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Pd-Catalyzed Cyanation of (Hetero)Aryl Halides Using Biphosphine Ligands

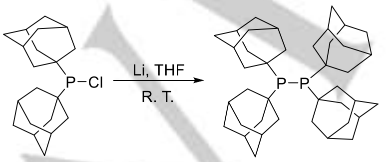
Shaoke Zhang,[a] Helfried Neumann,[a] Matthias Beller*[a]

Abstract: Tetraadamantylbiphosphine (**TABP**) **L1** has been synthesized as a new ligand, which shows superior activity in the palladium-catalyzed cyanation of 4-chloroanisole compared to standard phosphines. The generality of the new catalytic system is shown in the cyanation of around 30 (hetero)aryl halides including hindered, electron-rich and electron-poor aryl chlorides. These reactions constitute the first examples of using biphosphine ligands in Pd-catalyzed coupling reactions.

Ancillary ligands, especially phosphorous-based derivatives have emerged as the most powerful tool to control the activity and selectivity of molecularly-defined catalysts.[1] Among the plethora of phosphine ligands nowadays routinely applied in organometallic catalysis, tertiary mono-[2] and diphosphine ligands[3] dominate. In comparison, the use of secondary phosphines is rare and concentrated so far on secondary phosphine oxides.[4] Moreover, the use of phosphorous compounds with P-P bonds such as biphosphines is one of the first examples in catalysis.[5]

For some time we are interested in the use of phosphines with adamantyl substituents in metal-catalyzed coupling and related reactions.[6] Compared to other bulky phosphines, the introduction of an adamantyl substituent leads to improved stability and the resulting ligands are convenient to handle. As an example for this unusual stability diadamantylphosphine is a stable non-pyrophoric secondary phosphine.[7]

In order to synthesize novel adamantly-based PNP pincer ligands, recently we investigated the lithiation of diadamantylchlorophosphine **L9**, which is conveniently available in two steps from adamantane and PCl_3. Mixing **L9** with lithium in THF and stirring this mixture at room temperature for two days gave a white solid, which gradually precipitated from the solution. After filtration and washing the residue with water tetraadamantylbiphosphine (**TABP**) **L1** was obtained as pure product in 77% yield (Scheme 1).



L1

Scheme 1. Synthesis of tetraadamantlybiphosphine (**TABP**) **L1**

Notably, **TABP** is a highly moisture-stable compound, even in water at 80°C.[8] Due to the extraordinary stability and convenient access we believe that this and related sterically hindered biphosphines have a significant potential for catalysis, organic synthesis, and other fields. However, up to date, the utilization of this kind of phosphorous compounds is scarcely explored.[9]

Based on our renewed interest in metal-catalyzed cyanation reactions,[10] we got attracted to the influence of such potential ligands for the synthesis of aromatic nitriles. The nitrile group is an integral part of several natural products, but also of industrial dyes, herbicides, agrochemicals, and especially pharmaceuticals.[11] Traditionally, aromatic nitriles are prepared by the Rosenmund–von Braun reaction of aryl halides[12] or the diazotization of anilines with subsequent Sandmeyer reaction[13]. On a larger scale, heterogeneously-catalyzed ammoxidation at high temperature (300-550 °C) prevails.[14] All these processes suffer from lack of functional group tolerance or harsh reaction conditions.

Since Takagi et al. reported in 1973 the first example of a Pd-catalyzed cyanation of aryl halides,[15] this method attracted substantial attention.[16] Numerous cyanide sources such as MCN (M = Na, K, etc),[17] $Zn(CN)_2$,[18] acetone cyanohydrin,[19] Toluenesulfonyl Cyanide (TsCN)[20] and trimethylsilyl cyanide (TMSCN)[21] have been exploited for this catalytic transformation.[22] In 2004, we introduced $K_4[Fe(CN)_6]$ as a more benign cyanation source.[23] Since then, we as well as other groups demonstrated the usefulness of this low toxicity reagent in several cyanation reactions.[24] Meanwhile, phosphine ligands play an essential role for the activation of aryl bromide and chloride substrates.[25] In this respect, we report the first metal coupling reactions using biphosphine ligands. More specifically, Pd-catalyzed cyanations of (hetero)aryl halides proceed with good functional group tolerance and the corresponding aryl nitriles are obtained in good to excellent yields.

