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Cyanation of Aryl Bromides with $K_4[Fe(CN)_6]$ Catalyzed by Dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium, a Molecular Source of Nanoparticles, and the Reactions Involved in the Catalyst-Deactivation Processes

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Abstract: Dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2PdCl_2]$ (**1**) is a highly active and generally applicable C−C cross-coupling catalyst. Apart from its high catalytic activity in Suzuki, Heck, and Negishi reactions, compound **1** also efficiently converted various electronically activated, nonactivated, and deactivated aryl bromides, which may contain fluoride atoms, trifluoromethane groups, nitriles, acetals, ketones, aldehydes, ethers, esters, amides, as well as heterocyclic aryl bromides, such as pyridines and their derivatives, or thiophenes into their respective aromatic nitriles with $K_4[Fe(CN)_6]$ as a cyanating agent within 24 h in NMP at 140 °C in the presence of only 0.05 mol % catalyst. Catalyst-deactivation processes showed that excess cyanide efficiently affected the molecular mechanisms as well as inhibited the catalysis when nanoparticles were involved, owing to the formation of inactive cyanide complexes, such as $[Pd(CN)_4]^{2-}$, $[(CN)_3Pd(H)]^{2-}$, and $[(CN)_3Pd(Ar)]^{2-}$. Thus, the choice of cyanating agent is crucial for the success of the reaction because there is a sharp balance between the rate of cyanide production, efficient product formation, and catalyst poisoning. For example, whereas no product formation was obtained when cyanation reactions were examined with $Zn(CN)_2$ as the cyanating agent, aromatic nitriles were smoothly formed when hexacyanoferrate(II) was used instead. The reason for this striking difference in reactivity was due to the higher stability of hexacyanoferrate(II), which led to a lower rate of cyanide production, and hence, prevented catalyst-deactivation processes. This pathway was confirmed by the colorimetric detection of cyanides: whereas the conversion of β-solvato-α-cyanocobyrinic acid heptamethyl ester into dicyanocobyrinic acid heptamethyl ester indicated that the cyanide production of $Zn(CN)_2$ proceeded at 25 °C in NMP, reaction temperatures of >100 °C were required for cyanide production with $K_4[Fe(CN)_6]$. Mechanistic investigations demonstrate that palladium nanoparticles were the catalytically active form of compound **1**.

Keywords: aminophosphines · cyanides · deactivation · nanoparticles · palladium

Introduction

Aromatic nitriles are of great importance in organic and medicinal chemistry as they are integral moieties in various natural products, pharmacologically and biologically active compounds, herbicides, agrochemicals, and dyes.[1,2] Moreover, they also have applications as synthetic intermediates that can be converted into various other functional groups, such as aldehydes, amines, nitrogen-containing heterocycles, benzoic-acid derivatives, etc.[3–11] Thus, benzonitriles are highly valuable synthetic targets. Classical synthetic methods for their preparation include the Rosenmund von Braun reaction,[12] the diazotization of anilines followed by the Sandmeyer reaction, and the ammoxidation of toluene (and its derivatives).[13,14] However, these methods suffer from major drawbacks, such as the generation of equimolar amounts of heavy-metal waste and the need for very high reaction temperatures. Therefore, the transition-metal-catalyzed cyanation of aryl halides (Scheme 1) offers an efficient and powerful alternative for the high-yielding synthesis of aromatic nitriles under relatively mild reaction conditions, and thus has applications in process and medicinal chemistry as well as in ligand synthesis.[15]

$$\text{Ar-Br} + \text{CN}^- \xrightarrow{\text{Pd catalyst}} \text{Ar-CN} + \text{Br}^-$$

Scheme 1. Palladium-catalyzed cyanation of aryl bromides.

Besides nickel- and copper-catalyzed cyanation reactions,[16,17] palladium, for which molecular mechanisms (Pd^0/Pd^{II}) as well as catalytic cycles that involve nanoparticles have been proposed, is still the metal of choice for this transformation.[18–21] Even though recent developments have

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considerably increased the activity of cyanation catalysts to the point at which some tolerate the reaction of sterically hindered substrates or nonactivated aryl chlorides,[19e–i] even at temperatures below 100 °C,[19j,k] a typical reaction procedure still requires prolonged reaction times (up to 18 h), high reaction temperatures (140 or 160 °C), and catalyst loadings of up to 10 mol % for efficient product formation. Moreover, modified reaction conditions (catalyst loadings and reaction temperatures) are often required for different substrates. In addition, most catalysts suffer from low functional-group tolerance and/or from an unpredictable reactivity pattern. Therefore, the development of new, stable, and easy accessible cyanation catalysts that efficiently and reliably operate under uniform reaction conditions and also widen the scope of this reaction is of great importance for both academic and industrial applications.

Herein, we report the catalytic performance of dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2PdCl_2]$ (**1**), a universally applicable C−C cross-coupling catalyst, in the cyanation of (heterocyclic) aryl bromides with $K_4[Fe(CN)_6]$, which, apart from its environmental advantages, is cheap and—in contrast to all other sources of cyanide—nontoxic.[22] Furthermore, investigations into catalyst-deactivation processes have shown that excess cyanide affects both the molecular mechanisms at every step of the cycle as well as catalytic cycles where nanoparticles are involved. Moreover, colorimetric cyanide detection has shown that cyanide production with hexacyanoferrate(II) requires reaction temperatures of >100 °C (in contrast to, for example, $Zn(CN)_2$, where cyanides are already produced at 25 °C) and thus, provides a simple explanation for the high catalytic activity of compound **1** in the cyanation of aryl bromides with $K_4[Fe(CN)_6]$ as the cyanation agent, whilst almost no product formation was observed when $Zn(CN)_2$ was applied.

Results and Discussion

Catalyst synthesis: $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2PdCl_2]$ (**1**) was quantitatively formed within a few minutes by the treatment of a suspension of commercially available $[PdCl_2(cod)]$ (cod = cycloocta-1,5-diene) in toluene with two equivalents of 1-(dicyclohexylphosphanyl)piperidine at 25 °C under a N_2 atmosphere (Scheme 2).[23] Compound **1** was assumed to be the ideal cyanation catalyst because it has been demonstrated to efficiently promote both molecular (Pd^0/Pd^{II}) mechanisms and catalytic cycles involving nanoparticles.[24]

$$[PdCl_2(cod)] \xrightarrow[\text{toluene, 10 min, RT}]{2\ P(Cy)_2(NC_5H_{10})} [(P\{(NC_5H_{10})(C_6H_{11})_2\})_2PdCl_2]$$

Scheme 2. Synthesis of dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium (**1**).

