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Palladium-Catalyzed Reductive Carbonylation of Aryl Bromides with Phosphinite Ligands

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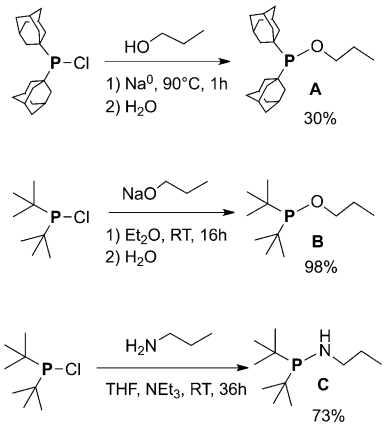
Aromatic aldehydes are an important class of compounds, that are widely used as building blocks in all areas of chemistry.[1] Traditionally, aromatic aldehydes were synthesized by Vielsmeier–Haag, Gattermann–Koch, Reimer–Tiemann, and Duff reactions. However, these reactions use high amounts of reagents and generate waste and side products.[2] Other synthetic strategies include the reduction of acid chlorides under an atmosphere of hydrogen[3] and the direct formylation of aryl bromides, which involves a halogen/metal exchange with *n*BuLi and a formylation agent added at low temperatures.[4] However, this approach is limited to aldehydes that bear stable functional groups. Another route is the palladium-catalyzed carbonylation of aryl halides using expensive silyl-[5] or tin[6] hydrides as the hydrogen source. In 1974, Heck reported a reductive carbonylation of aryl halides using synthesis gas, but relatively high palladium loadings, elevated pressures and temperatures were necessary.[7] In the course of our ongoing investigation of ligand synthesis, we found that di-1-adamantyl-*n*-butylphosphine ($BuPAd_2$) is an outstanding efficient ligand for the palladium-catalyzed reductive carbonylation. By using $BuPAd_2$ as a ligand, various aldehydes were prepared in good yields from the corresponding aryl bromides under mild reaction conditions. This methodology has been realized on an industrial 100 kg scale.[8] Further studies showed that the topology of the $BuPAd_2$, comprising of two large and one small fragment, plays an important role in this reaction. When the two adamantyl groups were substituted by *tert*-butyl groups, the activity did not change, but using tri-*tert*-butylphosphine with three bulky groups resulted in a complete loss of activity.[9] Thus, ligands that are designed to have two bulky groups and one small fragment are potentially suitable for reductive carbonylation reactions. As $BuPAd_2$ is not easy to synthesize and expensive, we believe there is a high demand to find alternative ligands.

Herein, we report the synthesis of phosphinite ligands for reductive carbonylations; these ligands can be prepared in one step and easily modified. The simplest variant of $BuPAd_2$ is obtained by substituting the butyl group with *n*-propanolate. Here the resulting scaffold is identical, but the electronic properties are different. Following the synthesis of phosphinites,[10] propyl diadamantylphosphinite (ligand **A**) was easily obtained by adding Ad_2PCl to in situ formed sodium propionate in *n*-propanol (Scheme 1).



Scheme 1. Syntheses of phosphinite ligands **A**, **B**, and aminophosphine ligand **C**.

Similarly, propyl di-*tert*-butylphosphinite (ligand **B**) can also be synthesized by treating solid sodium *n*-propylate and commercially available $(t\mathrm{Bu})_2PCl$ in diethyl ether. To the best of our knowledge, ligand **A** is a new compound and ligand **B** has only been used in a reaction with CCl_4,[11] but has not been employed as a ligand in coupling reactions. Similarly, the analogous N-containing ligand **C** can be synthesized easily from *n*-propylamine and $(t\mathrm{Bu})_2PCl$ in tetrahydrofuran (THF) at room temperature.[12] Next, we compared the activity of the phophinite ligands **A**, **B**, and **C** with $BuPAd_2$.

Table 1 shows that in the case of 4-bromoanisole and 4-chlorobromobenzene, the activities of the phosphinite ligands **A** and **B** were as good as those of $BuPAd_2$. In the case of ligand **C**, the yield was only 25% and thus no further

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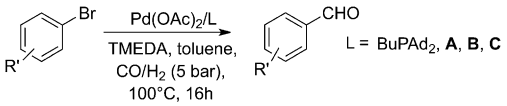
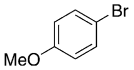
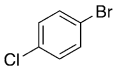
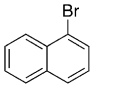
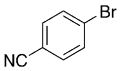
Table 1. Reductive carbonylation using $BuPAd_2$, **A**, **B**, and **C**.[a]



