Catalytic Conversions in Water. Part 23: Steric Effects and Increased Substrate Scope in the Palladium-Neocuproine Catalyzed Aerobic Oxidation of Alcohols in Aqueous Solvents#

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Abstract: The steric influence of substituents on the 2- and 9-positions of phenanthroline in the (2,9-R_2-1,10-phenanthroline)palladium(II)-catalyzed aerobic oxidation of 2-hexanol was investigated by means of high throughput experimentation. (Neocuproine)Pd-$(OAc)_2$ (R=CH_3) was found to be a highly active catalyst for alcohol oxidation in 1:1 water/DMSO mixtures. The catalyst is unique in that it tolerates water, polar co-solvents and a wide variety of functional groups in the alcohol. Turn-over frequencies of $> 1500\ h^{-1}$ were achieved and a series of alcohols was oxidised with 0.1 to 0.5 mol % of catalyst.

Keywords: alcohol oxidation, dioxygen, functional groups, palladium, phenanthroline, steric effects, water

Introduction

With ever-tightening environmental regulations and increasing costs, chemistry today focuses on new, cheaper and *greener* ways to carry out organic transformations.[1] In alcohol oxidation reactions this is most clear, as the heavily polluting protocols, with stoichiometric amounts of bichromate and permanganate, of the previous century are being replaced by modern methods involving catalytic amounts of metal catalysts in combination with oxidants such as dioxygen or hydrogen peroxide.[2] In the last four years some 30 fine articles have appeared, describing cobalt-,[3] copper-,[4] ruthenium-[5] and palladium[6]-catalyzed reactions with dioxygen as the terminal oxidant. However, many of the catalytic systems mentioned above have a few drawbacks: (1) a low tolerance towards water, while by definition water is formed in the reaction; (2) the combination of flammable solvent with pure dioxygen, which may lead to hazardous situations; and (3) an (often) tedious work-up procedure with accompanying catalyst decomposition.

One of our group's main research goals is the investigation of catalytic reactions in non-conventional media. In this program the use of water-soluble bathophenanthroline-palladium complexes – (PhenS*)Pd-$(OAc)_2$ (**1**, Figure 1) – for alcohol oxidation has proven successful, because the aforementioned drawbacks were avoided; the side product water is actually used as process solvent. Furthermore, the use of water as a process solvent significantly decreases the chance of explosions and enables separation and recycling of the catalysts from organic product layers.[7] The system has one disadvantage, however, which is the limited solubility of many substrates in neat water. A second and more general disadvantage from which nearly all catalyst systems seem to suffer,[5e,6b] is the low tolerance for (coordinating) functional groups in the solvent or the substrate. The (PhenS*)$Pd(OAc)_2$ system, for example, could only tolerate a single ether functionality (in butyl proxitol), and all other functional groups proved insurmountable, as these coordinated more tightly to palladium.[7b]

The mechanism that was postulated, based on our initial studies, is shown in Figure 1. The reaction is half-order in palladium and first order in the alcohol substrate. The resting catalyst is a dimeric complex containing bridging hydroxy groups. Reaction with the alcohol in the presence of a base, added as a cocatalyst (NaOAc) or free ligand, affords a monomeric alkoxy palladium(II) intermediate which undergoes β-hydride elimination to give the carbonyl compound, water and a palladium(0) complex. Oxidative addition of dioxygen to the latter affords a palladium(II) η-peroxo complex which can react with the alcohol substrate to regenerate the catalytic intermediate, presumably with concomitant formation of hydrogen peroxide as was observed in analogous systems. Recently Stahl et al. conducted

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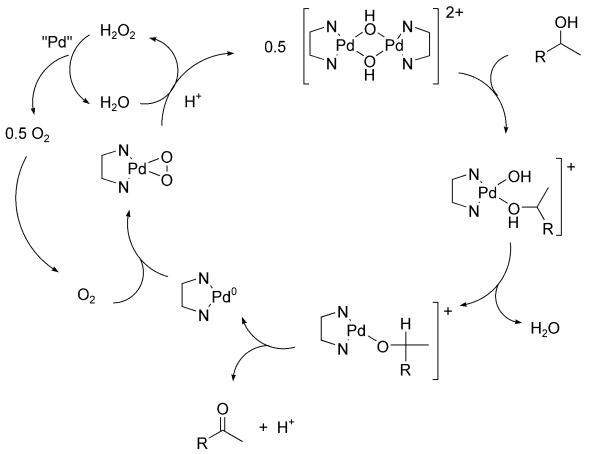
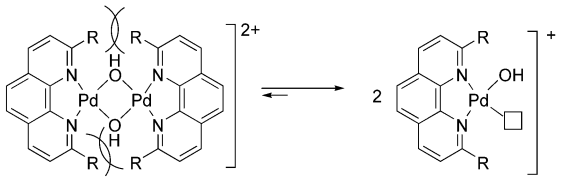


Figure 1. Mechanism of Pd-bathophenanthroline catalysed oxidation of alcohols.

mechanistic studies on the Pd/DMSO and Pd/pyridine systems and found that both pyridine and DMSO had a positive influence on the reoxidation of palladium(0).[8]

We envisaged that we could obtain a more active catalyst and improve the substrate tolerance with the introduction of steric groups on the 2- and 9-positions of the bathophenanthroline ligand. It is known that many diamine,[9] diimine[10] and diphosphine[11] complexes of palladium (and platinum) exist in solution as dimeric species [see Eq. (1)]. For instance, when dissolved in neutral aqueous solution, phenanthroline complexes of palladium acetate form dihydroxo-bridged dimers.[12] These dimers can dissociate into two monomers that are the active species in aerobic oxidation of, e.g., olefins to methyl ketones[13] (Wacker reaction) or oxidation of alcohols[7] to aldehydes, ketones and carboxylic acids. Kinetic investigations of our aqueous biphasic catalytic system based on Pd/PhenS*, revealed that only a small fraction of the palladium dimers is dissociated during the reaction.[7b] Possibly, steric hindrance on the 2- and 9-positions of the bathophenanthroline ligand could enhance the reactivity of the catalyst, through facilitating the dissociation of the palladium dimer into the two (active) monomers [Eq. (1)]. The introduction of the relatively small methyl substituent should already exert a fairly large effect. In the analogous (2,9-dimethylphenanthroline)platinum dimer, the methyl groups induce a significant repulsive interaction with the hydroxo-bridges and a small repulsive interaction with the opposite methyl groups.[14] Although a crystal structure of an analogous palladium complex is not yet available, it is likely that the effect is at least as significant.[15] The consequence of these steric effects is that the dimeric complexes bend from planarity and form a bowl-shaped dimer. Whether the bent platinum[16] and palladium complexes are more reactive than the respective planar complexes, remains somewhat unpredictable.



(1)

In the oxidative carbonylation of phenol,[17] and in CO[18] and alcohol[19] oxidations catalysed by palladium-phenanthroline complexes in water an increased reaction rate with increasing steric bulk of the 2,9-disubstituted phenanthroline ligand has been observed. This might, at least in part, be ascribed to facilitated dissociation of the palladium dimer. Once the catalyst has dissociated into the monomeric species, however, the substituents on phenanthroline play a second role by destabilizing square-planar palladium complexes with respect to trigonal complexes.[20] Hence, the catalyst can no longer accommodate all types of substrates.

To explore an optimum steric effect at the 2- and 9-position in the phenanthroline ligand in the palladium-catalysed alcohol oxidation, we set out to synthesize a series of palladium complexes and test these using a combinatorial approach.[21] The catalytic experiments were either conducted in a conventional autoclave or in a reactor array of 24 five-mL mini-autoclaves. The parallel catalytic experiments allowed quick catalyst/ligand screening and optimization of reaction conditions (co-solvents, additives) and also for rapid determination of substrate scope for a number of selected catalysts.