Whereas palladium nanoparticles were demonstrated to be the catalytically active form of compound **1** in Suzuki and Heck reactions,[24a,b] a homogeneous Pd^0/Pd^{II} mechanism was found to be operative in the Negishi reaction.[24c] However, mechanistic investigations demonstrated that palladium nanoparticles were the catalytically active form of compound **1** in the cyanation of aryl bromides.

Reaction conditions: To establish the most-efficient reaction conditions for the cyanation of aryl bromides with compound **1**, the reaction temperature, solvent, and base were varied, using 1-bromo-4-methoxybenzene as the aryl bromide (Table 1). The cyanating agent, potassium hexacyanoferrate(II) was not varied in these optimization experiments because all other cyanide sources tested, such as NaCN, KCN, and $Zn(CN)_2$ were found to be inferior.

Table 1. Initial optimization experiments for the cyanation of 1-bromo-4-methoxybenzene with $K_4[Fe(CN)_6]$, catalyzed by **1** under N_2-atmosphere.[a]

Entry	Base	Solvent	Cat. [mol %]	Equiv. $K_2[Fe(CN)_6]$	Conv. [%][b]
1	Na_2CO_3	NMP	0.05	0.25	97
2	K_2CO_3	NMP	0.05	0.25	47
3	NaOAc	NMP	0.05	0.25	30
4	K_3PO_4	NMP	0.05	0.25	1
5	$K_3PO_4 \cdot xH_2O$	NMP	0.05	0.25	0
6	NaOH	NMP	0.05	0.25	3
7	*t*BuOK	NMP	0.05	0.25	0
8	*t*BuONa	NMP	0.05	0.25	0
9	NEt_3	NMP	0.05	0.25	0
10	lutidine	NMP	0.05	0.25	0
11	Na_2CO_3	DMAc	0.05	0.25	89
12	Na_2CO_3	DMF	0.05	0.25	76
13	Na_2CO_3	1-hexanol	0.05	0.25	5
14	Na_2CO_3	ethylene glycol	0.05	0.25	3
15	Na_2CO_3	DMSO	0.05	0.25	0
16	Na_2CO_3	*p*-xylene	0.05	0.25	0
17	Na_2CO_3	NMP (2 mL)	0.05	0.25	100
18	Na_2CO_3	NMP (8 mL)	0.05	0.25	24[c]
19	Na_2CO_3	NMP	0.05	0.167	78
20	Na_2CO_3	NMP	0.05	0.333	100
21	Na_2CO_3	NMP	0.05	0.5	99
22	Na_2CO_3	NMP	0.05	1.0	56
23	Na_2CO_3	NMP	0.5	0.25	27
24	Na_2CO_3	NMP	0.2	0.25	93
25	Na_2CO_3	NMP	0.01	0.25	3

[a] Reaction conditions: 1-bromo-4-methoxybenzene (1.0 mmol), $K_4[Fe(CN)_6]$, base (1.0 mmol), solvent (4.0 mL total, unless otherwise stated), 140 °C, 6 h. [b] Determined by GCMS, based on the aryl halide. [c] Conversion obtained after 18 h.

Interestingly, whilst comparable conversion rates and yields were obtained for compound **1** at 140 and 120 °C,[25] a dramatic drop in activity was noticed when the reaction temperature was 100 °C; no catalytic activity was obtained when the reaction temperature was lowered further. Dramatic effects were also noticed when changing the solvent or base: For example, whereas 1-bromo-4-methoxybenzene was almost quantitatively converted into 4-methoxybenzonitrile within 6 h in *N*-methylpyrrolidone (NMP, 4 mL total) at 140 °C with Na_2CO_3 as the base (0.05 mol % catalyst and 0.25 equiv $K_4[Fe(CN)_6]$ relative to the aryl bromide), only 47 % and 30 % of the benzonitrile was obtained when K_2CO_3 and NaOAc were used as the base, respectively (Table 1, entries 1–3). Only trace amounts (<3 %) of 4-methoxybenzonitrile were detected when NaOH, *t*BuONa, *t*BuOK, K_3PO_4 or its hydrate were employed instead (Table 1, entries 4–8). By analogy, the use of amines, such as NEt_3 or lutidine, were also not appropriate because they efficiently inhibited the catalysis (Table 1, entries 9 and 10).

Similar effects were noticed by changing the solvent: whilst comparable performances were obtained for NMP and *N,N*-dimethylacetamide (DMAc), replacing these solvents with DMF led to a drop in activity (Table 1, entries 11 and 12). Notably, product formation of up to 5 % was found when protic solvents, such as 1-hexanol and ethylene glycol, were used (Table 1, entries 13 and 14).[26–28] However, no product formation was observed at all when the cyanation reactions were performed in DMSO or *p*-xylene (Table 1, entries 15 and 16). Moreover, the amount of solvent also strongly influenced the catalytic performance of compound **1**, according to the expected trend: the smaller the solvent/substrate ratio, the higher the conversion rate (Table 1, entries 1, 17, and 18; Figure 1). The amount of cyanating agent also had an influence on the rate of conversion and on product yields: whereas a successive increase in activity was observed when the amount of $K_4[Fe(CN)_6]$ was raised from 0.167 to 0.25 equivalents (relative to the aryl bromide), essentially the same level of activity was found within the range 0.25–0.5 equivalents. However, when the amount of cyanating agent was increased further, a successive drop in activity was noticed (Table 1, entries 19–22). For example, whereas almost-quantitative product formation was achieved within 6 h when 1-bromo-4-methoxybenzene was coupled with 0.25 equiv of $K_4[Fe(CN)_6]$ (NMP, 140 °C, Na_2CO_3, 0.05 mol % catalyst), only 56 % yield was achieved when the cyanation reaction was performed with an equimolar amount of $K_4[Fe(CN)_6]$. The same trend was noted by changing the amount of catalyst. Whereas the best results were achieved with 0.05 mol % compound **1**, decreased conversion rates and yields were noted when the amount of catalyst was lowered. The same observations were made when the reaction was performed with increased amounts of catalyst, presumably owing to the formation of palladium black (Table 1, entries 23–25).

