$ values with the substituent constant σ indicates that a radical mechanism is unlikely.[29,30] The moderate ρ-value of -0.58 further suggests that a mechanism where palladium attacks the alcohol hydride creating a benzyl cation[7b,31] can also be excluded (see Figure 4). For such reaction types ρ-values of -4.5 to -6.5 are commonly observed.[32] Electron-donating substituents in the alcohol are expected to favour beta hydride elimination by stabilising the developing positive charge on carbon, in accordance with our proposed mechanism.

The mechanism that is most consistent with the observed electronic effects is that depicted in Equation 2, where a palladium alkoxy complex undergoes a classical β-hydride elimination to form the carbonyl compound and a palladium hydride in the rate-limiting step. This mechanism is in accordance with our earlier data.[7b] The absence of a base effect already suggested that an intramolecular reduction step is operative and that the hydride migrates from the alkoxide to palladium. The mechanism depicted in Equation 4 involving a bimolecular reaction can therefore be excluded as well.



(4)

Conclusions

In conclusion, we have shown that electron-withdrawing substituents on the (diimine) ligand increase reactivity for palladium-catalysed alcohol oxidations. All evidence suggests that the reaction mechanism involves a palladium alkoxide complex that undergoes a β-hydride elimination in the rate-determining step.

Experimental Section

$(Benzonitrile)_2PdCl_2$ ($(bzn)_2PdCl_2$) was synthesised according to the method of Kharasch.[33]

2,2′-Bipyridine *N,N′*-Dioxide[14]

A commercial solution of peracetic acid (32 wt % in acetic acid, ~151 mmol, 36 mL) was added to 2,2′-bipyridine (38.5 mmol, 6.0 g) in glacial acetic acid (7 mL) at such a rate that the temperature was kept at 70–80 °C. After cooling the reaction mixture was stirred for *ca.* 66 h at 35 °C and then Me_2S was added to destroy excess peracid. The solvent was removed under reduced pressure and the residue stirred for 3 hours in boiling acetone (240 mL). After cooling, a white solid was filtered off and dried under vacuum; yield: 6.6 g (36.7 mmol, 97%, lit.[14] 90%); mp 307–309 °C (dec), lit.[14] (EtOH): 312–315 °C); ^{1}H NMR (300 MHz; D_2O; *t*-BuOH): δ = 8.44 (2H, d, *J* = 6.6 Hz, H6 + H6′), 7.83 (2H, dd, *J* = 6.8 and 1.1 Hz, H3 + H3′), 7.75 (4H, m, H4 + H4′ + H5 + H5′); ^{13}C NMR (75 MHz; D_2O; *t*-BuOH): δ = 143.4, 141.3, 133.3, 130.5, 130.1.

4,4′-Dinitro-2,2′-bipyridine *N,N′*-Dioxide[14]

2,2′-Bipyridine *N,N′*-dioxide (23.9 mmol, 4.5 g) was first dissolved in a mixture of oleum (65% SO_3, 2 mL) and sulphuric acid (96%, 13 mL) and then cooled to 0 °C. Fuming nitric acid (100%, 10 mL) was carefully added and the mixture was stirred at 100 °C for 4 hours. The solution then was cooled to 0 °C and *very cautiously* poured on ice-water (100 g). A yellow solid was filtered off and washed with water until neutral to afford a fine yellow powder; yield: 3.9 g (10.8 mmol, 45%, lit.[14] 49%); mp 271–272 °C (lit.[14] 272–275 °C); ^{1}H NMR (400 MHz; DMSO-d_6; Me_4Si): δ = 8.69 (2H, d, *J* = 3.2 Hz, H3 + H3′), 8.59 (2H, d, *J* = 7.2 Hz, H6 + H6′), 8.37 (2H, dd, *J* = 7.2 and 3.3 Hz, H5 + H5′); ^{13}C NMR (100 MHz; DMSO-d_6; Me_4Si): δ = 142.0, 141.1, 140.4, 123.7, 121.8; IR: ν_{max} = 1517 (s), 1342 (s), 1290 (s), 1114 (m), 340 cm^{-1} (m).