Results and Discussion

Oxidation of 2-Hexanol with Water-Soluble Palladium Complexes

In an initial study a small selection of water-soluble phenanthroline-derived ligands was investigated as ligands for the palladium-catalyzed aerobic oxidation of 2-hexanol in an aqueous biphasic medium (see Figure 2).

At this stage reactions were carried out in a conventional (175 mL) autoclave. In previous reports[7] we have shown that the palladium complex with sulfonated bathophenanthroline (**1**) was active in alcohol oxidation with a turn-over frequency (TOF) of 49 h^{-1} observed for 2-hexanol. When the commercially available water-soluble bathocuproine ligand (**2**) was used in combination with $Pd(OAc)_2$, the activity was tripled to TOF = 150 h^{-1}. This result is in agreement with our working-hypothesis that dissociation of the palladium dimer was facilitated and, thus, the activity was increased.[22] However, with the two sulfonated phenyl rings placed at the 2- and 9- positions instead of the 4- and 7-positions of phenanthroline, as in ligand (**3**), the palladium complex was completely inactive. This is possibly due

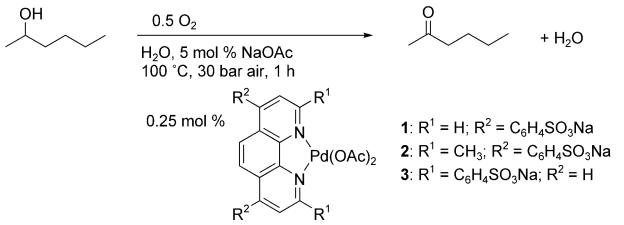
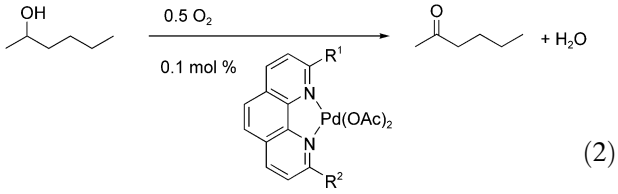


Figure 2. Oxidation of 2-hexanol with water-soluble palladium complexes.

to coordination of the sulfonate groups to the metal or due to metallation of a phenyl ring by the palladium. But, as no apparent changes of the catalyst solution were observed by UV-VIS, the effect could just be a consequence of an effective shielding of the catalyst by the large phenyl rings.[23]

Steric Effects in Phenanthroline Ligands

An extensive library of 2-substituted and 2,9-disubstituted phenanthroline ligands was synthesized, to identify a potential optimum in steric hindrance of ligands that, on the one hand, facilitate dissociation of the palladium dimer, but on the other hand do not hinder approach of the substrate alcohol too severely. As it would be too complicated to synthesize water-soluble analogues of all desired ligands (cf. Figure 1), we chose to prepare non-sulfonated phenanthroline derivatives. Aqueous conditions were mimicked by using water/DMSO mixtures (e.g., 1:1, vol/vol) that conveniently dissolved all of these palladium complexes. The catalysts were thus tested in the aerobic oxidation of 2-hexanol in a parallel fashion and in a single liquid phase reaction [Eq. (2) and Table 1].



(2)

Table 1 shows that in this series neocuproine (**4**) is by far the best ligand for alcohol oxidation with palladium. With longer *n*-alkyl substituents on the ligand [2,9-di-*n*-butylphenanthroline (**6**) and 2-*n*-pentylphenanthroline (**7**)] the reaction rates decreased considerably to circa 110 h^{-1}. With *sec*-butyl substituents on phenanthroline [2-*sec*-butylphenanthroline (**14**) and 2,9-di-*sec*-butylphenanthroline (**15**)] the reaction rate is very low at 25 h^{-1}, possibly a sign of too much steric hindrance. When phenyl rings were placed at the 2- or both 2- and 9-positions of phenanthroline, respectively, similar reactivity was observed to that with **14** and **15**. Comparing these steric effects it is remarkable that the unsubstituted (phen)$Pd(OAc)_2$ catalyst showed such a low activity under these reaction conditions.

Table 1. Steric effects at the 2,9-positions of phenanthroline.[a]

Ligand	R^1	R^2	TOF_0 (h^{-1})
4	**CH_3**	**CH_3**	**170**
5	CF_3	CF_3	125
6	*n*-Bu	*n*-Bu	115
	No ligand	**No ligand**	110
7	*n*-pentyl	H	110
8	CCl_3	H	75
9	CH_3	H	60
10	COOH	COOH	55
11	COOH	H	35
12	C_6H_5	C_6H_5	30
13	CN	H	25
14	*sec*-Bu	H	25
15	*sec*-Bu	*sec*-Bu	25
16	Cl	Cl	15
17	C_6H_5	H	10
18	H	H	5
19	CCl_3	CCl_3	0

[a] Conditions: 0.002 mmol (0.1 mol %) (ligand)$Pd(OAc)_2$, 2 mmol 2-hexanol, 0.1 mmol NaOAc, 1.5 mL water/DMSO (1:1), 2 h, 80 °C, 30 bar air, 200 rpm, selectivity was 100% in all cases.

As we had previously discovered that electron-withdrawing substituents on the ligand improved the reaction rate,[22] we had high hopes of good reactivity of several other ligands. However, these proved disappointing for various reasons. The 2,9-dichlorophenanthroline (**16**) – although approximately similar in steric size as neocuproine – gave a poorly reactive complex, which might be attributed to the relatively reactive chloro substituents being replaced by other groups.[24] The trichloromethyl and trifluoromethyl groups are more stable electron-withdrawing substituents, and indeed with 2,9-bis(trifluoromethyl)phenanthroline (**5**, TOF $\sim$125 h^{-1}) and monosubstituted 2-(trichloromethyl)phenanthroline (**8**, TOF $\sim$75 h^{-1}) better results were obtained. With the bulkier 2,9-bis(trichloromethyl)phenanthroline (**19**), the complex was inactive. This shows that, contrary to the expectation of Drago et al.[25] complexation to palladium had taken place, but that the steric bulk on the ligand created a nearly inactive complex. Palladium-catalysed hydration of 2-cyanophenanthroline (**12**),[10c] and coordination of the cyano group to palladium could account for the poor reactivity of the palladium complex with this ligand. Lastly, the ligands with the electron-withdrawing carboxylate substituents (**10** and **11**) formed moderately active complexes with $Pd(OAc)_2$. Although these substituents might assist somehow in deprotonation of the alcohol, a clear beneficial effect was not observed.

A striking result shown in Table 1 is that the reaction proceeds very well without any ligand present. Normally, such a reaction does not proceed in neat water because unreactive palladium black is formed after one cycle. However, in water/DMSO (1:1) the reaction is catalytic in simple $Pd(OAc)_2$. The salt has already been shown to be active in the oxidation of both aliphatic[26] and activated benzylic or allylic alcohols,[6i] when neat DMSO was used as solvent. Stahl et al. observed some deactivation of the catalyst in neat DSMO when 1 bar of dioxygen was used as the terminal oxidant.[8a] Under the high oxygen pressures (30 bar air) that we used the water/DMSO solution remained bright yellow and no Pd(0) was formed. Although the results are not shown in the table, it is apparently important to start the catalytic cycle with a palladium(II) species, because the *complexes* $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ showed almost no activity, whereas simple $Pd(OAc)_2$ in DMSO was highly active.

The fact that neocuproine is commercially available and that the palladium complex can be made in high purity makes this the most convenient ligand for catalysis and further reactions were carried out with this catalyst.