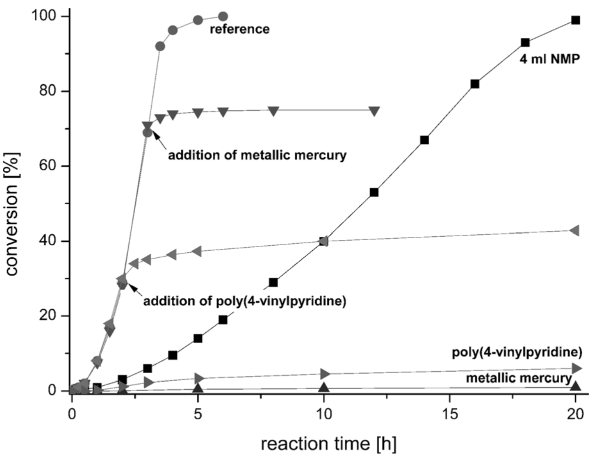


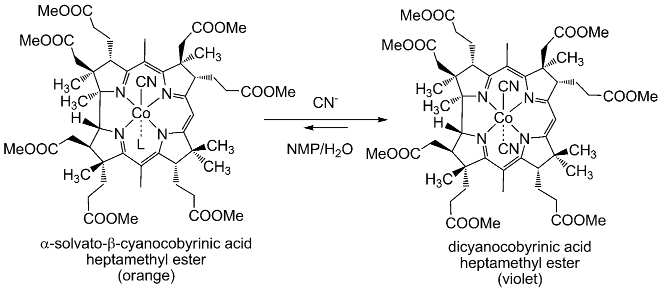
Figure 1. Kinetics of the cyanation of 1-bromo-4-methoxybenzene (1.0 mmol) with $K_4[Fe(CN)_6]$ (0.25 mmol) in the presence and absence of additives, catalyzed by 0.05 mol % of dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium (**1**) at 140 °C in NMP (2.0 mL).

Catalyst-deactivation processes and colorimetric cyanide detection: The decreased catalytic activity of compound **1** in the presence of a large excess of cyanating agent was assumed to be a result of the higher concentration of "free" cyanide ions in solution, and hence, (partial) catalyst deactivation owing to the formation of (catalytically inactive) palladium(II)–cyano complexes, such as $[Pd(CN)_4]^{2-}$, $[(CN)_3Pd(H)]^{2-}$, and $[(CN)_3Pd(Ar)]^{2-}$.[29] Indeed, when an excess (about 5 equiv) of $[Bu_4N]^{13}CN$ ($\delta = 161.7$ ppm) was added to a solution of compound **1** in NMP, $[Pd(^{13}CN)_4]^{2-}$ ($\delta = 126.4$ ppm) was instantly and quantitatively formed at 25 °C [Eq. (1)]. Similarly, $[Pd(^{13}CN)_4]^{2-}$ was detected when an excess (about 20 equiv relative to Pd) of $[Bu_4N]^{13}CN$ was added to a suspension of palladium on charcoal (5 %) in NMP and stirred for 18 h at 25 °C [Eq. (2)]. Furthermore, when an excess (about 20 equiv) of $[Bu_4N]^{13}CN$ was added to a solution of $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd]$[24c] in NMP at 25 °C, $[(^{13}CN)_3Pd(H)]^{2-}$ (^1H NMR: $\delta = -10.8$ ppm (dt, $J_{CH} = 64.9$ and 2.6 Hz), $^{13}C\{^1H\}$ NMR: $\delta = 148.2$ and 137.8 ppm) was smoothly and quantitatively formed at 25 °C when trace amounts of water were present.[29] Subsequent heating (140 °C) of these reaction mixtures induced their complete conversion into $[Pd(^{13}CN)_4]^{2-}$ within 18 h [Eq. (1)].

$$\underset{(\mathbf{1})}{[(PR_3)_2Pd^{II}Cl_2]} \xrightarrow[\substack{\text{NMP, 25°C} \\ -2\,PR_3,\ 2\,NBu_4Cl}]{[NBu_4]CN} [Pd^{II}(CN)_4]^{2-} \xleftarrow[\substack{NMP/H_2O,\ 140°C \\ -H_2,\ NBu_4OH}]{[NBu_4]CN} [(CN)_3Pd^{II}(H)]^{2-} \xleftarrow[\substack{NMP/H_2O,\ 25°C \\ -2\,PR_3,\ NBu_4OH}]{[NBu_4]CN} [Pd^0(PR_3)_2] \quad (1)$$

$$Pd/C\ (5\%) \xrightarrow[\substack{NMP/H_2O,\ 25°C \\ -H_2,\ -2KOH}]{[NBu_4]CN} [Pd^{II}(CN)_4]^{2-} \not\xleftarrow[NMP/H_2O,\ 140°C]{K_4[Fe(CN)_6]} Pd/C\ (5\%) \quad (2)$$

Even though $[(CN)_3Pd(Ar)]^{2-}$ may be considered as an intermediate in both molecular mechanisms and in catalytic cycles where palladium nanoparticles are involved, reductive elimination of the respective benzonitrile was recently shown to occur from tricoordinate $[(CN)_2Pd(Ar)]^-$, and therefore required the predissociation of one of the cyanide groups from $[(CN)_3Pd(Ar)]^{2-}$.[30] However, cyanide dissociation from $[(CN)_3Pd(Ar)]^{2-}$ is known to be efficiently inhibited in the presence of even small quantities of cyanide in solution: whereas reductive elimination of benzonitrile was observed at 25 °C when up to 3 equivalents of cyanide ($[Bu_4N]CN$) were added to a solution of $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(Br)(Ph)]$ in NMP,[24c] the formation of the aromatic nitrile was not detectable when 4 equivalents (or more) of $[Bu_4N]CN$ were present.[30] Consequently, the presence of cyanide inhibits catalysis, independent of the character of the catalytically active species of compound **1**, and hence, independent of an operative molecular mechanism or a catalytic cycle where palladium nanoparticles are involved. The addition of an excess (about 10 equiv relative to the catalyst) of $[Bu_4N]^{13}CN$ to the cyanation reaction catalyzed by compound **1** efficiently inhibited catalysis owing to the formation of $[Pd(^{13}CN)_4]^{2-}$ and $[Pd(^{13}CN)_2]$ ($\delta = 116.2$ ppm), as confirmed by NMR spectroscopy of the reaction mixtures. The same was true for KCN or $Zn(CN)_2$, which demonstrated the crucial role of the cyanating agent in the successful cyanation of aryl halides and illustrated the sharp balance between the rate of cyanide generation, efficient product formation, and catalyst deactivation owing to excess cyanide. Indeed, whereas, for example, the generation of cyanide in a solution of $Zn(CN)_2$ in NMP was indicated by its colorimetric detection with the corrin-based chemosensor β-solvato-α-cyanocobyrinic acid heptamethyl ester (Scheme 3) at 25 °C (the reaction of β-solvato-α-cyanocobyrinic acid heptamethyl ester with cyanide yielded the dicyanocobyrinic acid heptamethyl ester and was accompanied by a characteristic color change from orange to violet, with the absorption maxima for the α-band at $\lambda_{max} = 587$ nm),[31] thermal treatment (>100 °C) was required to induce cyanide production with hexacyanoferrate(II), and hence its colorimetric detection.