Entry	Ligand	Aryl bromide	Yield [%][b]	Conv. [%][b]
1	$BuPAd_2$		91	100
2	**A**		86	98
3	**B**		92	92
4	**C**		25	25
5	$BuPAd_2$		89	89
6	**A**		93	100
7	**B**		84	94
8	$BuPAd_2$		86	100
9	**A**		58	92
10	**B**		51	96
11	$BuPAd_2$		57	77
12	**A**		23	44
13	**B**		25	44

[a] Reaction conditions: aryl bromide (2 mmol), $Pd(OAc)_2$ (0.25 mol%), TMEDA (0.75 equiv), ligand **B** (1.5 mol%), toluene (2 mL), CO/H_2 (1:1; 5 bar), 100°C, 16 h. [b] Conversion and yields were determined by GC using hexadecane as an internal standard.

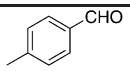
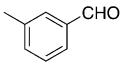
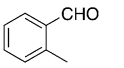
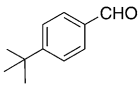
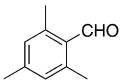
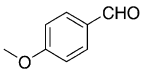
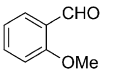
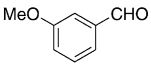
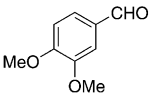
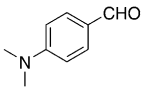
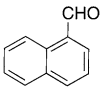
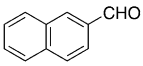
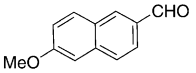
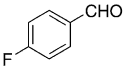
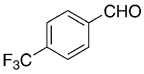
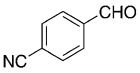
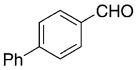
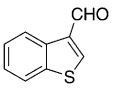
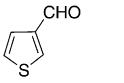
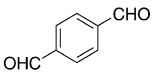
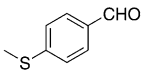
reactions were carried out with this ligand. However, with 1-bromonaphthalene and 4-bromobenzonitrile, the phosphinite ligands **A** and **B** gave significantly lower yields of the corresponding aldehyde than those of $BuPAd_2$. These results indicate that the electronic nature is also important in this reaction. However, when we doubled the catalyst loading of ligand **B** and increased the reaction time, we were able to convert 1-bromonaphthalene and 4-bromobenzonitrile into the desired aldehydes in 83% and 77% yields, respectively (Table 2, entries 11 and 16).

With these new reaction conditions in hand, we were successful in transforming many aryl bromides into their corresponding aldehydes. While sterically unhindered and electronic-rich aryl bromides gave high yields of aldehydes in the range of 72–98% (Table 2, entries 1, 2, 4, 6, 8, 9, 10, and 21), the yields with *ortho*-substituted arene aldehydes reduced to 35–81% (Table 2, entries 3, 5, and 7). Aryl bromides with electron-withdrawing groups were also converted into the corresponding aldehydes in 65–88% yields (Table 2, entries 14–16, and 20). Heteroaryl bromides such as 3-bromobenzothiophene and 3-bromothiophene were successful in the reaction and gave 1-benzothiophene 3-carbaldehyde and 3-thiophenecarbaldehyde in 65 and 82% yield, respectively (Table 2, entries 18 and 19). Unfortunately, 3-bromopyridine and 2-bromobenzothiophene gave no product under these conditions.

As ligand **B** is easy to synthesize, the reductive carbonylation can be further simplified by preparing this ligand in situ. At the beginning of the procedure, ligand **B** can be formed either by simply adding *n*-propanol to a solution of $(t\mathrm{Bu})_2\mathrm{PCl}$ and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) or by reverse addition in which $(t\mathrm{Bu})_2\mathrm{PCl}$ is added to solid sodium propanolate.

According to in situ protocol 1 (Scheme 2) we obtained a 95% yield of benzaldehyde, whereas only a 65% yield

Table 2. Scope and limitations.[a]

Entry	Product	Yield [%][b]	Conv. [%][b]
1		90	100
2		89	99
3		81	99
4		97	99
5		35	60
6		96	99
7		65	72
8		81	98
9		72	88
10		95	99
11		83	91
12		89	100
13		93	99
14		88	99
15		65	100
16		77	90
17		89	99
18		65	89
19		82	100
20		68	84
21		88	95

[a] Reaction conditions: aryl bromide (1 mmol), $Pd(OAc)_2$ (0.5 mol%), TMEDA (0.75 equiv), ligand **B** (1.5 mol%), toluene (2 mL), CO/H_2 (1:1; 5 bar), 100°C, 20 h. [b] Conversion and yield were determined by GC using hexadecane as an internal standard.