4,4′-Dinitro-2,2′-bipyridine[15]

A suspension of 4,4′-dinitro-2,2′-bipyridine *N,N′*-dioxide (7.2 mmol, 2.0 g) and PCl_3 (20 mL) was refluxed for 21 hours in a

flask equipped with cooler and calcium chloride tube. The reaction mixture was cooled and cautiously poured on ice-water (180 g). A concentrated hydroxide solution was added until pH = 13 and a brown suspension was extracted exhaustively with $CHCl_3$. The combined organic phases were dried over $CaCO_3$. The solid was filtered off and the filtrate evaporated under vacuum to give a yellow-brown solid, which was crystallised from CH_2Cl_2/P.E. (40 – 60 °C) to afford small yellow-brown shiny plates; yield: 1.05 g (4.3 mmol, 60%; lit.[15] 69%); mp [P.E. (40 – 60 °C)/CH_2Cl_2) 194 – 195 °C (lit.[15] mp 185 – 186 °C, lit[14] mp 195 – 197 °C); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ= 9.21 (2H, dd, J = 2.2 and 0.6 Hz, H3 + H3′), 9.03 (2H, dd, J = 5.3 and 0.6 Hz, H6 + H6′), 8.12 (2H, dd, J = 5.3 and 2.2 Hz, H5 + H5′); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si): δ = 157.2 (C2 + C2′), 155.2 (C4 + C4′), 151.7 (C6 + C6′), 117.1 (C3 + C3′), 114.3 (C5 + C5′); IR: ν_{max} = 1538 (s), 1356 (s), 911 (m), 852 (m), 739 (m), 699 (s), 325 cm^{-1} (m).

4,4′-Dichloro-2,2′-bipyridine *N,N′*-Dioxide[14]

A suspension of 4,4′-dinitro-2,2′-bipyridine *N,N′*-dioxide (13.6 mmol, 3.8 g) in glacial acetic acid (60 mL) and acetyl chloride (40 mL) was stirred for 2 hours at 100 °C. The resulting yellow-brown solution was cooled to 0 °C and poured on ice (125 g) and neutralised with a concentrated sodium hydroxide solution. An off-white solid was filtered off, washed with water and air-dried; yield: 2.7 g (10.5 mmol, 77%, lit.[14] 98%) [crystallisation from DMF or DMSO caused significant decomposition, but the desired compound precipitated as a white powder on cooling, while side-products that arose from decomposition remained in solution]; mp (DMF) 274 – 276 °C (lit.[14] 276 – 282 °C); ^{1}H NMR (300 MHz; DMSO-d_6 + CF_3COOH; Me_4Si): δ = 8.83 (2H, d, J = 7.0 Hz, H6 + H6′), 8.32 (2H, d, J = 2.7 Hz, H3 + H3′), 8.08 (2H, dd, J = 7.0 and 2.8 Hz, H5 + H5′); ^{13}C NMR (75 MHz; DMSO-d_6 + CF_3COOH; Me_4Si): δ = 144.4 (C2 + C2′), 143.0 (C6 + C6′), 142.7 (C4 + C4′), 132.0 (C5 + C5′), 131.0 (C3 + C3′); IR: ν_{max} = 1452 (s), 1374 (s), 1248 (s), 827 (s), 687 (s), 342 cm^{-1} (m).

4,4′-Dichloro-2,2′-bipyridine[15]

A suspension of 4,4′-dichloro-2,2′-bipyridine *N,N′*-dioxide (2.2 mmol, 0.58 g) and PCl_3 (46 mmol, 4 mL) in anhydrous acetonitrile (100 mL) was refluxed for 4 hours. The resulting yellow-brown solution was poured on ice-water (200 g). Concentrated sodium hydroxide solution was added to pH ~11 and the yellow/white suspension that formed was extracted exhaustively with $CHCl_3$. The combined organic layers were dried over Na_2CO_3. After filtration the filtrate was evaporated under reduced pressure and the residue was crystallised from water/ethanol to give small off-white crystals; yield: 0.45 g (2.0 mmol, 90%, lit.[15] 96%); mp 130 °C (lit.[15] mp 128.5 °C); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ = 8.57 (2H, dd, J = 5.3 and 0.6 Hz, H6 + H6′), 8.45 (2H, dd, J = 2.0 and 0.6 Hz, H3 + H3′), 7.35 (2H, dd, J = 5.3 and 2.0 Hz, H5 + H5′); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si): δ = 156.4 (C2 + C2′), 150.1 (C6 + C6′), 145.4 (C4 + C4′), 124.5 (C3 + C3′), 121.8 (C5 + C5′); IR: ν_{max} = 1571 (s), 1541 (s), 1354 (m), 826 (s), 730 (s), 520 (m), 348 cm^{-1} (m).