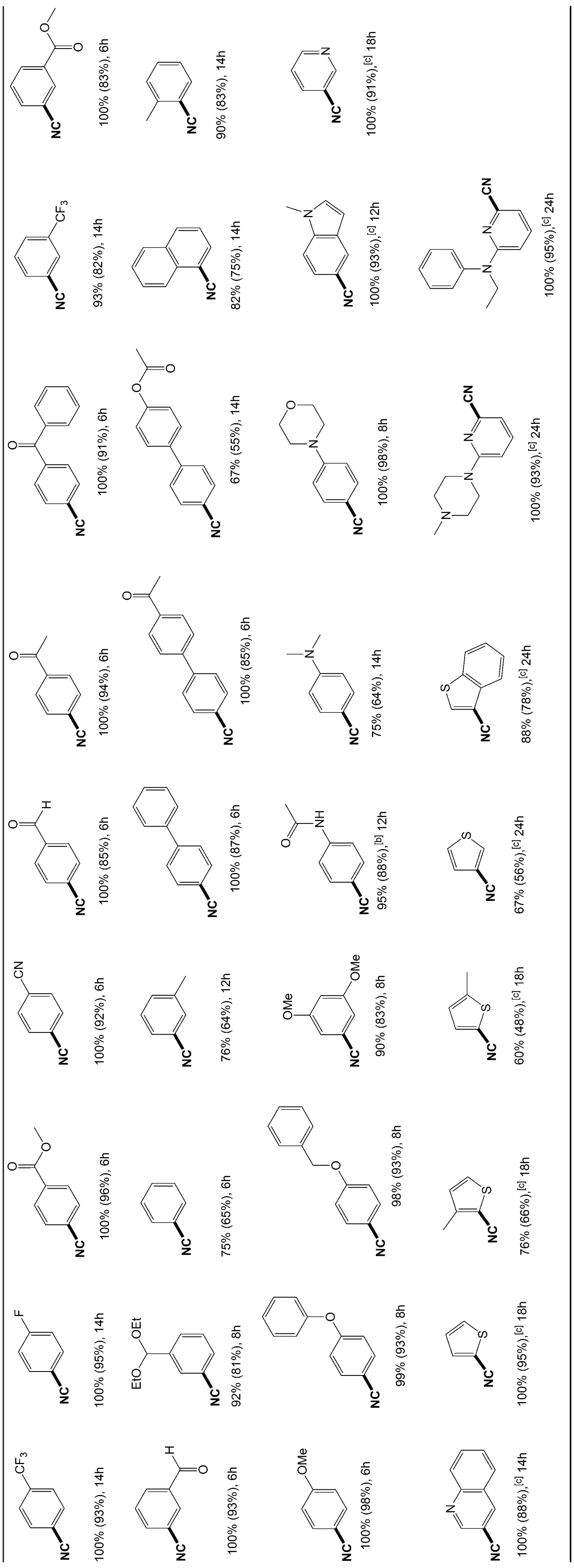
Scheme 3. Colorimetric detection of cyanide in NMP solutions of $K_4[Fe(CN)_4]$ (at 140 °C) and $Zn(CN)_2$ (at 25 °C) with the corrin-based chemosensor β-solvato-α-cyanocobyrinic acid heptamethyl ester.

Consequently, the (main) reason for the successful cyanation of aryl bromides with $K_4[Fe(CN)_6]$ as the cyanating agent (with catalyst **1**) was the high stability of hexacyanoferrate(II), and thus the slow (optimal) rate of cyanide production under the reaction conditions used. Even though slow cyanide production may also have a retarding effect on catalysis, too fast cyanide production would lead to its excess in the reaction mixture, and hence affect molecular catalytic mechanisms as well as inhibit catalysis when nanoparticles were involved.[32] Indeed, whereas no reaction was observed when about 20 equivalents of $K_4[Fe(^{13}CN)_6]$ were added to a solution of compound **1** in NMP and stirred for 48 h at 25 °C, slow cyanide transfer, and thus the stepwise transformation of compound **1** into $[Pd(^{13}CN)_2]$ and $[Pd(^{13}CN)_4]^{2-}$, was observed at 140 °C. Complete conversion of compound **1** into $[Pd(^{13}CN)_4]^{2-}$ was achieved after 48 h. Similarly, $[Pd(^{13}CN)_4]^{2-}$ was quantitatively formed at 140 °C within 18 h when an excess (about 20 equiv) of $K_4[Fe(^{13}CN)_6]$ was added to a solution of $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd]^{[24c]}$ in NMP [Eq. (3)]. On the other hand, palladium–cyano complexes were not detected when suspensions of palladium on charcoal (5 %) in NMP were thermally treated in the presence of a large excess of $K_4[Fe(^{13}CN)_6]$ for 24 h [Eq. (2)]. Thus, this result indicates that catalyst deactivation with hexacyanoferrate(II) as the cyanating agent was too slow (if observable at all) to be relevant for the catalytic performance of compound **1**, in particular when palladium nanoparticles were its catalytically active form.

$$[Pd^0(PR_3)_2] \xrightarrow[\substack{NMP/H_2O,\ 140^\circ C\\ -2\,PR_3,\ H_2,\ 2\,KOH}]{K_4[Fe(CN)_6]} [Pd^{II}(CN)_4]^{2-} \xleftarrow[NMP,\ 140^\circ C]{K_4[Fe(CN)_6]} [Pd^{II}(CN)_2] \xleftarrow[\substack{NMP,\ 140^\circ C\\ -2\,PR_3,\ 2\,KCl}]{K_4[Fe(CN)_6]} \underset{(\mathbf{1})}{[(PR_3)_2Pd^{II}Cl_2]} \qquad (3)$$