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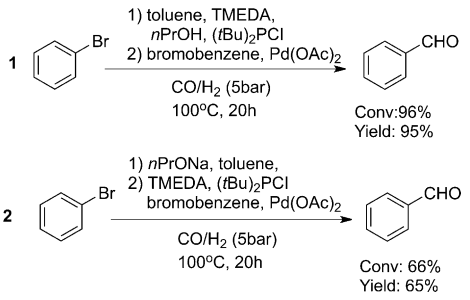

Scheme 2. In situ protocol 1 and 2.

was achieved with the in situ protocol 2. The former protocol is more efficient because $(t\text{Bu})_2\text{PCl}$ and *n*-propanol blend better in this case and ligand **B** is formed more easily than if solid sodium propanolate is used. In situ preparation of ligands is a strong tool for optimizing a model reaction. To improve the conversion of mesitylbromide to mesitylaldehyde (Table 2, entry 5), we screened different solvents such as MeOH, EtOH, BuOH, and *i*PrOH using in situ protocol 1. Unfortunately, the yield was in the range of 3–6% and 5–10% for conversion. These results emphasize that the topology of the ligand is very important in the reductive carbonylation.

In conclusion, we have developed efficient phosphinite ligands for the palladium-catalyzed reductive carbonylation of aryl bromides to aromatic aldehydes. Several aryl bromides with electron-donating and electron-withdrawing substituents reacted to give aldehydes in good to excellent yields. Additionally, the reductive carbonylation can be carried out using in situ prepared propyl di-*tert*-butylphosphinite (ligand **B**), which is synthesized by a treating commercially available $(t\text{Bu})_2\text{PCl}$ with *n*-propanol in the presence of TMEDA. As $(t\text{Bu})_2\text{PCl}$ is significantly cheaper than BuPAd_2, this new synthetic methodology is a valuable alternative to the established synthesis of BuPAd_2.

Experimental Section

*Ligand **A***

Sodium (43.7 mg, 1.9 mmol) was added to absolute *n*-propanol (20 mL) in a 100 mL Schlenk tube. When the sodium was dissolved, Ad_2PCl (500 mg, 1.48 mmol) was added in portions. Then, the mixture was heated to 90°C for 1 hour. After the *n*-propanol was removed under vacuum, water (15 mL) and CH_2Cl_2 (20 mL) were added to the residual white solid. The phases were separated and the organic phase was dried over Na_2SO_4. When the solvent was removed, a white solid (560 mg) was obtained. For further purification, the solid was dissolved in CH_2Cl_2 (5 mL) and MeOH (20 mL). Keeping the solution in the refrigerator overnight afforded a white solid, which is stable to air over a few weeks. 31% yield (165 mg); ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.62$ (q, $J =$ 7,1 Hz, 3H, OCH_2), 1.97–1.90 (m, 6H, CH), 1.90–1.84 (m, 12H, CH_2) 1.75–1.69 (m, 12H, CH_2), 1.63 (sext, $J = 7.3$ Hz, 2H, CH_2), 0.93 ppm (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 76.1$ (d, $J =$ 19.2 Hz, OCH_2), 39.3 (d, $J = 23.6$ Hz, C), 38.6 (d, $J = 12.6$ Hz, CH_2), 28.4 (d, $J = 8.2$ Hz, CH), 37.2 (CH_2), 24.7 (d, $J = 6.8$ Hz, CH_2), 10.5 ppm (CH_3); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 157.9$ ppm; MS (EI, 70 eV): *m*/*z* (%) = 360 (0.84) $[M]^+$, 169 (19), 135 (100), 93 (19), 91(16), 60(14), 58(25), 56(17), 48(28); HRMS (EI, 70 eV) *m*/*z*: calcd for $C_{23}H_{37}OP$: 360.25765; found: 360.257829.

*Ligand **B***

Sodium (276 mg, 12 mmol) was dissolved in *n*-propanol (20 mL) in a 100 mL Schlenk tube under an atmosphere of argon. Then the solvent was removed under high vacuum to afford a white solid. Diethyl ether (30 mL) and $(t\text{Bu})_2\text{PCl}$ (1.52 mL, 8 mmol) were then added to the suspension at room temperature. The reaction mixture was left overnight and degassed water (20 mL) was added. The organic phase was separated and dried over Na_2SO_4 under argon. By a cannula, the solution was filtered under argon through a Celite pad and diethyl ether was removed under vacuum. A colorless, clear, and pyrophoric liquid was obtained in 98% yield (1.61 g). ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.68$ (q, $J =$ 6,7 Hz, 3H, OCH_2), 1.62 (sext, $J = 6.7$ Hz, 2H, CH_2), 1.08 (d, $J = 11.3$ Hz, 18H, *t*Bu), 0.93 ppm (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 75.4$ (d, $J = 19.4$ Hz, OCH_2), 34.9 (d, $J = 23.2$ Hz, C), 27,4 (d, $J = 15.1$ Hz, *t*Bu), 24.8 (d, $J = 7.2$ Hz, CH_2), 10.5 ppm (CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 159.6$ ppm. MS (EI, 70 eV): *m*/*z* (%) = 204 (24) $[M]^+$, 163 (23), 162 (15), 107 (59), 106 (35), 105(23), 87(42), 63(25), 57-(100). HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{26}OP$: 205.17158; found: 205.17182.