Initial experiments were performed using 4-chloroanisole **1a** as a benchmark substrate in the presence of different ligands. Based on previous work on cyanation of aryl chlorides,[24f] we used 0.5 mol% $Pd(OAc)_2$, 1 mol% ligand (2 mol% for monophosphines), 20 mol% Na_2CO_3, 0.5 mmol $K_4[Fe(CN)_6]$ at 140 °C in NMP as solvent. As shown in Figure 1, surprisingly tetra-*tert*-butylbiphosphine (**TBBP**) and **TABP** showed better activity than standard phosphines including dppf, PCy_3, PPh_3, $BuPAd_2$ and well-known electron-rich pyrrole- and imidazole-based ligands. In order to prove whether secondary phosphides might be involved as active ligands, di-*tert*-butylphosphine and diadamantylphosphine were tested.[26] However, both ligands induced only minor product formation. Similarly, diadamantylchlorophosphine showed only little activity. Furthermore, to verify if P-C bond formation took place between **TABP** and arenes, Ad_2PPh and Mor-DalPhos (L7 and L14) were

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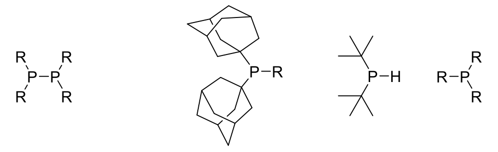
tested as ligands. Interestingly, they gave 41% and 57% yield of the desired product, respectively.

Notably, variation of the substituent of the biphosphine ligand caused a drastic change of the activity. While the adamantly- and *tert*-butyl-based ligands gave 77% and 63% yield, respectively, the phenyl derivative gave only 1% yield.

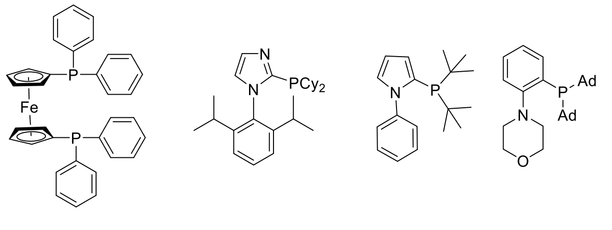


L1: R = Adamantyl (Ad)
L2: R = *t*-Butyl (*t*-Bu)
L3: R = Phenyl (Ph)

L4: R = *n*-Butyl (*n*-Bu)
L5: R = Cl
L6: R = H
L7: R = Ph

L8

L9: R = Ph
L10: R = Cyclohexyl (Cy)



L11 **L12** **L13** **14**

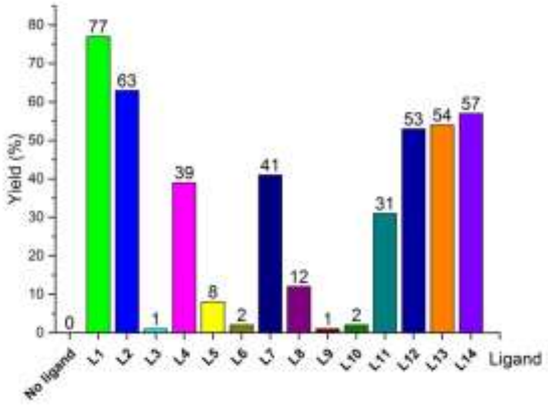
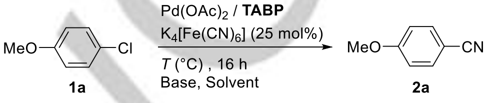


Figure 1. Pd-catalyzed cyanation of 4-chloroanisole in the presence of selected phosphine ligands. Reaction conditions: 4-Chloroanisole (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.5 mol%), ligand (1 mol% for diphosphines, 2 mol% for monophosphines), NMP (2 mL), Na_2CO_3 (20 mol%), 140 °C, 16 h; GC yields with hexadecane as an internal standard.