Catalysis: Complex **1** is a highly active, reliable, and versatile cyanation catalyst that efficiently and cleanly converts electronically activated, nonactivated, and deactivated, as well as heterocyclic aryl bromides into their respective benzonitriles (140 °C, NMP solvent, Na_2CO_3 base, 0.05 mol % catalyst, 0.25 equiv $K_4[Fe(CN)_6]$ relative to the aryl bromide, under a N_2 atmosphere) within 6–8 h in typically good to excellent yields (Table 2). For example, the cyanation of electronically activated aryl bromides, such as 4-bromobenzonitrile, 4-bromobenzaldehyde, 1-(4-bromophenyl)ethanone, methyl-4-bromobenzoate, 4-bromobenzophenone or 3-bromobenzaldehyde, 3-bromobenzaldehyde diacetal, and methyl-3-bromobenzoate afforded their respective benzonitriles within 6 h in almost quantitative yields. The same yields but slightly lower conversion rates were noticed when fluorinated aryl bromides, such as 1-bromo-4-(trifluoromethyl)benzene, 1-bromo-3-(trifluoromethyl)benzene, and 1-bromo-4-fluorobenzene were applied. High conversions were also achieved after 6 h when nonactivated aryl bromides, such as phenyl bromide, 1-bromo-3-methylbenzene, 4-bromobiphenyl, and 1-(4′-bromobiphenyl-4-yl)ethanone were applied. The same yield but a retarded conversion was noticed for 4-bromoacetanilide. Further retardation was obtained for 4′-bromobiphenyl-4-yl acetate, for which a moderate yield of 67 % was achieved after 14 h. This result was in contrast to electronically deactivated aryl bromides, such as 1-bromo-4-methoxybenzene, 1-bromo-4-phenoxybenzene, 1-(benzyloxy)-4-bromobenzene, and 1-bromo-3,5-dimethox-

Table 2. Cyanation of aryl bromides with $K_4[Fe(CN)_6]$, catalyzed by **1**.[a]



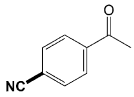
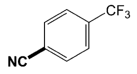
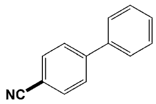
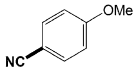
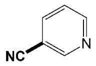
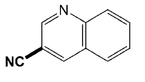
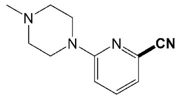
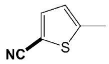
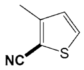
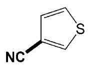
[a] Reaction conditions: aryl bromide (1.0 mmol), $K_4[Fe(CN)_6]$ (0.25 mmol), Na_2CO_3 (1.0 mmol), NMP (2.0 mL), catalyst (0.05 mol %, as a solution in NMP), 140°C; conversions determined by GCMS based on the aryl bromide; yields of isolated products are given in brackets. [b] Reactions were performed in the presence of Na_2CO_3 (2.0 mmol). [c] Reactions were performed in the presence of 0.1 mol % catalyst.

ybenzene, for which full conversions into their respective benzonitriles were typically achieved within only 6–8 h. On the other hand, when nitrogen-containing substrates, such as 5-bromo-1-methyl-1*H*-indole and 4-(4-bromophenyl)morpholine were applied, the same yields but retarded conversions were noticed. For example, whereas the quantitative formation of 4-morpholin-4-yl-benzonitrile into 4-(4-bromophenyl)morpholine was achieved within 8 h, 12 h were required to fully convert 5-bromo-1-methyl-2,3-dihydro-1*H*-indole into 1-methyl-2,3-dihydro-1*H*-indole-5-carbonitrile. Further retardation was found in the cyanation of 4-bromo-*N,N*-dimethylbenzene: 75 % conversion into 4-(dimethylamino)benzonitrile was obtained after 14 h. Whereas similar rates of conversion and yields were obtained when (nonactivated, sterically hindered) 1-bromonaphthalene and 2-bromotoluene were applied, a drop in activity was noted when using 2-bromobenzonitrile as a substrate (46 % conversion after 24 h). Further retardation and even lower product yields (about 30 %) were obtained when *ortho*-substituted aryl bromides with increased electron density, such as 1-bromo-4-methoxy-2-methylbenzene or 1-bromo-2-methoxybenzene, were applied. Almost no catalytic activity was noticed when 2,6-di-substituted aryl bromides, such as 2-bromo-1,3-dimethylbenzene, were applied. Notably, protic substrates, such as phenols, alcohols, carboxylic acids, acetic acids, and primary and secondary amines were not tolerated, most probably owing to HCN formation, and thus afforded their respective benzonitriles in typically < 25 % yield.[26]

On the other hand, an impressive level of activity was typically obtained when cyanation reactions were performed with heterocyclic aryl bromides. For example, whereas quantitative product formation was observed in 14–18 h when 3-bromopyridine, 3-bromoquinoline, and 2-bromothiophene were used as substrates, 24 h was required to achieve conversions of 60–90 % when 3-bromothiophene, 3-bromo-1-benzothiophene, 2-bromo-3-methylthiophene, and 2-bromo-5-methylthiophene were applied. No product formation was observed when 2-bromopyridine was used. However, this result was in striking contrast to 6-bromo-*N*-ethyl-*N*-phenylpyridin-2-amine and 1-(6-bromopyridin-2-yl)-4-methylpiperazine, two randomly chosen 6-bromopyridine-2-amines,[24,33] for which quantitative conversion into 6-[ethyl(phenyl)amino]pyridine-2-carbonitrile and 6-(4-methylpiperazin-1-yl)pyridine-2-carbonitrile was achieved after 24 h, respectively.[34]