4,4′-Dimethoxy-2,2′-bipyridine *N,N′*-Dioxide[16]

Solid 4,4′-dinitro-2,2′-bipyridine *N,N′*-dioxide (5.4 mmol, 1.5 g) was added to a freshly prepared solution of NaOMe (20 mmol) in dry methanol (60 mL). The yellow suspension was stirred for 3 hours at 30 – 35 °C and the resulting yellow solution was cooled to 3 °C, before it was neutralised with concentrated sulphuric acid. A white salt was filtered off and the yellow/orange filtrate was evaporated under vacuum. The dark yellow sludge was extracted exhaustively with boiling $CHCl_3$, and the combined organic fractions were treated with charcoal. The solid was filtered off and the filtrate reduced to *ca.* 80 mL. To the warm solution P.E. (bp 60 – 80 °C, 50 mL) was added and a dark yellow solid was filtered off, which was dried under vacuum to give a fine yellow powder; yield: 1.0 g (4.0 mmol, 74%, lit.[16] 89%); mp 223 – 226 °C (dec), (lit.[16] mp 224 – 225 °C); ^{1}H NMR (400 MHz; CD_3OD; Me_4Si): δ = 8.35 (2H, s broad, H6 + H6′), 7.41 (2H, d, J = 3.2 Hz, H3 + H3′), 7.31 (2H, s broad, H5 + H5′), 3.99 (6H, s, 2 OCH_3); ^{13}C NMR (100 MHz; CD_3OD; Me_4Si): δ = 162.2, 144.4, 142.3, 115.4, 114.9, 57.6; IR: ν_{max} = 1476 (s), 1428 (s), 1211 (s), 1016 (m), 778 (m), 323 cm^{-1} (m).

4,4′-Dimethoxy-2,2′-bipyridine[16]

A suspension of 4,4′-dimethoxy-2,2′-bipyridine *N,N′*-dioxide (3.6 mmol, 0.89 g) in dry $CHCl_3$ (40 mL) was cooled to 0 °C and PCl_3 (5.6 mL) was added. The mixture was refluxed for 3 hours, cooled to room temperature and poured on ice/water (200 g). The organic layer was separated and the aqueous layer extracted once with $CHCl_3$ (50 mL). The volume of the aqueous phase was reduced under vacuum to 100 mL and basified to pH ~10 with a concentrated sodium hydroxide solution. A brownish solid was filtered off, washed with water until neutral and dissolved in CH_2Cl_2. This solution was treated overnight with charcoal and Na_2SO_4. The solid was filtered off and the filtrate evaporated to leave a fine green/white powder, which was crystallised from ethanol to give an off-white solid; yield: 0.40 g (1.85 mmol, 51%, lit.[16] 69%); mp 170 – 171 °C (lit.[16] mp 170 – 172 °C); ^{1}H NMR (400 MHz; DMSO-d_6; Me_4Si): δ = 8.50 (2H, d, J = 5.7 Hz, H6 + H6′), 7.93 (2H, d, J = 2.7 Hz, H3 + H3′), 7.04 (2H, dd, J = 5.7 and 2.7 Hz, H5 + H5′), 3.92 (6H, s, 2 OCH_3); ^{13}C NMR (100 MHz; DMSO-d_6; Me_4Si): δ = 166.1 (C4 + C4′), 156.7 (C2 + C2′), 150.4 (C6 + C6′), 110.6 (C5 + C5′), 105.9 (C3 + C3′), 55.3 (2 OCH_3); IR: ν_{max} = 1586 (s), 1560 (s), 1460 (s), 1291 (s), 1230 (s), 1022 (s), 831 (m), 573 (m), 420 (w), 318 cm^{-1} (w).