With these exciting results in hand, we studied the influence of key reaction parameters on this transformation. Selected results are shown in Table 1. Firstly, [Pd] loading and [Pd] ligand ratio were optimized. A two-fold excess of ligand (with respect to [Pd]) and higher loading of [Pd] are favorable for the generation of **2a** (Table 1, entries 1-4). Higher ligand loading decreased the activity, which might be explained by blocking free coordination sites on the central metal (Table 1, entry 5). Increasing the temperature from 120 °C to 140 °C, improved the yield of **2a** from 42% to 83% (Table 1, entry 6). At 160 °C another slight improvement is observed (Table 1, entry 7).

Notably to say, the reaction is quite sensitive to the solvent. Although comparable results could be obtained with NMP and DMAc (Table 1, entry 9), in the presence of other tested solvents very low yield of **2a** were achieved (Table 1, entries 10-12). In agreement with previous findings,[24f] also this novel palladium-catalyzed cyanation is highly sensitive to the base present in the reaction medium. Using other organic and inorganic bases commonly applied in coupling reactions gave less than 20% of **2a** (Table 1, entries 13-18). Optimal results were observed with 20 mol% of inexpensive Na_2CO_3 (Table 1, entry 19).

Table 1. Pd-catalyzed cyanation of 4-chloroanisole **1a**: Influence of different reaction conditions[a]



Entry	[Pd]: Ligand	[Pd] /mol%	Solvent	*T* / °C	Base (mol%)	Yield[b] /%
1	1:2	0.1	NMP	120	Na_2CO_3 (100)	23
2	1:1	0.5	NMP	120	Na_2CO_3 (100)	26
3	1:1.5	0.5	NMP	120	Na_2CO_3 (100)	41
4	1:2	0.5	NMP	120	Na_2CO_3 (100)	42
5	1:3	0.5	NMP	120	Na_2CO_3 (100)	19
6	1:2	0.5	NMP	140	Na_2CO_3 (100)	83
7	1:2	0.5	NMP	160	Na_2CO_3 (100)	90
8	1:2	0.5	DMSO	140	Na_2CO_3 (100)	0
9	1:2	0.5	DMAc	140	Na_2CO_3 (100)	63
10	1:2	0.5	DMF	140	Na_2CO_3 (100)	18
11	1:2	0.5	dioxane	140	Na_2CO_3 (100)	7
12	1:2	0.5	CH_3CN	140	Na_2CO_3 (100)	22
13	1:2	0.5	NMP	140	K_2CO_3 (100)	15
14	1:2	0.5	NMP	140	Cs_2CO_3 (100)	0
15	1:2	0.5	NMP	140	K_3PO_4 (100)	4
16	1:2	0.5	NMP	140	KF (100)	19
17	1:2	0.5	NMP	140	TMEDA (100)	10
18	1:2	0.5	NMP	140	NaO*t*Bu (100)	0
19	1:2	0.5	NMP	140	Na_2CO_3 (20)	77

[a] **1a** (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.1-0.5 mol%), **TABP** (0.2-1.5 mol%), solvent (2 mL), base (20-100 mol%), 16 h, 120-160 °C. [b] Yields were determined by GC analysis using hexadecane as an internal standard.

In order to elucidate the structure of the active catalyst in situ ^{31}P NMR spectroscopic measurements were made. After mixing **TABP** and $Pd(OAc)_2$ in toluene, the parent ligand (δ = 33.70 ppm) was fully converted and mainly two other phosphorous species were detected (δ = 60.01 and 121.70 ppm, ratio of 1:14), which unfortunately could not be assigned. Meanwhile, several attempts to crystallize Pd/TABP complexes were undertaken. However, no suitable crystals for X-ray crystallography were

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obtained. Stirring **TBBP** instead of **TABP** in the presence of $Pd(OAc)_2$ in toluene resulted mainly in the formation of a new phosphorous species at 125.82 in the ^{31}P NMR. Crystallization of this species showed the formation of a phosphido-bridged dimer ((di-*t*-butylphosphinato)-(di-*t*-butylphosphinato)-(di-*t*-butylphosphinous acid)-palladium), which is a known compound.[27] Based on this result, we guess that the P-P bond is cleaved at some point during catalysis. However, the structure of the active complex is yet unknown. Nevertheless, due to the interesting catalytic results in the benchmark system, the substrate scope was further evaluated.