Catalytic performance: Dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium (**1**) is a highly active, versatile, easy accessible, and convenient palladium-based cyanation catalyst that was able to convert a large variety of substituted aryl bromides, containing fluoride atoms, trifluoromethane groups, nitriles, acetals, ketones, aldehydes, ethers, esters, amides, as well as heterocyclic aryl bromides, such as pyridines and their derivatives, or thiophenes into their respective aromatic nitriles with $K_4[Fe(CN)_6]$ as the cyanating agent (0.25 equiv) at 140 °C in NMP solvent, with Na_2CO_3 as the base and 0.05 mol % catalyst (or 0.1 mol % when heterocyclic substrates were used). Comparisons with the literature data of other catalysts are difficult to draw because almost every cyanation catalyst operates under different reaction conditions (solvent, reaction temperature, base, catalyst loading, cyanating agent, additive, etc.), which are crucial for their successful application. Therefore, a comparative study was performed between compound **1**, $[Pd(OAc)_2]$,[19b] and $[Pd(OAc)_2]$/dppf (dppf = 1,1′-bis(diphenylphosphino)ferrocene)[19l] (Table 3), for which similar reaction conditions were applied. This study demonstrated that the aminophosphine-based system was indeed one of the most-active cyanation catalysts. For example, whereas conversions of > 95 % for 4-bromobiphenyl or 3-bromoquinoline were observed with all of the catalysts tested (Table 3, entries 3 and 6, respectively), significantly lower conversions of 33, 68, and 56 % were achieved with palladium acetate in the cyanation of 1-(4-bromophenyl)-ethanone, 1-bromo-4-methoxybenzene or 3-bromopyridine, respectively (Table 3, entries 1, 4, and 5). On the other hand, whereas excellent performance was noted for compound **1** and $[Pd(OAc)_2]$ when 1-bromo-4-(trifluoromethyl)-benzene and 3-bromothiophene were used as the substrates (Table 3, entries 2 and 12), lower conversions were observed with $[Pd(OAc)_2]$/dppf. Moreover, significantly improved catalytic activity was found for catalyst **1** when compared to both $[Pd(OAc)_2]$ and $[Pd(OAc)_2]$/dppf in the cyanation of 1-(6-bromopyridin-2-yl)-4-methylpiperazine and 2-bromo-5-methylthiophene (Table 3, entries 7 and 8, respectively): whilst 6-(4-methylpiperazin-1-yl)pyridine-2-carbonitrile was almost quantitatively formed with compound **1**, conversions of 40 and 53 % were achieved with palladium acetate and $[Pd(OAc)_2]$/dppf, respectively. Similarly, whilst a conversion of 60 % into 5-methylthiophene-2-carbonitrile was achieved with compound **1**, only 10 and 23 % of the reaction product was achieved with $[Pd(OAc)_2]$ and $[Pd(OAc)_2]$/dppf, respectively. Slightly lower catalytic activity of compound **1** (compared to $[Pd(OAc)_2]$/dppf) was noticed with 2-bromo-3-methylthiophene as the substrate. Overall, the catalytic activity of compound **1** was superior to $[Pd(OAc)_2]$ and comparable to $[Pd(OAc)_2]$/dppf. Therefore, the aminophosphine-based system is one of the most-active cyanation catalysts reported to date. The improved catalytic activity of the aminophosphine-based system in cyanation reactions when compared to other pre-catalysts (see mechanistic investigations below), such as $[Pd(OAc)_2]$, was attributed to the slow and controllable heat-induced degradation of catalyst **1** by hydroxide anions (involving the cleavage of the P–N bond), which resulted in the formation of palladium nanoparticles. Consequently, Na_2CO_3 is an excellent promoter for the mild and controlled formation of nanoparticles from dichlorobis(aminophosphine) complexes of palladium, because hydroxide anions are slowly generated from the equilibrium between HCO_3^-, OH^-, and CO_2.[35] Thus, the formation of small, highly active nanoparticles (the ratio between palladium on the outer rim and palladium on the inside of the particles increased favorable with decreasing particle size) was a direct consequence of the slow release of palladium from catalyst **1**, promoted by hydroxide anions generated by Na_2CO_3.[36]

Table 3. Comparison of compound **1**, $[Pd(OAc)_2]$, and $[Pd(OAc)_2]$/dppf in the cyanation of aryl bromides with $K_4[Fe(CN)_6]$ under a N_2 atmosphere.[a]

Entry	Cyanation product	Catalyst	Conv. [%][b]	*t* [h]
1		**1**	100	6
		$[Pd(OAc)_2]$	33	
		$[Pd(OAc)_2]$/dppf	96	
2		**1**	100	14
		$[Pd(OAc)_2]$	96	
		$[Pd(OAc)_2]$/dppf	83	
3		**1**	100	6
		$[Pd(OAc)_2]$	98	
		$[Pd(OAc)_2]$/dppf	100	
4		**1**	100	6
		$[Pd(OAc)_2]$	68	
		$[Pd(OAc)_2]$/dppf	100	
5[c]		**1**	100	18
		$[Pd(OAc)_2]$	56	
		$[Pd(OAc)_2]$/dppf	100	
6[c]		**1**	100	14
		$[Pd(OAc)_2]$	100	
		$[Pd(OAc)_2]$/dppf	100	
7[c]		**1**	100	24
		$[Pd(OAc)_2]$	40	
		$[Pd(OAc)_2]$/dppf	53	
8[c]		**1**	60	18
		$[Pd(OAc)_2]$	10	
		$[Pd(OAc)_2]$/dppf	23	
9[c]		**1**	76	18
		$[Pd(OAc)_2]$	57	
		$[Pd(OAc)_2]$/dppf	100	
10[c]		**1**	67	24
		$[Pd(OAc)_2]$	72	
		$[Pd(OAc)_2]$/dppf	20	

[a] Reaction conditions: aryl bromide (1.0 mmol), $K_4[Fe(CN)_6]$ (0.25 mmol), base (1.0 mmol), NMP (4.0 mL total), catalyst (0.05 mol %), 140 °C. [b] Determined by GCMS based on the aryl halide. [c] Reactions were performed in the presence of 0.1 mol % catalyst.

Mechanistic investigations: The following experimental observations indicated that compound **1** was indeed a pre-catalyst, which transformed into palladium nanoparticles:[37] 1) The addition of a large excess of metallic mercury to the reaction mixture of an aryl bromide, $K_4[Fe(CN)_6]$, a base, and a catalyst efficiently stopped the catalysis process. Consequently, no product formation was observed when Hg^0 was added at the beginning of the reaction (Figure 1). The same observations were also made when poly(4-vinylpyridine) (PVPy; 2% cross-linked with divinylbenzene) was used.[38,39] 2) Sigmoidal-shaped kinetics with induction periods, which is characteristic for metal-particle formation, and autocatalytic surface growth that can lead to soluble monodisperse nanoclusters (or insoluble bulk-metal formation), were observed in all of the reactions examined.[40] 3) Whilst the presence of 0.1 equivalent of CS_2 or triphenylphosphine (relative to the catalyst) efficiently inhibited the catalysis, only slightly lowered conversion rates and yields were noticed in the presence of about 20 mol% NBu_4Br (relative to the aryl bromide).[41] 4) The UV/Vis spectrum of the reaction mixtures exhibited a continuous absorption, with a steep rise in absorbance at shorter wavelengths. This observation was a clear indication of the presence of palladium nanoparticles (Figure 2).[42] 5) Lastly, catalyst loadings >0.2 mol% led to significantly lower conversions, most probably owing to the formation of inactive palladium black.[43]

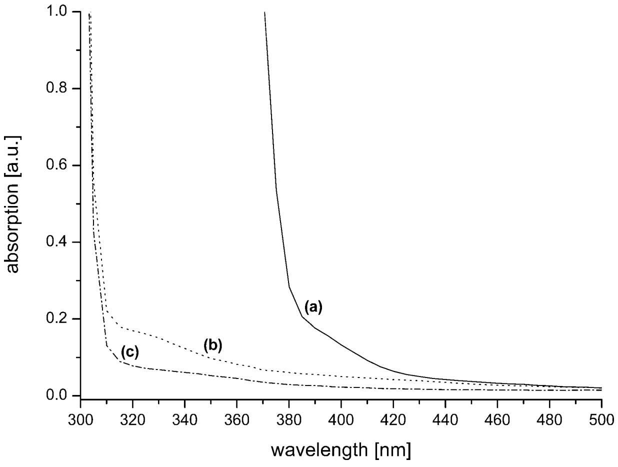


Figure 2. UV/Vis spectra for diluted reaction mixtures of the cyanation of 1-bromo-4-methoxybenzene, recorded after 2 h: a) with $K_4[Fe(CN)_6]$ (0.25 equiv relative to the aryl bromide), catalyzed by 0.1 mol% of compound **1**; b) with $K_4[Fe(CN)_6]$ (0.25 equiv relative to the aryl bromide) in the absence of compound **1**; and c) in the absence of both $K_4[Fe(CN)_6]$ and compound **1**.