4,4′-Bis(*N,N*-diethylamino)-2,2′-bipyridine *N,N′*-Dioxide[16]

A suspension of 4,4′-dichloro-2,2′-bipyridine *N,N′*-dioxide (5.8 mmol, 1.5 g) in water (10 mL) and Et_2NH (10 mL) was stirred in an autoclave at 135 °C for 10 hours. After cooling the solvent was removed under reduced pressure and ether was added to solidify 4,4′-bis(*N,N*-diethylamino)-2,2′-bipyridine *N,N′*-dioxide contaminated with $Et_2NH \cdot HCl$. ^{1}H NMR (400 MHz; acetone-d_6; Me_4Si): δ = 8.23 (2H, d, J = 7.6 Hz, H6 + H6′), 7.15 (2H, d, J = 3.5 Hz, H3 + H3′), 7.00 (2H, dd, J = 7.6 and 3.5 Hz, H5 + H5′), 3.60 (8H, q, J = 7.1 Hz, 4 NCH_2), 1.24 (12H, t, J = 7.1 Hz, 4 CH_3); ^{13}C NMR (100 MHz; acetone-d_6; Me_4Si): δ = 148.9, 143.8, 140.4, 110.8, 109.4, 45.4, 12.4.

4,4′-Bis(*N,N*-diethylamino)-2,2′-bipyridine[16]

The crude mixture of the *N,N*′-dioxide and $Et_2NH \cdot HCl$ in dry $CHCl_3$ (40 mL) was cooled to 0 °C and PCl_3 (8 mL) was added. The suspension was refluxed for 3 hours and poured on ice/water (250 g). The organic layer was separated and extracted with water (50 mL). The volume of the combined aqueous phases was reduced under vacuum to 100 mL and basified to pH ~11-12 with concentrated hydroxide solution. A grey solid was filtered off, air-dried and crystallised from aqueous ethanol to give white shiny crystals; yield: 1.2 g (4.0 mmol, 69%, lit.[16] 50%); mp 154 – 155 °C, (lit.[16] mp 156 – 157 °C); ^{1}H NMR (400 MHz; $CDCl_3$/DMSO-d_6; Me_4Si): δ = 8.21 (2H, d, J = 5.9 Hz, H6 + H6′), 7.60 (2H, d, J = 2.8 Hz, H3 + H3′), 6.48 (2H, dd, J = 5.9 and 2.8 Hz, H5 + H5′), 3.46 (8H, q, J = 7.1 Hz, 4 NCH_2), 1.22 (12H, t, J = 7.1 Hz, 4 CH_3); ^{13}C NMR (100 MHz; $CDCl_3$/DMSO-d_6; Me_4Si): δ = 157.0, 152.7, 149.1, 105.9, 103.5, 43.6, 12.4; IR: ν_{max} = 1581 (s), 1464 (s), 1358 (s), 1271 (m), 1194 (m), 1074 (m), 1012 (m), 980 (m), 809 (m), 318 cm^{-1} (w).

4,4′-Bis(methylthio)-2,2′-bipyridine[14]

Solid 4,4′-dichloro-2,2′-bipyridine (0.9 mmol, 0.20 g) was added to a solution of NaSMe (14.3 mmol, 1.0 g) in dry MeOH (20 mL) and the mixture was refluxed for 20 h. The suspension was filtered hot and the filtrate was cooled to give small white needles that were washed with cold methanol; yield: 0.18 g (0.72 mmol, 80%, lit.[14] 76%); mp 155 – 156 °C, (lit.[14] mp 153 – 156 °C); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ = 8.44 (2H, dd, J = 5.3 and 0.6 Hz, H6 + H6′), 8.25 (2H, dd, J = 2.0 and 0.6 Hz, H3 + H3′), 7.12 (2H, dd, J = 5.3 and 1.8 Hz, H5 + H5′), 2.57 (6H, s, 2 SMe); ^{13}C NMR (75 MHz; $CDCl_3$; Me_4Si): δ = 155.3, 151.4, 148.3, 120.1, 117.1, 13.8; IR: ν_{max} = 1559 (s), 1532 (s), 1428 (s), 822 (m), 740 (m), 707 (m), 523 (m), 407 (m), 341 cm^{-1} (m).