Solvent Effect

The choice to use DMSO as a co-solvent was rather arbitrary. Therefore, we decided to test a range of other water-miscible co-solvents in a 1:1 (vol/vol) ratio with water in the oxidation of 2-hexanol. Table 2 shows that not only water/DMSO mixtures lead to high catalyst activity (TOF = 170 h^{-1}). Comparable reaction rates of TOF = 170 h^{-1} were obtained when NMP was used as co-solvent. Also in the other co-solvents containing an amide functionality good reactivity (TOF $\sim$120 for DMAC and $\sim$85 h^{-1} for DMF) was found. However, when the reaction was carried out in DMF the reaction rate was nearly zero on a few occasions, possibly due to well-known decomposition of this solvent in CO and $HNMe_2$. In all these cases a bright yellow solution was obtained after reaction. In ethylene carbonate, on the other hand, the initially bright yellow solution turned brown-black. Still, the catalyst maintained good activity (TOF $\sim$140 h^{-1}). When sulfolane was used as a (1:1) co-solvent with water the reaction rate was very low and an in some reactors an orange precipitate was formed. It is possible that impurities containing sulfide groups (e.g., tetrahydrothiophene) caused this deactivation. Indeed, when the solvent was pretreated with some hydrogen peroxide in an attempt to convert any sulfide groups into sulfoxide (sulfone) functionalities, less precipitate was formed and a slightly higher reaction rate was obtained (TOF $\sim$15 h^{-1} vs. 5 h^{-1}). It is noteworthy that by investigating these co-solvents, we have shown that – contrary to PhenS*$Pd(OAc)_2$ – the (neocuproine)$Pd(OAc)_2$ catalyst tolerates several functional groups, notably sulfoxides, amides and carbonates.

Table 2. Comparison of various co-solvents.[a]

Co-solvent	TOF (h^{-1})
DMSO	170
NMP	170
Ethylene carbonate	140
DMAC	120
DMF	85
sulfolane	5

[a] Conditions: 0.002 mmol (0.1 mol %) (neocuproine) $Pd(OAc)_2$, 2 mmol 2-hexanol, 0.1 mmol NaOAc, 1.5 mL water/co-solvent (1:1), 2 h, 80 °C, 30 bar air, 200 rpm, selectivity was 100% in all cases. NMP = *N*-methylpyrrolidinone, DMAC = dimethylacetamide.

In previous experiments an arbitrary (1:1) mixture of water and co-solvent was used as solvent (see Tables 1 and 2). Therefore the influence of the fraction of co-solvent (DMSO) on the reaction rate was determined (see Figures 3a, 3b). Traditionally, this is an extremely time-consuming task. However, with the combinatorial approach 12 reactions were followed simultaneously in duplo, and a detailed picture was obtained in only 24 hours (see Figure 3).

Using the (neocuproine)$Pd(OAc)_2$ catalyst in neat water a TOF of 50 h^{-1} was reached at 80 °C. Addition of small amounts (5–10 vol %) of DMSO had little effect. Combined with the results from Table 2 this indicates that DMSO does not necessarily play a special role in (neocuproine)$Pd(OAc)_2$-catalyzed alcohol oxidations, as DMSO is believed to do in $Pd(OAc)_2$-catalysed reactions.[8a,26] An increase in the DMSO fraction also leads to increased solubility of 2-hexanol in the 'aqueous' phase where the catalyst resides. In this way the reaction rate increased to an optimum rate of circa 170 h^{-1} at 50–60% DMSO. At higher DMSO fractions the reaction rate decreased significantly to a (relatively) low 70 h^{-1} in neat DMSO. Several explanations can be envisaged for this decrease. First, the polarity of water ($\varepsilon \sim 78$) is considerably higher than that of DMSO ($\varepsilon \sim 48$). A high polarity of the solvent can be beneficial to oxidation reactions. Second, it is likely that DMSO is able to compete with the alcohol or hydroxide ligand[7b] for coordination to the (neocuproine)Pd^{2+} centre at high DMSO concentrations.[27,28]

When only 0.05 mol % catalyst was used instead of 0.1 mol % catalyst, the turn-over frequency *increased* by a factor of circa 1.5 for the reaction catalysed by (neocuproine)$Pd(OAc)_2$ in DMSO. This reflects the order of ½ in catalyst concentration also found earlier for the (PhenS*)$Pd(OAc)_2$-catalysed alcohol oxidation.[7b,29] This order of ½ is a consequence of the catalyst being a palladium dimer, which is in equilibrium with 2 equivalents of an active palladium monomer. In neat

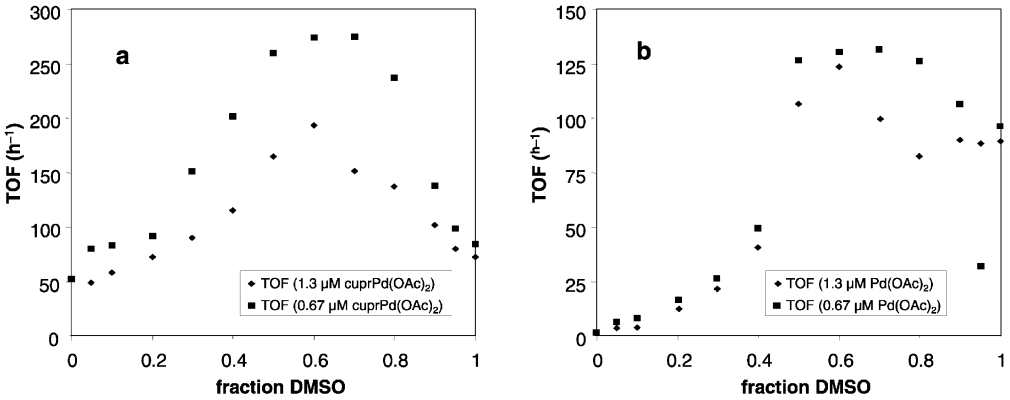


Figure 3. Influence of water/DMSO ratio on reaction rate in palladium-catalyzed oxidation of 2-hexanol. Conditions: $1-2 \times 10^{-3}$ mmol (0.05 – 0.1 mol %) catalyst, 2 mmol 2-hexanol, 0.1 mmol NaOAc, 1.5 mL (water + DMSO), 2 h, 80 °C, 30 bar air, 200 rpm; **a**: (neocuproine)$Pd(OAc)_2$; **b**: $Pd(OAc)_2$.

DMSO the difference in reaction rates for different catalyst concentrations is nearly zero, probably because not enough water is present to form a dihydroxo-bridged palladium dimer.

Interestingly, for reactions catalysed by simple $Pd(OAc)_2$ (see Figure 3b) the highest reaction rates were found at high concentrations of DMSO and not in aqueous ($\sim$1:1) mixtures, showing that water plays a significant role only in the (neocuproine)$Pd(OAc)_2$-catalyzed reactions. The fact that the *turn-over frequency* remained roughly constant at different concentrations of $Pd(OAc)_2$, indicates that here the catalyst is a monomeric species.[30]

Although DMSO is sometimes used as a reagent in the oxidation of alcohols,[31] it is unlikely that a non-catalytic mechanism is operative here.[8a] No dimethyl sulfide was found after the reaction and other inert solvents (DMAC, NMP, ethylene carbonate) lead to nearly equally active catalyst systems. An alternative mechanism where DMSO is used as co-oxidant with dioxygen forming dimethyl sulfone and water can be discarded for similar reasons.[8a] In conclusion, the main benefit of these co-solvents seems to come from an increased solubility of the substrate.

Effect of Sodium Acetate

As has been noted before,[7b] many catalyst systems that involve the Pd^0/Pd^{II} redox couple benefit from the addition of alkali salts of carboxylic acids, because these salts improve reoxidation of Pd^0. In the (neocuproine)$Pd(OAc)_2$-catalyzed oxidation of 2-hexanol a clear effect of the concentration of NaOAc on the reaction rate was observed (see Figure 4).