Conclusion

Dichloro[bis{1-(dicyclohexylphosphanyl)piperidine}]palladium $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2PdCl_2]$ (**1**) is a highly active and generally applicable C–C cross-coupling catalyst that, apart from successfully catalyzing the Suzuki, Heck, and Negishi reactions, also efficiently converts various electronically activated, nonactivated, and deactivated as well as heterocyclic aryl bromides into their respective benzonitriles in high yields. A comparison study with $[Pd(OAc)_2]$ and $[Pd(OAc)_2]$/dppf showed that the catalytic activity of the aminophosphine-based system was superior to $[Pd(OAc)_2]$ and comparable to $[Pd(OAc)_2]$/dppf under the reaction conditions applied. Catalyst-deactivation processes were studied and excess cyanide was found to efficiently affect the molecular catalytic mechanisms as well as inhibit the catalysis when nanoparticles were involved (owing to the formation of $[Pd(CN)_4]^{2-}$, $[(CN)_3Pd(H)]^{2-}$, and $[(CN)_3Pd(Ar)]^{2-}$). Even though slow cyanide production may retard catalysis, too fast cyanide production led to excess cyanide in the reaction mixtures, thereby affecting the molecular catalytic mechanisms at every step of the cycle as well as inhibiting the catalysis when nanoparticles were involved. Consequently, the choice of cyanating agent is crucial for the successful cyanation of aryl halides. Therefore, the (main) reason for the successful cyanation of aryl bromides with $K_4[Fe(CN)_6]$ as the cyanating agent (at least with catalyst **1**) was its high stability and hence the optimal (slow) rate of cyanide production (at least under the reaction conditions applied). Colorimetric cyanide detection involving the conversion of β-solvato-α-cyanocobyrinic acid heptamethyl ester into dicyanocobyrinic acid heptamethyl ester in NMP indicated that cyanide production with hexacyanoferrate(II) started at reaction temperatures > 100 °C. Mechanistic investigations demonstrated that palladium nanoparticles were the catalytically active form of compound **1**.

Experimental Section

General procedure for the cyanation reactions: In a Young Schlenk tube (10 mL) were added dried $K_4[Fe(CN)_6]$ (0.25 mmol), K_2CO_3 (1.0 mmol), anhydrous 1-methyl-2-pyrrolidinone (NMP, 2.0 mL), aryl bromide (1.0 mmol), and an appropriate amount of catalyst (dissolved in NMP) under a N_2 atmosphere. The mixture was vigorously stirred at 140 °C. Samples were periodically taken from the reaction mixture, quenched with H_2O (or with sat. NH_4Cl when pyridines were used as substrates), extracted with EtOAc, and analyzed by GCMS. At the end of reaction, the mixtures were allowed to cool to RT, quenched with H_2O (or sat. NH_4Cl), and extracted with EtOAc (3×15 mL). The combined extracts were dried ($MgSO_4$) and evaporated to remove the solvent. The crude material was purified by column chromatography on silica gel as necessary.

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lar for the 5-ht$_6$ subtype).[5] Hence, these nitriles are useful for the treatment of diseases for which modulation of the activity of the 5-ht receptor is desired. Thus, 6-aminopyridine-2-carboxamides could find their application in the enhancement of cognition and memory in patients with Alzheimer's disease,[6] in the treatment of attention deficit hyperactivity disorder (ADHD),[7] and in the treatment of diseases of the central nervous system, such as schizophrenia and depression.[8] In addition, 5-ht$_6$-receptor antagonists are useful in the treatment of obesity.[9] Another class of compound with pharmaceutical importance that involve 6-aminopyridine-2-carbonitriles as synthetic intermediates are 3-substituted imidazo-[1,5−*a*]pyridin-5-amines, which are sodium/proton exchange inhibitors that are useful antianginal and cardioprotective agents.[10,11]

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[20] In the classical (Pd^0/Pd^{II}) mechanism, coordinatively unsaturated ($14e^-$) Pd^0 complexes of type $[Pd(L)_2]$ (L = phosphine, etc.) are assumed to be the catalytically active species. The oxidative addition of an aryl halide onto the metal center of $[Pd(L)_n]$ ($n = 1$ or 2) and subsequent transmetalation (with M−CN) yield Pd^{II} intermediates of type $[Pd(Ar)(CN)(L)_n]$ (and M−X). Reductive elimination of Ar−CN regenerates the catalyst.[19c–e]

[21] For examples where palladium nanoparticles have been proposed as the catalytically active form: a) K. Chattopadhyay, R. Dey, B. C. Ranu, *Tetrahedron Lett.* **2009**, *50*, 3164; b) I. P. Beletskaya, A. V. Selivanova, V. S. Tyurin, V. V. Matveev, A. R. Khokholov, *Russ. J. Org. Chem.* **2010**, *46*, 157; c) G. Cheng, J. Wenig, Z. Zheng, X. Zhu, Y. Cai, J. Cai, Y. Wan, *Eur. J. Org. Chem.* **2008**, 3524; d) S. Velmathi, N. E. Leadbeater, *Tetrahedron Lett.* **2008**, *49*, 4693.

[22] $K_4[Fe(CN)_6]$ is nontoxic (the Ld_{50} of $K_4[Fe(CN)_6]$ is lower than that of NaCl) and is even used in the food industry for metal precipitation in wine, see: *Römpp Lexikon Chemie—Version 2.0*, Thieme, Stuttgart/New York, **1999**. $K_4[Fe(CN)_6]$ was recently introduced as a cyanating agent by M. Beller and co-workers.[19l]

[23] J. L. Bolliger, C. M. Frech, *Chem. Eur. J.* **2010**, *16*, 4075.

[24] a) J. L. Bolliger, M. Oberholzer, C. M. Frech, *Adv. Synth. Catal.* **2011**, *353*, 945; b) M. Oberholzer, R. Gerber, C. M. Frech, unpublished results; c) J. L. Bolliger, C. M. Frech, *Chem. Eur. J.* **2010**, *16*, 11072.