2,2′-Bipyridine-4,4′-dicarboxylic Acid[14]

Commercially available 4,4′-dimethyl-2,2′-bipyridine (2.9 mmol, 0.53 g) and $KMnO_4$ (31 mmol, 3.3 g) in water (40 mL) were refluxed for 14 h. The mixture was cooled to room temperature and filtered. The filtrate was washed with ether and the volume was reduced under vacuum to 20 mL and acidified with 1 M HCl. An off-white solid was filtered off and washed subsequently with water, ethanol and ether and then air-dried to afford an off-white powder; yield: 0.15 g (0.61 mmol, 21%, lit.[14] 45%); mp 365 – 367 °C (dec), (lit.[14] mp > 360 °C); ^{1}H NMR (300 MHz; DMSO-d_6; Me_4Si): δ = 13.9 (2H, s, 2 COOH), 8.92 (2H, d, J = 5.0 Hz, H6 + H6′), 8.84 (2H, s, H3 + H3′), 7.92 (2H, dd, J = 5.0 and 1.5 Hz, H5 + H5′); ^{13}C NMR (75 MHz; DMSO-d_6; Me_4Si): δ = 155.4 (C2 + C2′), 150.8 (C6 + C6′), 139.5 (C4 + C4′), 123.4 (C3 + C3′), 119.5 (C5 + C5′); IR: ν_{max} = 2449 (s), 1889 (s), 1718 (s), 1289 (s), 1268 (s), 1071 (m), 1013 (m), 766 (m), 681 cm^{-1} (m).

All syntheses below were carried out in dry solvents stirring under nitrogen at room temperature.

(2,2′-Bipyridine)$PdCl_2$

A solution of 2,2′-bipyridine (0.70 mmol, 111 mg) in acetone (10 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.65 mmol, 250 mg) in acetone. After 4 hours P.E. (40 – 60 °C) (50 mL) was added for complete precipitation of an orange-yellow complex. The solvent was decanted, the residue was washed with P.E. (40 – 60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.19 g (0.57 mmol, 88%, lit.[19] 97%); IR: ν_{max} = 1602 (m), 1448 (s), 1164 (m), 762 (s), 353 cm^{-1} (m).

(4,4′-Dimethyl-2,2′-bipyridine)$PdCl_2$

A solution of 4,4′-dimethyl-2,2′-bipyridine (1.43 mmol, 263 mg) in acetone (10 mL) and CH_2Cl_2 (5 mL) was added to a solution of $(bzn)_2PdCl_2$ (1.3 mmol, 500 mg) in acetone (25 mL). After two hours P.E. (40 – 60 °C) (80 mL) was added for complete precipitation of a light peach-yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40 – 60 °C) (2 × 50 ml) and dried under vacuum; yield: 0.433 g (1.2 mmol, 92%, lit.[19] 98%); IR: ν_{max} = 1616 (m), 1447 (s), 1031 (m), 841 (m), 831 (m), 512 (m), 420 (m), 398 (m), 377 (m), 330 cm^{-1} (w).

(4,4′-Diphenyl-2,2′-bipyridine)$PdCl_2$

A solution of 4,4′-diphenyl-2,2′-bipyridine (0.72 mmol, 222 mg) in acetone (25 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.65 mmol, 250 mg) in acetone (25 mL). After four hours P.E. (40 – 60 °C) (80 mL) was added for complete precipitation of a dark-yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40 – 60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.20 g (0.5 mmol, 77%); IR: ν_{max} = 1613 (m), 1411 (m), 761 (m), 685 (m), 398 (w), 316 cm^{-1} (w).

(4,4′-Dinitro-2,2′-bipyridine)$PdCl_2$

A solution of 4,4′-dinitro-2,2′-bipyridine (1.1 mmol, 270 mg) in CH_2Cl_2 (25 mL) was added to a solution of $(bzn)_2PdCl_2$ (1.0 mmol, 375 mg) in acetone (25 mL) and stirred for 3 hours. Addition of P.E. (40 – 60 °C) (100 mL) completed precipitation of an intense dark-yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40 – 60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.38 g (0.9 mmol, 90%); IR: ν_{max} = 1539 (s), 1528 (s), 1403 (m), 1353 (s), 1238 (m), 379 (s), 310 cm^{-1} (w).