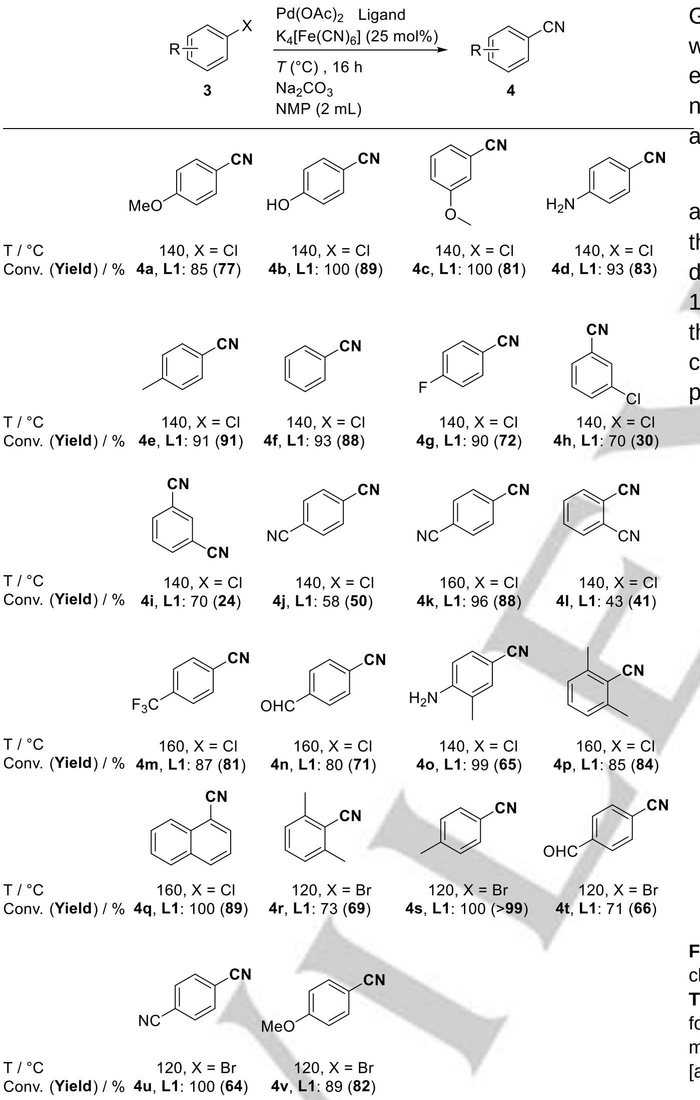

Figure 3. Pd-catalyzed cyanation of aryl halides. Reaction conditions for chlorides: Substrate (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.5 mol%), **TABP** (1 mol%), NMP (2 mL), Na_2CO_3 (20 mol%), 16 h. Reaction conditions for bromides: Substrate (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.1 mol%), **TABP** (0.2 mol%), NMP (2 mL), Na_2CO_3 (1 eq.), 16 h. Conversion and yields were determined by GC using hexadecane as an internal standard.

Next, the substrate scope with respect to aryl chlorides and bromides was tested under the optimal reaction conditions (Figure 3). Using the new **TABP** ligand, aryl chlorides containing electron-donating groups such as –OMe, –Me, –OH, and $–NH_2$, were successfully cyanated to the corresponding nitriles with good to excellent yields (**4a** - **4e**). Substrates having another halide substituent in *para*- or *meta*- position are also converted to the corresponding nitriles (**4g** - **4h**). As a special case, 1,3-dichlorobenzene gave 30% of the single cyanated product and 24% of the double cyanated product (**4h** - **4l**). Furthermore, aryl chlorides containing electron-withdrawing groups such as –CN, –CHO, and $–CF_3$ gave the desired benzonitriles in good to excellent yields (**4j** – **4k**, and **4m** – **4n**), albeit at 160°C. This catalytic system is also successfully applicable to multi-substituted aryl chlorides and chloronaphthalene (**4o** – **4r**). Gratifyingly, sterically hindered 2-chloro-1,3-dimethylbenzene was converted with an excellent yield of 84% to give **4p**. As expected aryl bromides could be converted to the corresponding nitriles **4r** – **4v** with excellent yields at lower temperature (120°C) and catalyst loading (0.1 mol% [Pd]).