Figure 4 indicates that a certain amount of NaOAc is vital for a good reaction rate. Below 0.02 M NaOAc the reaction rate decreased rapidly with decreasing NaOAc concentration. The catalyst solution after reaction was increasingly darker at lower acetate concentrations, and more palladium black was formed. Above 0.05 M NaOAc the reaction rate remained constant at 160 – 170 h^{-1}. Furthermore, at high NaOAc concentrations the catalyst solution remained bright yellow and no palladium black was formed. Variation of the pH (*via* addition of solid NaOH) between pH 6.5 and 10 did not lead to an increase in reactivity. These observations are in agreement with the notion that sodium acetate improves reoxidation of Pd^0, thereby preventing formation of palladium clusters or palladium black. It is also possible that anionic complexes, e.g., $LPd(OAc)_3^-$, play an important role as has been postulated for palladium-catalyzed Heck and cross-coupling reactions.[32] Alternatively, NaOAc may facilitate dissociation of the dimer, thereby enhancing the rate of the reaction.

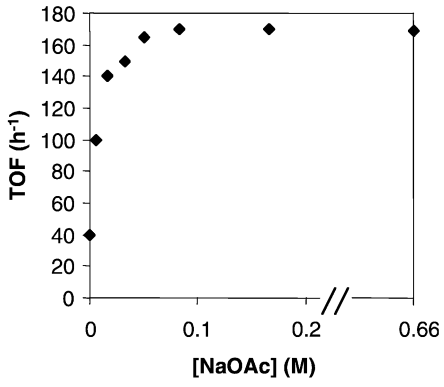
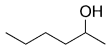
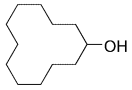
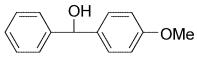
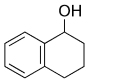
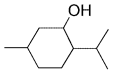
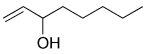
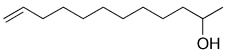
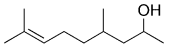
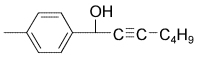
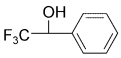
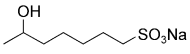
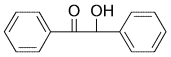
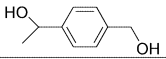


Figure 4. Influence of NaOAc concentration on the reaction rate. Conditions: 0.002 mmol (0.1 mol %) (neocuproine) $Pd(OAc)_2$, 2 mmol 2-hexanol, 1.5 mL (water/DMSO, 1:1), 2 h, 80 °C, 30 bar air, 200 rpm.

Table 3. Substrate scope for the (neocuproine)$Pd(OAc)_2$-catalyzed *sec*-alcohol oxidation.[a]

Entry	Substrate	Conv (%)	Sel. (%)
3.1		90	100
3.2		58	100
3.3		100	100
3.4		90	100
3.5		71	100
3.6		30	95+[b]
3.7		30	99+[c]
3.8		37	95
3.9		15	100
3.10		0	-
3.11		60	100
3.12		10	99+
3.13		50	3:1[d]

[a] Conditions: 0.002 mmol (0.5 mol %) (neocuproine)$Pd(OAc)_2$, 0.4 mmol alcohol, 1.5 mL water/DMSO (40:60), 0.1 mmol NaOAc, 4 h, 80 °C, 30 bar air, 200 rpm.
[b] Main side-product 1-hydroxy-3-octanone.
[c] Only 1-dodecen-11-one was formed.
[d] Aldehyde/ketone ratio.

Substrate Scope

The results obtained so far (increased solubility of the substrate and functional group tolerance) could provide a significant improvement in the substrate scope of alcohol oxidation catalysed by homogeneous metal complexes.[33] With an optimised system in hand a series of alcohols (primary, secondary, aliphatic, cyclic, allylic and benzylic) were tested in a water/DMSO (40:60) mixture (see Table 3). It should be emphasised that, in order to compare reactivities of the various substrates, reactions were performed for a standard time (4 h). This results in lower conversions for the less reactive alcohols but, in most cases, complete conversion can be attained by running the reactions for 12–24 h.

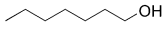
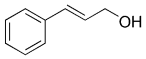
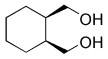
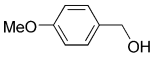
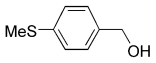
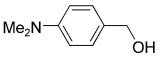
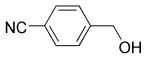
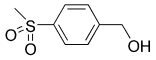
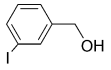
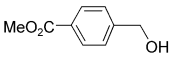
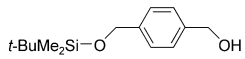
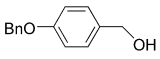
Table 3 shows a large selection of functionalized alcohols that are selectively oxidised by (neocuproine)$Pd(OAc)_2$. First of all, in 60% DMSO large substrates are much more soluble than in neat water and react faster, therefore (see also Figure 3a). Apolar substrates, such as cyclododecanol, diphenylmethanol, 1,2,3,4-tetrahydro-1-naphthol and menthol (entries 3.2–3.5), reacted quickly. The introduction of methyl substituents on phenanthroline did not seem to hinder approach of these substrates in a significant way.

The allylic alcohol 1-octen-3-ol (entry 3.6) was oxidised to the enone. The reaction rate decreased to a certain extent due to competing coordination of olefin and alcohol functionalities.[6f] Interestingly, however, when the olefinic group was farther removed from the alcohol functionality, (1-dodecen-11-ol, entry 3.7) the catalyst selectively oxidised the alcohol functionality. This is somewhat surprising, because the (PhenS*)P-d$(OAc)_2$ catalyst in water selectively converted the olefinic group to form 11-hydroxy-2-dodecanone (Wacker-type reaction), and afterwards converted the ketoalcohol into 2,11-dodecanedione. Probably, the substrate selectively coordinated *via* the olefinic moiety, but the presence of the two methyl substituents on the ligand prevented the substrate from turning into the plane of the catalyst for *cis*-hydroxypalladation.[34] With more steric bulk on the olefin (2,6-dimethylnon-2-en-8-ol, entry 3.8) the alcohol was converted slightly faster and the olefin was left unaffected. The propargylic alcohol (entry 3.9) behaved similarly to the allylic 1-octen-3-ol, but increased electronegativity and possibly stronger coordination of the $C\equiv C$ bond to palladium caused a slow conversion to the corresponding ynone. The catalyst could not cope with a further increase in electronegativity of α-substituents. The 2,2,2-trifluoro-1-phenylethanol is best converted with powerful metal-oxo complexes in high oxidation states,[35] rather than with low-valent late transition metal catalysts,[5e] such as Ru^{II} or Pd^{II}. We note that a copper-based system[4c] was also effective in the aerobic oxidation of alcohols containing a trifluoromethyl moiety at the α-position.

Intramolecular competition experiments between primary and secondary alcohol functionalities showed a slightly increased preference for oxidation of the primary alcohol group compared with that observed with (PhenS*)$Pd(OAc)_2$. For example, in 1-(4-hydroxymethylphenyl)ethanol (entry 3.13) the primary alcohol functionality was oxidized with some preference [$k_{prim}/k_{sec} \sim 3$, vs. 2 for the (PhenS*)$Pd(OAc)_2$ catalyst]. In an intermolecular competition experiment between benzyl alcohol and 1-phenylethanol (not shown), the former was also oxidised slightly faster [$k_{prim}/k_{sec} \sim 2$ vs. 1–1.5 for the (PhenS*)$Pd(OAc)_2$ catalyst]. In contrast, in separate experiments 2-hexanol was oxidised faster than 1-heptanol (see Tables 3 and 4) suggesting that in competition experiments there is preferential coordination of the primary alcohol to the palladium(II).