(4,4′-Dichloro-2,2′-bipyridine)$PdCl_2$

A solution of 4,4′-dichloro-2,2′-bipyridine (0.57 mmol, 129 mg) in acetone (10 mL) and CH_2Cl_2 (10 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.52 mmol, 200 mg) in acetone (20 mL) and stirred for 6 hours. Addition of P.E. (40 – 60 °C) (50 mL) completed precipitation of a yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40 – 60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.14 g (0.35 mmol, 67%, lit.[19] 95%); IR: ν_{max} = 1598 (s), 1547 (m), 1462 (m), 1403 (s), 861 (m), 376 cm^{-1} (m).

(4,4′-Dimethoxy-2,2′-bipyridine)$PdCl_2$

A solution of 4,4′-dimethoxy-2,2′-bipyridine (1.25 mmol, 270 mg) in acetone (10 mL) and CH_2Cl_2 (40 mL) was added to a solution of $(bzn)_2PdCl_2$ (1.14 mmol, 400 mg) in acetone (40 mL) and stirred overnight. Addition of P.E. (40–60 °C) (150 mL) completed precipitation of a peach-yellow complex. The solvent was removed *via* decantation, and the residue was washed with P.E. (40–60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.39 g, (1.0 mmol, 88%, lit.[19] 95%); IR: ν_{max} = 1610 (s), 1474 (s), 1418 (s), 1342 (m), 1280 (s), 1947 (s), 839 (m), 356 (w), 345 cm^{-1} (w).

[4,4′-Bis(*N,N*-diethylamino)-2,2′-bipyridine]$PdCl_2$

A solution of 4,4′-bis(*N,N*-diethylamino)-2,2′-bipyridine (1.07 mmol, 318 mg) in acetone (20 mL) and CH_2Cl_2 (20 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.98 mmol, 375 mg) in acetone (40 mL) and stirred overnight. Addition of P.E. (40–60 °C) (150 mL) completed precipitation of an ochrous-yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40–60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.43 g (0.9 mmol, 92%); ^1H NMR (300 MHz; DMSO-d_6; Me_4Si): δ = 8.40 (2H, d, *J* = 7.3 Hz, H6 + H6′), 7.32 (2H, d, *J* = 2.9 Hz, H3 + H3′), 6.81 (2H, dd, *J* = 7.3 and 2.8 Hz, H5 + H5′), 3.59 (8H, q, *J* = 7.0 Hz, 4 NCH_2), 1.16 (12H, t, *J* = 7.0 Hz, 4 CH_3); ^{13}C NMR (75 MHz; DMSO-d_6; Me_4Si): δ = 156.2, 153.1, 147.7, 107.2, 104.0, 43.8, 11.9; IR: ν_{max} = 1617 (s), 1540 (s), 1517 (s), 1358 (m), 1269 (s), 1045 (m), 830 (m), 803 (m), 432 cm^{-1} (w).