For applications in life sciences (pharmaceuticals, agrochemicals), it is interesting to note that **TABP** is effective in the cyanation of heteroaryl halides. As shown in Figure 4 derivatives of quinazoline **6a**, quinoline **6b** - **6c**, pyridine **6d** - **6e**, 1,3-benzodioxole **6f** - **6g**, were all successfully coupled to give the corresponding nitriles in good to excellent yields. However, comparing to **6e**, 2-chloropyridine was much less active in the presence of this catalytic system. [28]

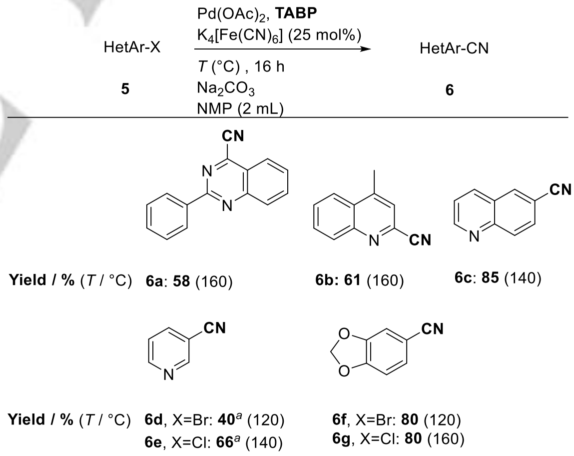

Figure 4. Pd-catalyzed cyanation of heteroaryl halides. Reaction conditions for chlorides: Substrate (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.5 mol%), **TABP** (1 mol%), NMP (2 mL), Na_2CO_3 (20 mol%), 16 h. Reaction conditions for bromides: Substrate (2 mmol), $K_4[Fe(CN)_6]$ (0.5 mmol), $Pd(OAc)_2$ (0.1 mol%), **TABP** (0.2 mol%), NMP (2 mL), Na_2CO_3 (1 eq.), 16 h. Isolated yields. [a] GC yields using hexadecane as an internal standard.

In conclusion, we have synthesized the new biphosphine ligand **L1**, which is stable and can be conveniently handled and prepared. In one of the first examples, this class of ligands is being used in Pd-catalyzed coupling reactions. In more detail, **L1** permits the effective cyanation of various aryl (hetero) chlorides as well as aryl (hetero) bromides. Although the nature of the exact active species remains unknown, we assume further catalytic application of bi- or mutiphosphines, specifically in

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coupling reactions. Further works applying such ligands and to elucidate the active complex are currently under way.

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Keywords: biphosphine • cyanation • Pd catalysts • coupling reaction • aryl halide •

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[28] 2-Chloropyridine was tested under identical conditions compared to 3-chloropyridine. However, the former gave only 10% conversion and 8% yield.

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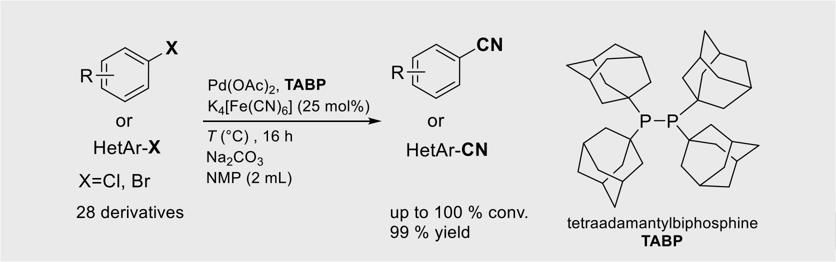

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Pd-Catalyzed Cyanation of (Hetero)Aryl Halides Using Biphosphine Ligands

Give me two phosphorous atoms. A new biphosphine ligand combined with [Pd] allows for smooth cyanation of all kinds of (hetero)aryl chlorides and bromides.

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