[25] Even though reaction temperatures of 120 °C could be used for most of the substrates without a noticeable loss of activity, the advantage of applying 140 °C lay in the reliability and scope of the procedure, which would allow the direct adoption of the procedure to other aryl bromides without the necessity of its modification.

[26] Cyanation reactions performed in protic solvents or with protic aryl halides (see below) are not appropriate because hydrolysis of CN^- into HCN could occur, which competes with the aryl halide for oxidative addition onto the metal center. We assumed that the oxidative addition of HCN onto a bis-phosphine palladium(0) metal center generates palladium–hydride complexes of type $[(PR_3)_2Pd(H)(CN)]$, which can react with another equivalent of HCN to give complexes of the type $[(PR_3)_2Pd(CN)_2]$ and H_2.[27,28]

Subsequent phosphine substitution by cyanide generates $[Pd(CN)_4]^{2-}$, which was indeed formed when the reactions were performed in protic solvents or protic aryl bromides.

[27] a) V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011; b) R. Gerber, T. Fox, C. M. Frech, *Chem. Eur. J.* **2010**, *16*, 6771.

[28] For an excellent paper about the mechanisms of catalyst poisoning in palladium-catalyzed cyanation reactions, see: S. Erhardt, V. V. Grushin, A. H. Kilpatrick, S. A. Macgregor, W. J. Marshall, D. C. Roe, *J. Am. Chem. Soc.* **2008**, *130*, 4828.

[29] a) J. E. Marcone, K. G. Moloy, *J. Am. Chem. Soc.* **1998**, *120*, 8527; b) J. Huang, C. M. Haar, S. P. Nolan, J. E. Marcone, K. G. Moloy, *Organometallics* **1999**, *18*, 297.

[30] K. D. Dobbs, W. J. Marshall, V. V. Grushin, *J. Am. Chem. Soc.* **2007**, *129*, 30.

[31] a) C. Männel-Croisé, F. Zelder, *Inorg. Chem.* **2009**, *48*, 1272; b) C. Männel-Croisé, B. Probst, F. Zelder, *Anal. Chem.* **2009**, *81*, 9493.

[32] Another reason for the high catalytic performance of compound **1** with $K_4[Fe(CN)_6]$ as the cyanating agent might be the reduction power of hexacyanoferrate(II), which could reduce (inactive)palladium(II)–cyano complexes into catalytically active palladium(0) species. By analogy, hexacyanoferrate(II) could also reduce traces of oxygen and other impurities from the reaction mixture.

[33] J. L. Bolliger, C. M. Frech, *Tetrahedron* **2009**, *65*, 1180.

[34] Notably, even though full conversion of 1-(6-bromopyridin-2-yl)-4-methylpiperazine into 6-(4-methylpiperazin-1-yl)pyridine-2-carbonitrile was achieved within 24 h, no product formation was noted when 2-bromo-6-piperidin-1-ylpyridine or 4-(6-bromopyridin-2-yl)-morpholine were used. The reason for the striking difference in reactivity of these structurally closely related compounds is unknown. Nevertheless, because no product formation at all was observed when $[Pd(OAc)_2]$ or $[Pd(OAc)_2]$/dppf (dppf = 1,1′-bis(diphenylphosphino)ferrocene) was used as the catalyst, it cannot be excluded that trace amounts of an impurity is the reason for their unsuccessful cyanation.

[35] X. Wang, W. Conway, R. Burns, N. McCann, M. Maeder, *J. Phys. Chem. A* **2010**, *114*, 1734.

[36] The morphologies of the nanoparticles also determine their catalytic activity. However, nanoparticle morphology decisively depends on the conditions in which they are grown, such as the concentration of palladium and the rate of catalyst degradation, and hence, on the rate of nanoparticle growth, the presence of ligands and other additives, as well as on the palladium source itself. This dependence explains the different catalytic activities of the pre-catalysts. Moreover, apart from the excellent catalytic activity of dichloro-bis(1-(dicyclohexylphosphanyl)piperidine)palladium (**1**) in the cyanation reaction, aminophosphines have an additional advantage when compared to water-insoluble phosphine-based ligand systems: the treatment of compound **1** under work-up conditions in air was recently shown to lead to rapid and complete catalyst degradation into decomposition products that were easily separated from the coupling products—an often ignored but very important issue for the preparation of pharmaceutically active compounds etc.

[37] For a comprehensive review on the problem of distinguishing truly homogeneous catalysis from soluble- or heterogeneous catalysis with other metal particles under reducing conditions, see: J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317.

[38] PVPy is a palladium trap that can effectively inhibit catalysis when nanoparticles are involved in the catalytic cycle. Nevertheless, Pd nanoparticles that were immobilized on PVPy spheres have been applied as catalyst in Heck reactions.[39] Therefore, this test is not definitive and does neither conclusively confirm nor rule out either catalysis by the surface of Pd nanoparticles or by molecular Pd^0 species but can strongly support the conclusions drawn from other tests performed. For details, see: K. Yu, W. Sommer, M. Weck, C. W. Jones, *J. Catal.* **2004**, *226*, 101 and the references therein.

[39] S. Pathak, M. T. Greci, R. C. Kwong, K. Mercado, G. K. S. Prakash, G. A. Olah, M. E. Thompson, *Chem. Mater.* **2000**, *12*, 1985.

[40] a) M. A. Watzky, R. G. Finke, *J. Am. Chem. Soc.* **1997**, *119*, 10382; b) J. A. Widegren, M. A. Bennett, R. G. Finke, *J. Am. Chem. Soc.* **2003**, *125*, 10301.

[41] Tetrabutylammonium bromide is known to stabilize palladium nanoparticles. For example, see: a) T. Jeffery In *Advances in Metal-Organic Chemistry, Vol. 5* (Ed.: L. S. Liebeskind), JAI, Greenwich, **1996**, p 153; b) M. T. Reetz, E. Westermann, *Angew. Chem.* **2000**, *112*, 170; *Angew. Chem. Int. Ed.* **2000**, *39*, 165; c) A. Zapf, M. Beller, *Chem. Eur. J.* **2001**, *7*, 2908.

[42] J. A. Creighton, D. G. Eadon, *J. Chem. Soc. Faraday Trans.* **1991**, *87*, 3881.

[43] a) A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285; b) A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. M. Walet, J. G. de Vries, *Adv. Synth. Catal.* **2002**, *344*, 996; c) M. Beller, H. Fischer, K. Kühlein, C.-P. Reisinger, W. A. Herrmann, *J. Organomet. Chem.* **1996**, *520*, 257.

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