[4,4′-Bis(methylthio)-2,2′-bipyridine]$PdCl_2$

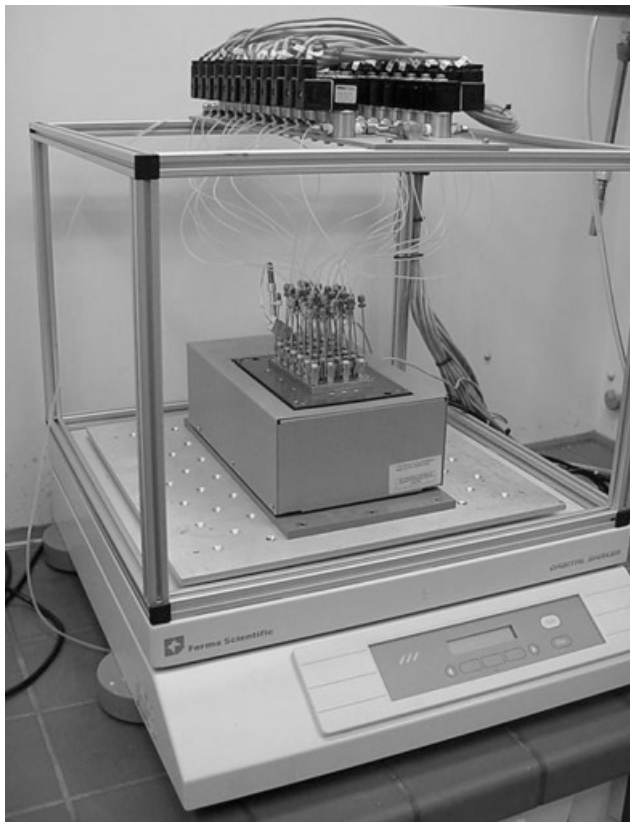
A solution of 4,4′-bis(methylthio)-2,2′-bipyridine (0.45 mmol, 112 mg) in acetone (15 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.40 mmol, 150 mg) in acetone (25 mL) and stirred for 4 hours. Addition of P.E. (40–60 °C) (50 mL) completed precipitation of an orange-yellow complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40–60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.15 g (0.35 mmol, 88%); IR: ν_{max} = 1597 (m), 1430 (m), 1413 (m), 1113 (m), 827 (m), 523 (w), 344 cm^{-1} (m).

(2,2′-Bipyridine-4,4′-dicarboxylic acid)$PdCl_2$

A solution of 2,2′-bipyridine-4,4′-dicarboxylic acid (0.45 mmol, 110 mg) in acetone (25 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.40 mmol, 150 mg) in acetone (50 mL) and stirred for 4 hours. Addition of P.E. (40–60 °C) (50 mL) completed precipitation of a pale yellow-white complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40–60 °C) (2 × 50 mL) and dried under vacuum; yield: 0.15 g (0.35 mmol, 88%); IR: ν_{max} = 1731 (s), 1411 (s), 1288 (s), 1210 (s), 821 (m), 766 (m), 663 (m), 329 cm^{-1} (m).

[4,4′-Bis(trifluoromethyl)-2,2′-bipyridine]$PdCl_2$

A solution of 4,4′-bis(trifluoromethyl)-2,2′-bipyridine (0.14 mmol, 42 mg) in acetone (10 mL) was added to a solution of $(bzn)_2PdCl_2$ (0.13 mmol, 50 mg) in acetone (20 mL) and stirred



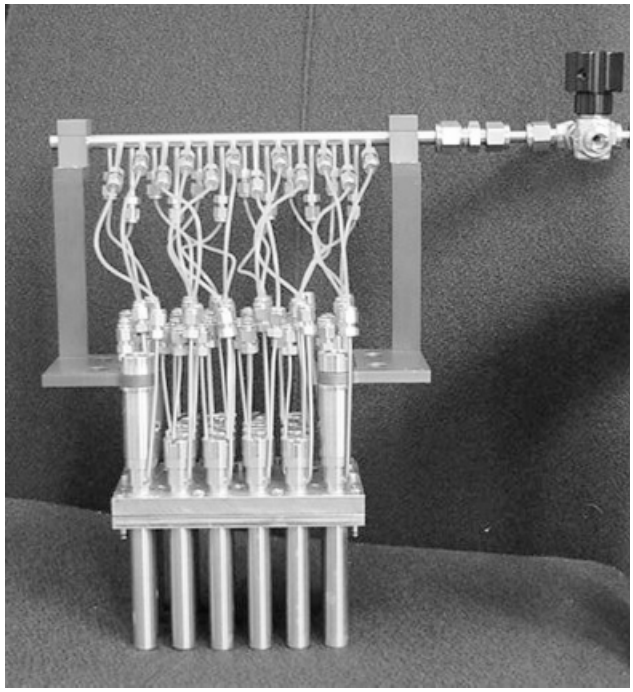


Figure 5. 24 mini-autoclave high pressure unit.

for 4 hours. Addition of P.E. (40–60 °C) (50 mL) caused precipitation of a pale yellow-white complex. The solvent was removed *via* decantation and the residue was washed with P.E. (40–60 °C) (2 × 25 mL) and dried under vacuum; yield: 56 mg (0.12 mmol, 92%, lit.[19] 89%); IR: $\nu_{max} = 1631$ (m), 1420 (s), 1344 (s), 1301 (s), 1188 (s), 1127 (s), 853 (m), 688 (m), 357 cm^{-1} (m).