Primary alcohols are oxidised selectively to the corresponding aldehyde in the presence of TEMPO (5 mol%), which was previously shown to inhibit further

Table 4. Substrate scope for the (neocuproine)$Pd(OAc)_2$-catalyzed 1° alcohol oxidation.[a]

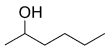
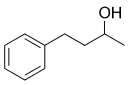
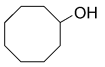
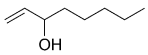
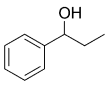
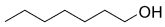
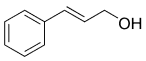
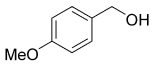
Entry	Substrate	Conv (%)	Sel. (%)
4.1		40	60[b]
4.2		30	90[c]
4.3		28	100
4.4		75	99[d]
4.5		94	100
4.6		86	100
4.7		60	99
4.8		37	100
4.9		31	100
4.10		22	100[e]
4.11		30	90[f]
4.12		62	100
4.13		90	99

[a] Conditions, see Table 3.
[b] Selectivity to *heptanoic acid*, side-products heptanal (~20%), heptenal (~20%).
[c] TEMPO (5 mol %) added, selectivity to *heptanal*, side-products heptanoic acid (6%), heptenal (~3 %).
[d] Racemic *cis*-lactol + lactone formed.
[e] t = 2 h.
[f] Side product *p*-hydroxymethylbenzoic acid.

autoxidation of the aldehyde.[5e,7a] Thus 1-heptanol afforded mainly heptanoic acid in the absence of TEMPO (entry 4.1) but in its presence heptanal was formed in 90% selectivity (entry 4.2). In both cases reaction rates were significantly lower than with secondary, allylic or benzylic alcohols.

Concomitant with the oxidation of primary aliphatic alcohols some palladium black formation was observed. The allylic cinnamyl alcohol (entry 4.3) was oxidized to cinnamaldehyde, which was far less susceptible to autoxidation. Even under an oxygen atmosphere and without addition of TEMPO the product remained stable. The diol, *cis*-1,2-bis(hydroxymethyl)cyclohexane (entry 4.4), was oxidised to the (mono-)aldehyde, which formed a lactol by intramolecular ring closure. This lactol was partly further oxidised to the lactone.

Table 5. Large scale alcohol oxidation reactions with (cupr)$Pd(OAc)_2$.[a]

Substrate	t (h)	TOF_0 (h^{-1})	Conv, (%)	Sel. (%)
	2	>>500	100	100
	2	>>500	99	99[b]
	3	400	93	99+[c]
	3	400	95	96[d]
	3	300	80	99+
	2.5	200	40	75[e]
	10	135	88	99+
	3	>>330	100	100

[a] Conditions: 0.02 mmol (0.1 mol %) (neocuproine)$Pd(OAc)_2$, 20 mmol alcohol, 50 mL water/DMSO (1:1), 1 mmol NaOAc, 100 °C, 50 bar 8% O_2/N_2, 750 rpm; Sel% x conv% = yield (%). Isolated yields (not given) are generally 10% lower.
[b] Side-product 1-phenyl-1-buten-3-one.
[c] Side-product cyclooctenone.
[d] Side-products 1-hydroxy-3-octanone (2%) and 3-octanone (1%).
[e] Selectivity to heptanoic acid, side-products heptanal (20%), 2-heptenal (5%), 60 bar 8% O_2/N_2, Pd(0) was formed.

A wide range of functional groups was tested with *meta*- and *para*-substituted benzaldehydes. Not only *p*-methoxybenzyl alcohol, but also *p*-thiomethyl- and *p*-dimethylaminobenzyl alcohol (entries 4.5 – 4.7) were quickly converted to the corresponding benzaldehydes. Other substituted benzyl alcohols with a *p*-cyano or *p*-methylsulfonyl substituent (entries 4.8 and 4.9) could be oxidized as well, albeit slowly, due to the electron-withdrawing properties of the substituents. The catalyst also tolerated halides in the substrate, even the relatively sensitive iodide group in *m*-iodobenzyl alcohol (entry 4.10) was not attacked. Lastly, benzylic alcohols containing protective groups were oxidized selectively to the respective benzaldehydes. Only in the case of 4-hydroxymethylbenzoic acid methyl ester (entry 4.11) was some hydrolysis of the methyl ester observed.

For all these reactions it should be noted that the general aim was to demonstrate the usefulness of the catalyst and the substrate scope. The use of the 24 parallel mini-autoclaves quickly provided an indication of the reactivity of many different substrates and proved a very realistic model for large-scale reactions in a conventional autoclave (see Table 5). One reason for this lies in the reaction mechanism of these aerobic alcohol oxidation reactions: under the reaction conditions that we used reoxidation of the palladium with

dioxygen comes after the rate limiting step.[7b] Consequently, pressure and stirring rate are less important than in e.g. hydrogenation reactions. From Tables 3 and 4 a fair estimate can be made regarding the reaction conditions (t, T, mol % catalyst) that are required for complete conversion. In Table 5 this is shown for a few substrates on a synthetically useful scale.

Large-Scale Reactions

The large scale (20 mmol) reactions were carried out in a conventional autoclave at 100 °C and with 0.1 mol % (neocuproine)$Pd(OAc)_2$. At these temperatures the catalyst is perfectly stable and highly active (see Table 5). Upon comparison of Tables 3, 4 and 5 it follows that the results from the parallel mini-reactors are in agreement with those obtained at a larger scale: secondary aliphatic alcohols reacted very quickly to give the corresponding ketones, and occasionally some dehydrogenation of the ketones took place. It is noteworthy that under these conditions 2-hexanol is converted at rates *two orders of magnitude faster* than with existing catalytic methods.[3–6] With 0.005 mmol (0.025 mol %) (neocuproine)$Pd(OAc)_2$ catalyst, the turn over frequency increased even further to ca. 1800 h^{-1}!

Conclusions

We have developed a new catalytic system for the aerobic alcohol oxidation that tolerates many sensitive or coordinating functional groups: C=C bonds, C≡C bonds, halides, α-carbonyls, ethers, thioethers, silyl ethers, sulfoxides, sulfones, sulfonates, amines, cyanides, amides, carbonates and esters. The optimum catalyst structure, reaction conditions and also the substrate scope of selected catalysts were quickly determined with the use of high throughput experimentation. It should be noted that the (neocuproine)$Pd(OAc)_2$ catalyst converts, e.g., 2-hexanol at rates *two orders of magnitude faster* than with other catalytic methods. We expect that the catalyst system will have broad synthetic utility.

Experimental Section

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 Büchi 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 or carbowax column.

Materials

$Pd(OAc)_2$ (98%), bathophenanthrolinedisulfonic acid disodium salt (98%), bathocuproinedisulfonic acid disodium salt (97%), phenanthroline (99 + %), neocuproine (99 + %), *n*-BuLi (1.6 M in hexane), *sec*-BuLi (1.3 M in cyclohexane/hexane), phenyllithium (2 M in cyclohexane/ether), 1-hexyne (98%), *p*-methylsulfonylbenzaldehyde (95%), *p*-cyanobenzaldehyde (98%), NCS (98 + %), DMAP (99%), DMSO (98%), DMF (99%), DMAC (99 + %), sulfolane (99%) and ethylene carbonate (99 + %) were purchased from Acros; 4-hydroxymethylbenzoic acid methyl ester (98%), *tert*-butyldimethylsilyl chloride (99%) from Aldrich; levo-citronellal (97%) from Janssen; acetone (99.5 + %) from Baker; NMP (99%), anhydrous toluene (99.5 + %), anhydrous THF (99.5 + %), anhydrous CH_2Cl_2 (99.5%), 2-hexanol (99%), from Fluka; CH_3CN (99.99%) from Fisher; *p*-tolualdehyde (99%), $NaOAc.3H_2O$ (99.5%), MnO_2 from Merck; commercial substrates and solvents were used without further purification.

Syntheses of Ligands

2,9-Bis(trifluoromethyl)-1,10-phenanthroline (**5**),[25] 2,9-di-*n*-butyl-1,10-phenanthroline (**6**),[36] 2-Methyl-1,10-phenanthroline (**9**),[37] 2,9-dichloro-1,10-phenanthroline (**16**),[38] 2-phenyl-1,10-phenanthroline (**17**),[39] 2,9-bis(trichloromethyl)-1,10-phenanthroline (**19**),[40] were prepared according to literature procedures. Previously unreported data are given below.