Catalytic Experimentation in a Conventional Closed Hastelloy C Autoclave (175 mL)

The (4,4′-X_2-2,2′-bipy)$PdCl_2$ catalysts (0.05 mmol), 2-hexanol (10 mmol), NaOAc (1 mmol) were dissolved in 50 mL DMSO/water (1:1). The autoclave was charged with the catalyst solution and internal standard (*n*-heptane). The autoclave was pressurised with 8% O_2 in N_2 and heated to 100 °C (30 bar) while stirring at 750 rpm, t = 5–15 h, conversion < 10%. After reaction the autoclave was cooled to room temperature and depressurised. Any volatile material was collected in a liquid nitrogen trap. The product mixture was extracted with Et_2O, and the organic layer was dried over $MgSO_4$. A different external standard (*n*-dodecane or *n*-hexadecane) was added and the solutions were analysed by GC. Recoveries were always 100 ± 2% with this procedure. No blank reaction was observed. The $\log(k_X/k_H)$ values for the 4,4′-X_2-2,2′-bipyridines ligands were determined from the initial reaction rate (below 10% conversion) in separate experiments. No stoichiometric oxidation reactions were carried out for comparison with catalytic reactions.

Catalytic Experimentation in a 24 Mini-Autoclave High Pressure Unit

In a typical experiment, 1.5 mL of water/DMSO (40/60) containing (neocuproine)$Pd(OAc)_2$ (0.002 mmol), benzyl alcohol (0.4 mmol) and NaOAc (0.1 mmol) were dispensed manually in each of the 24 tubes. Oxidation experiments were performed in a high-pressure multi-reactor system, consisting of 24 parallel reactors (12 mm internal diameter, 70 mm height). The reactors were heated uniformly in a steel heater block to 70 °C and air pressure (30 bar) was applied to each individual reactor by means of a gas manifold to ensure identical pressures over all reactors. The whole assembly was agitated at 200 rpm by an orbital shaker. After reaction the autoclave was cooled to room temperature and depressurised. Water (1 mL) was added to each reactor and the product mixtures were extracted with Et_2O, and the organic layers were dried over $MgSO_4$. Further analysis was as described above.

Apparatus

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 or Varian VXR-400S spectrometer using TMS as an external reference. GC measurements were carried out with a Varian Star 3400 instrument equipped with a CP Sil 5-CB column (50 m × 0.53 mm) or carbowax column (50 m × 0.53 mm). Melting points were determined on a Buchi B540 Melting Point Apparatus with open capillary. Gas chromatography/mass spectrometry (GC/MS) analyses were performed on a VG 70-SE mass spectrometer equipped with a CP Sil 5-CB column.

Materials

Anhydrous solvents on molecular sieves 3 Å (CH_2Cl_2, $CHCl_3$, acetone) were purchased from Fluka. 2,2′-Bipyridine (99 + %), $PdCl_2$, NaSMe (95%), HOAc (100%), acetonitrile (< 0.05% H_2O) and benzonitrile (98%) were purchased from Acros; 4,4′-dimethylbipyridine (99%) from Fluka; 4,4′-diphenylbipyridine (tech), peracetic acid (32 wt % in acetic acid) and acetyl chloride (98%) from Aldrich; oleum (65% SO_3), HNO_3 (100%) and PCl_3 (99 + %) from Merck; H_2SO_4 (96%) from Baker.

p-Cyanobenzyl alcohol was synthesised *via* reduction of *p*-cyanobenzaldehyde with $NaBH_4$;[34] *m*-iodobenzyl alcohol (98%) was purchased from Lancaster, other benzyl alcohols (98-99%) from Janssen/Acros.

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P. Wehman is thanked for a gift of 4,4′-bis(trifluoromethyl)-2,2′-bipyridine. The complex was synthesised via $NiCl_2$/Zn coupling of 2-chloro-4-(trifluoromethyl)pyridine.[35] Avantium Technologies B.V. is acknowledged for financial support.

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