2,9-Diphenyl-1,10-phenanthroline:[36] mp 186–187 °C (lit. 185–186 °C); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 7.1 Hz, 4H, PhH_{ortho}), 8.28 (d, *J* = 8.4 Hz, 2H, H4 + H7), 8.13 (d, *J* = 8.4 Hz, 2H, H3 + H8), 7.76 (s, 2H, H5 + H6), 7.59 (t, *J* = 7.4 Hz, 4H, PhH_{meta}), 7.49 (t, *J* = 7.4 Hz, 2H, PhH_{para}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 146.2, 139.5, 136.9, 129.4, 128.8, 127.9, 127.7, 126.0, 120.0.

Disodium 2,9-bis(3-sulfonatophenyl)-1,10-phenanthroline (3): Sulfonation of 2,9-diphenyl-1,10-phenanthroline was carried out with ortho-boric acid/sulfuric acid/oleum;[41] mp >360 °C; ^1H NMR (300 MHz, D_2O): δ = 8.05 (d, *J* = 1.4 Hz, 2H, PhH2 + PhH2′), 7.97 (d, *J* = 8.0 Hz, 2H, PhH4 + PhH4′), 7.80 (dd, *J* = 7.9 Hz, 1.3 Hz, 2H, PhH6 + PhH6′), 7.60 (d, *J* = 8.4 Hz, 2H, H4 + H7), 7.35 (m, 4H, PhH5 + PhH5′ + H3 + H8), 7.16 (s, 2H, H5 + H6); ^{13}C NMR (75 MHz, D_2O): δ = 155.2, 145.0, 144.3, 139.8, 139.1, 131.8, 131.1, 129.1, 127.9, 127.7, 125.4, 121.4.

2-*n*-Pentyl-1,10-phenanthroline (7):[37] Starting from 8-aminoquinoline (13.9 mmol, 2.0 g) and oct-2-enal (23.3 mmol, 3.5 ml) a red syrup was obtained. The product was purified *via* column chromatography (silica, Et_2O/P. E., 1:1, R_f ~0.03, then Et_2O) to afford a pale yellow oil; yield: 0.83 g (3.3 mmol, 24%); ^1H NMR (300 MHz, $CDCl_3$): δ = 9.22 (dd, *J* = 4.6 Hz, 1.8 Hz, 1H, H9), 8.21 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H, H7), 8.13 (d, *J* = 8.2 Hz, 1H, H4), 7.74 (d, *J* = 8.8 Hz, 1H, H5/6), 7.69 (d, *J* = 8.8 Hz, 1H, H5/6), 7.59 (dd, *J* = 8.1 Hz, 4.4 Hz, 1H, H8), 7.53 (d, *J* = 8.2, 1H, H3), 3.20 (t, *J* = 8.3 Hz, 2H, $ArCH_2$), 1.40 (m, 6H, $CH_2CH_2CH_2$), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 163.8, 150.2, 146.0, 145.7, 136.2, 136.1, 128.8, 126.9, 126.5, 125.5, 122.8, 122.7, 39.6, 32.0, 30.2, 22.6, 14.0.

2-(Trichloromethyl)-1,10-phenanthroline (8):[40] Product was purified *via* column chromatography (silica, CH_2Cl_2/MeOH, 95/5, R_f ~0.66) to afford a pale yellow solid; yield: 1.4 g (4.7 mmol, 90%); mp 164–166 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (dd, *J* = 4.4 Hz, 1.7 Hz, 1H, H9), 8.41 (d, *J* = 8.5 Hz, 1H, H3), 8.33 (d, *J* = 8.5 Hz, 1H, H2), 8.27 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H, H7), 7.89 (d, *J* = 8.8 Hz, 1H, H5), 7.83 (d, *J* = 8.8 Hz, 1H, H6), 7.67 (dd, *J* = 8.1 Hz 4.4 Hz, 1H, H8); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 151.3, 146.1, 143.9, 138.0, 136.2, 129.3, 128.8, 128.7, 125.6, 123.4, 119.7, 98.1.

1,10-Phenanthroline-2,9-dicarboxylic acid (10):[42] mp 238 °C (dec.) (lit. 238 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.74 (d, *J* = 8.2 Hz, 2H, H4 + H7), 8.43 (d, *J* = 8.2 Hz, 2H, H3 + H8), 8.21 (s, 2H, H5 + H6), 6.4 (s broad, 2 COOH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.1, 148.1, 144.6, 138.1, 130.4, 128.3, 123.3.

1,10-Phenanthroline-2-carboxylic acid (11): 2-Cyano-1,10-phenanthroline (4.9 mmol, 1.0 g) in concentrated HCl (35%, 20 mL) was stirred for 6 hours at 90 °C. After cooling the solution was poured on ice (250 g) and concentrated $NaHCO_3$ was added to pH ~4. A white precipitate was filtered off at 0 °C, and air-dried; yield: 1.0 g (4.5 mmol, 91%); mp 263–265 °C (dec.); ^{1}H NMR (400 MHz, D_2O): δ = 7.74 (d, *J* = 5.2 Hz, 1H, H9), 7.69 (d, *J* = 8.2 Hz, 1H, H7), 6.94 (dd, *J* = 8.2 Hz, 5.5 Hz, 1H, H8), 6.82 (d, *J* = 8.4 Hz, 1H, H3), 6.58, (d, *J* = 8.3 Hz, 1H, H4), 6.55 (d, *J* = 9.0 Hz, 1H, H6), 6.42 (d, *J* = 9.0 Hz, 1H, H5); ^{13}C NMR (100 MHz, D_2O): δ = 168.0, 149.1, 148.0, 144.7, 139.8, 138.0, 137.1, 131.7, 131.0, 130.4, 128.5, 126.9, 126.6.

2-Cyano-1,10-phenanthroline (13):[43] mp 263–265 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.26 (dd, *J* = 4.4 Hz, 1.6 Hz, 1H, H9), 8.40 (d, *J* = 8.2 Hz, 1H, H4), 8.30 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H, H7), 7.94 (d, *J* = 8.5, 2H, H5 and H3), 7.83 (d, *J* = 8.8 Hz, 1H, H6), 7.72 (dd, *J* = 8.1 Hz, 4.4 Hz, 1H, H8); ^{13}C NMR (75 MHz, $CDCl_3$; 12 signals!): δ = 151.9, 146.7, 145.3, 137.3, 136.4, 133.4, 129.9, 129.3, 126.3, 125.8, 124.2, 117.5.

2-*sec*-Butyl-1,10-phenanthroline (14): A solution of *sec*-BuLi (33.3 mmol, 1.3 M in cyclohexane) was added in 2 hours at −10 °C to a solution of 1,10-phenanthroline (30 mmol, 5.4 g) in anhydrous toluene/Et_2O (250 mL/50 mL). The mixture was stirred for 6 h at 0 °C, then overnight at room temperature. Work-up was as usual.[36] The product was purified *via* column chromatography (silica, P. E./Et_2O, 40/60, R_f ~0.04) to afford a yellow syrup; yield: 1.9 g (8.1 mmol, 27%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (dd, *J* = 4.4 Hz, 1.8 Hz, 1H, H9), 8.12 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H, H7), 8.10 (d, *J* = 8.3 Hz, 1H, H4), 7.66 (d, *J* = 8.7, 1H, H5/6), 7.61 (d, *J* = 8.7, 1H, H5/6), 7.52 (dd, *J* = 8.1 Hz, 4.4 Hz, 1H, H8), 7.49 (d, *J* = 8.2 Hz, 1H, H3), 3.49 (q, *J* = 7.2 Hz, 1H, ArCH), 1.82 (m, 2H, CH_2), 1.41 (d, *J* = 7.2 Hz, 3H, $CHCH_3$), 0.95, (t, *J* = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 150.2, 146.2, 145.4, 136.4, 135.9, 128.7, 127.1, 126.4, 125.4, 122.5, 120.4, 44.6, 30.2, 20.7, 12.2.

2,9-Di-*sec*-butyl-1,10-phenanthroline (15)[36] (mixture of isomers): A very pure fraction was obtained *via* column chromatography (silica, CH_2Cl_2, R_f ~0), which solidified upon standing; mp 65–68 °C (uncrystallized); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.4 Hz, 2H, H4 + H7), 7.68 (s, 2H, H5 + H6), 7.50 (d, *J* = 8.2 Hz, 2H, H3 + H8), 3.32 (m, 2H, 2 ArCH), 2.0–1.7 (m, 4H, 2 CH_2), 1.46 (d, *J* = 7.0 Hz, 6H, 2 $CHCH_3$), 1.0–0.8 (t, *J* = 7.3 Hz, 6H, 2 CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 145.5, 136.2, 127.3, 125.5, 120.5, 44.3, 30.3 and 30.1, 20.2 and 20.1, 12.2.

2,9-Bis(trichloromethyl)-1,10-phenanthroline (19):[40] mp 214–215 °C (lit. 214–216 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 8.5 Hz, 2H, H4 + H7), 8.33 (d, *J* = 8.5 Hz, 2H, H3 + H8), 7.96 (s, 2H, H5 + H6); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 143.3, 138.2, 129.2, 127.6, 120.5, 98.2.

Syntheses of Palladium Complexes

(Neocuproine)Pd(OAc)$_2$: A solution of neocuproine (5.5 mmol, 1.25 g) in anhydrous CH_2Cl_2 (20 mL) was added to a solution of $Pd(OAc)_2$ (5.0 mmol, 1.12 g) in anhydrous toluene (100 mL) at room temperature under nitrogen. The mixture was stirred overnight and P. E. (40–60 °C) was added to precipitate the complex. A yellow solid was filtered off, washed with acetone and dried under vacuum; yield: 1.78 g (4.0 mmol, 80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.4 Hz, 2H, H4 + H7), 7.88 (s, 2H, H5 + H6), 7.41 (d, *J* = 8.4 Hz, 2H, H3 + H8), 2.89 (s, 6H, 2 $ArCH_3$), 2.08 (s, 6H, 2 O_2CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.5 (2 CO), 165.2 (C2 + C9), 147.2 (C10a + C10b), 138.5 (C4 + C7), 127.9 (C4a + C6a), 126.7 and 126.4 (C3 + C5 + C6 + C8), 24.5 (2 $ArCH_3$), 23.0 (2 O_2CCH_3).

Other complexes were prepared similarly. Complexation times ran from 5 h for unhindered **8** and **9** to circa 60 h for **15** and **19**.

Syntheses of Substrates

2,6-Dimethylnon-2-en-8-ol: A solution of citronellal (40 mmol, 6.16 g, 7.24 ml) in anhydrous ether (80 mL) was added under nitrogen to a solution of MeMgI (44 mmol) in anhydrous ether (60 mL) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C and then for 1 hour at reflux temperature. The solution was cooled to 0 °C, hydrolysed and neutralised with 1 M HCl to pH ~7. The organic phase was separated; the aqueous phase was extracted with 2 × 50 mL ether. The combined organic phases were washed with water (25 mL) and dried over $MgSO_4$. After filtration the filtrate was concentrated under reduced pressure and the residue was purified *via* bulb-to-bulb distillation (bp 100 °C/0.5 mbar) to afford a colourless liquid; yield: 5.1 g (30 mmol, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.11 (t, *J* = 7.1 Hz, 1H, =CH), 3.90 (m, 1H, C*H*OH), 1.99 (m, 2H), 1.90 (s, 1H, OH), 1.68 (s, 3H, $=CCH_3$), 1.60 (s, 3H, $=CCH_3$), 1.55–1.45 (m, 2H), 1.36 (t, *J* = 6.7 Hz, 2H), 1.18 (t, *J* = 6.3 Hz, 4H), 0.91 (dd, *J* = 6.6 Hz, 2.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$; mixture of stereoisomers): δ = 131.2, 131.2, 124.8, 66.3, 65.6, 46.9, 46.8, 37.7, 37.0, 29.5, 29.1, 25.7, 25.5, 25.4, 24.3, 23.6, 20.0, 19.3, 17.7; MS: *m/z* = 170 (M^+, 15), 137 (7), 109 (55), 96 (46), 95 (46), 87 (67), 82 (100), 81 (55), 69 (75), 67 (41), 55 (50), 45 (52).

1-(*p*-Tolyl)-hept-3-yn-1-ol: BuLi (21 mmol, 1.6 M in hexane) was added under nitrogen to a solution of 1-hexyne (20 mmol, 1.64 g, 2.3 mL) in anhydrous THF (40 mL) at −78 °C. After 1 hour stirring at −78 °C, the mixture was stirred for 1 hour at 0 °C and cooled again to −78 °C. A solution of *p*-tolualdehyde (20 mmol, 2.4 g, 2.4 mL) in THF (20 mL) was added drop-wise and the reaction mixture was allowed to

warm-up to room temperature overnight. Further work-up was as usual. The product was purified *via* bulb-to-bulb distillation (bp 160 °C/0.2 mbar) to afford a colourless oil; yield: 3.2 g (16 mmol, 80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.4 Hz, 2H, H2 + H6), 7.16 (d, *J* = 8.4 Hz, 2H, H3 + H5), 5.39 (s, 1H, ArC*H*OH), 2.34 (s, 3H, $ArCH_3$), 2.26 (dt, *J* = 7.1 Hz, 2.0 Hz, 3H, OH + ≡ CCH_2?), 1.57 – 1.35 (m, 4H, CH_2CH_2), 0.91 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (C1), 137.9 (C4), 129.2 (C3 + C5), 126.6 (C2 + C6), 87.4 (C ≡ C), 80.1 (C ≡ C), 64.6 (CHOH), 30.7 ($CH_2CH_2CH_2$), 22.0 (CH_2CH_3), 21.1 (ArCH3), 18.5 (≡ CCH_2), 13.6 (CH_2CH_3); MS: *m/z* = 202 (M^+, 86), 187 (100), 159 (23), 145 (57), 141 (20), 131 (26), 129 (25), 128 (23), 119 (23), 117 (21), 115 (44), 105 (27), 93 (22), 91 (62), 77 (21), 65 (25), 63 (25), 51 (26), 50 (20).

***p*-Methylsulfonylbenzyl alcohol:**[44] The *p*-methylsulfonylbenzaldehyde (20 mmol, 3.9 g) was reduced in 2 h with $NaBH_4$ (0.3 g) in 96% EtOH (50 mL) at 10 °C. After reaction the solvent was removed and the residue was continuously extracted with warm Et_2O. The product was crystallized from Et_2O to afford white fluffy crystals; yield: 2.54 g (13.7 mmol, 67%); mp 83.5 – 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 6.3 Hz, 2H, H3 + H5), 7.52 (d, *J* = 8.3 Hz, 2H, H2 + H6), 4.78 (s, 2H, $ArCH_2$), 3.03 (s, 3H, SO_2CH_3), 2.56 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6 (C1), 139.1 (C4), 127.4 (C2 + C6), 127.2 (C3 + C5), 64.0 (CH_2O), 44.5 (SO_2CH_3); MS: *m/z* = 186 (M^+, 23), 171 (12), 157 (40), 107 (67), 105 (25), 89 (48), 79 (47), 77 (100), 63 (35), 51 (47), 50 (36), 45 (25).

***p*-Cyanobenzyl alcohol:**[45] *p*-Cyanobenzaldehyde was reduced in a solid phase reaction with $NaBH_4$ on silica. The alcohol was purified *via* bulb-to-bulb distillation (bp 160 °C/0.5 mbar) to afford a colourless oil that solidified upon cooling; yield: 1.80 g (13.5 mmol, 68%); mp 42 – 44 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.4 Hz, 2H, H3 + H5), 7.47 (d, *J* = 8.4, 2H, H2 + H6), 4.76 (s, 2H, $ArCH_2$), 2.43 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C1), 132.2 (C3 + C5), 127.0 (C2 + C6), 118.9 (CN), 111.0 (*C*4-CN), 64.1 (CH_2OH); MS: *m/z* = 133 (M^+, 33), 132 (34), 104 (100), 77 (41), 76 (20), 75 (16), 63 (13), 51 (38), 50 (30).

4-(*tert*-Butyldimethylsilyloxymethyl)benzoic acid methyl ester:[46] To a solution of DMAP (1.0 mmol, 0.12 g) in anhydrous CH_3CN (50 mL) was added solid 4-hydroxymethylbenzoic acid methyl ester (10 mmol, 1.66 g) and consecutively Et_3N (11 mmol, 1.11 g, 1.54 mL). The mixture was stirred for 5 minutes and *tert*-butyldimethylsilyl chloride (10 mmol, 1.51 g) was added. After 45 minutes stirring was stopped, the salts were filtered off, and the residue was washed with ether. About 95% of the solvent was evaporated, the residue was purified *via* column chromatography (10% EtOAc/P. E. 40 – 60, R_f ~ 0.39) to afford a colourless oil; yield: 2.0 g (7.1 mmol, 71%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.1 Hz, 2H, H2 + H6), 7.38 (d, *J* = 8.1 Hz, 2H, H3 + H5), 4.79 (s, 2H, $ArCH_2$), 3.90 (s, 3H, OCH_3), 0.95 (s, 9H, *tert*-Bu), 0.15 [s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (CO), 146.8 (C4), 129.6 (C2 + C6), 128.8 (C1), 125.7 (C3 + C5), 64.5 ($ArCH_2$), 52.0 (OCH_3), 25.9 [$C(CH_3)_3$], 18.4 [$C(CH_3)_3$], − 5.3 [$Si(CH_3)_2$]; MS: *m/z* = 280 (M^+, 0), 265 (1), 223 (35), 193 (13), 149 (23), 121 (27), 90 (30), 89 (37), 75 (17), 59 (30), 57 (100), 56 (22), 45 (25).

4-(*tert*-Butyldimethylsilyloxymethyl)benzyl alcohol: A solution of 4-(*tert*-butyldimethylsilyloxymethyl)benzoic acid methyl ester (5 mmol, 1.4 g) in anhydrous Et_2O (25 mL) was added drop-wise under nitrogen to $LiAlH_4$ (4 mmol, 0.15 g) in Et_2O (25 mL). The reaction mixture was refluxed for 2 hours, cooled to 0 °C, and hydrolyzed. Further work-up was as usual to afford a colourless oil; yield: 0.9 g (3.6 mmol, 71%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (s, 4H, 4 ArH), 4.72 (s, 2H, $ArCH_2$), 4.60 (s, 2H, $ArCH_2$), 2.19 (s, 1H, OH), 0.94 (s, 9H, *tert*-Bu), 0.09 [(s, 6H, $Si(CH_3)_2$)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8 (C1), 139.6 (C4), 126.7 (C3 + C5), 126.3 (C2 + C6), 65.0 ($ArCH_2OH$), 64.8 ($ArCH_2OSi$), 26.0 [$C(CH_3)_3$], 18.4 [$C(CH_3)_3$], − 5.2 [$Si(CH_3)_2$]; MS: *m/z* = 252 (1), 237 (2), 195 (100), 177 (20), 165 (46), 121 (43), 91 (27), 75 (62).

Syntheses of Products

***p*-Cyanobenzaldehyde:** MS: *m/z* = 131 (M^+, 52), 130 (100), 102 (65), 76 (42), 75 (34), 51 (36), 50 (42).

1-(*p*-Tolyl)-hept-3-yn-1-one: MS: *m/z* = 200 (M^+, 44), 185 (25), 171 (26), 158 (100), 157 (25), 129 (54), 128 (28), 119 (94), 115 (20), 109 (21), 91 (63), 79 (34), 65 (40), 51 (20).

***m*-Iodobenzaldehyde:** MS: *m/z* = 232 (M^+, 100), 231 (63), 203 (26), 127 (26), 105 (12), 77 (65), 76 (62), 75 (20), 74 (29), 51 (62), 50 (79).

***p*-Thiomethylbenzaldehyde:** MS: *m/z* = 152 (M^+, 100), 151 (74), 123 (M^+, 21), 109 (31), 108 (24), 82 (20), 77 (25), 74 (30), 69 (41), 51 (55), 50 (68), 45 (95).

***p*-(*tert*-Butyldimethylsilyloxymethyl)benzaldehyde:** MS: *m/z* = 250 (M^+, ~0), 193 (51), 163 (15), 119 (25), 91 (99), 90 (23), 89 (25), 75 (32), 65 (25) 63 (27), 59 (34), 57 (100), 51 (28), 45 (37).

***p*-Methylsulfonylbenzaldehyde:** MS: *m/z* = 184 (M^+, 36), 169 (14), 122 (62), 121 (33), 105 (77), 78 (68), 77 (61), 63 (100), 51 (75), 50 (51), 47 (41), 45 (64).

2,6-Dimethylnon-2-en-8-one: MS: *m/z* = 168 (M^+, 18), 135 (18), 110 (54), 95 (85), 85 (40), 69 (100), 67 (65), 56 (31), 55 (72), 53 (68), 51 (52), 50 (36).

Parallel Catalytic Experiments

Parallel catalytic screening trials were performed in an orbitally shaken multi-autoclave unit, which has a maximum operating pressure of 30 bar and a maximum reaction temperature of 150 °C. The unit contains 24 reactors, each provided with a Teflon™ insert. The unit performed best when the reactors were filled with *ca.* 2 mL of reaction mixture. For effective stirring, a metal stirring rod was added to each reactor. The reactors were filled with catalyst, substrate, solvent and internal standard (*n*-heptane, *n*-octane or *n*-dodecane). Subsequently the reactor block was closed and each reactor was pressurised through a manifold with air. The reactors were heated uniformly in a steel heating block, while agitating the reactor contents by vortex mixing. The total gas uptake was monitored. After reaction the reactor block was cooled to room temperature and depressurized. Water (0.5 mL) was added to each reaction mixture, the products were extracted with Et_2O, the organic layers were washed with water, dried over $MgSO_4$ and analyzed with GC.

Catalytic Experiments (Large Scale)

Standard catalytic experiments were carried out in a closed Hastelloy C autoclave (175 mL). The (neocuproine)$Pd(OAc)_2$

catalyst (0.02 mmol, 8.6 mg) and $NaOAc \cdot 3\,H_2O$ (1.0 mmol) were dissolved in 1:1 DMSO/water (50 mL). The autoclave was charged with the catalyst solution, alcohol (20 mmol) and internal standard (*n*-heptane, *n*-octane or *n*-dodecane) and was pressurised with 8% O_2 in N_2 and heated to 100 °C (30 – 60 bar), while stirring at 750 rpm. After reaction the autoclave was cooled to room temperature and depressurised. The product mixture was extracted with Et_2O, and the organic layer was washed with water and dried over $MgSO_4$. For water/DMSO mixtures above 50 – 55 vol% water, virtually no DMSO is extracted with ether. Below this value, the organic layer can be washed with water to remove DMSO. A different external standard (*n*-dodecane or *n*-hexadecane) was added to the organic solutions and the latter were analysed by GC/MS. Recoveries were always 98 ± 4% with this procedure. No blank reaction was observed. Isolated yields were generally above 90%.

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References and Notes

[#] For Part 22, see G.-J. ten Brink, I. W. C. E. Arends, M. Hoogenraad, G. Verspui, R. A. Sheldon, *Adv. Synth. Catal.* **2003**, *345*, 497 – 505.

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