*Ligand **C***

THF (13 mL), *n*-propylamine (1.48 mL, 18 mmol), and triethylamine (1.66 mL, 12 mmol) were added under argon to a 50 mL Schlenk flask equipped with a stirring bar and septum. After cooling the reaction mixture to 0°C with an ice bath, $(t\text{Bu})_2\text{PCl}$ (1.5 mL, 7.9 mmol) was slowly added and a white solid precipitated. The reaction solution was stirred for 1.5 days at room temperature. The white precipitate was allowed to settle and through a cannula the solution was filtrated and the solid was extracted with THF (3 × 5 mL). The solvent and the excess amine were removed under high vacuum and a cloudy liquid remained, which was diluted with diethyl ether (7 mL). After filtering the solution over Celite, a clear liquid was obtained. The solvent was removed under vacuum, and a clear, pyrophoric liquid was obtained in 73% yield (1.5 g). ^{1}H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.94$–2.83 (m, 2H, NCH_2), 1.46 (sext, $J =$ 7.2 Hz, 2H, CH_2), 1.04 (d, $J = 11.3$ Hz, 18H, *t*Bu), 0.68 ppm (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 52.5$ (d, $J = 26.9$ Hz, NCH_2), 33.8 (d, $J = 18.8$ Hz, C), 28,2 (d, $J = 14.5$ Hz, *t*Bu), 26.4 ppm (d, $J = 6.6$ Hz, CH_2), $\delta = 11.4$ ppm (CH_3). ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta =$ 78.3 ppm. MS (EI, 70 eV): *m*/*z* (%) = 203 (12) $[M]^+$, 146 (31), 90 (100), 57 (8). HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{27}NP$: 204.18756; found: 204.18794.

Reaction procedure for the reductive carbonylation

A stock solution was prepared, in which each 2 mL contains $Pd(OAc)_2$ (1.10 mg, 0.5 mol%) and ligand **B** (3.10 mg, 1.5 mol%). A 2 mL stock solution was added under an argon atmosphere to each of the six vials (4 mL reaction volume) placed in an alloy plate, equipped with a septum, cannula, and stirring bar. After adding TMEDA (113.2 μL, 0.75 mmol, 0.75 equiv), aryl bromide (1 mmol), and hexadecane (60 μL) to the vials, the alloy plate was transferred into a 300 mL autoclave (Parr Instruments, 4560 series) under an argon atmosphere. After flushing the autoclave three times with CO/H_2 and then pressurized to 5 bar CO/H_2, the reaction was performed for 20 h at 100°C. When the reaction was finished the autoclave was cooled down to room temperature, CO/H_2 was released and a sample was analyzed by GC to determine the yield and conversion.

In situ protocol 1

Toluene (4 mL), TMEDA (565.9 μL, 3.75 mmol, 0.75 equiv), $(t\text{Bu})_2\text{ClP}$ (14.2 μL, 1.5 mol%), and *n*-propanol (1.5 mol%) were added to a 12 mL vial equipped with a stirring bar, septum, and small cannula under an argon atmosphere. After the solution was stirred for 10 min, bromobenzene (523.4 μL, 5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.5 mol%), and hexadecane (300 μL) were added. The vial was placed in an alloy plate, which was transferred into a 300 mL autoclave (Parr Instruments, 4560 series) under

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an argon atmosphere. After flushing the autoclave three times with CO/H_2 and then pressurized to 5 bar CO/H_2, the reaction was performed for 20 h at 100 °C. After cooling down to room temperature, CO/H_2 was released carefully and a sample was analyzed by GC to determine the yield and conversion (95 % yield, 96 % conversion).

In situ protocol 2

The procedure is similar to that of in situ protocol 1, but first the 12 mL vial was charged with sodium propionate (6.2 mg, 1.5 mol %) and then toluene (4 mL), TMEDA (565.9 μL, 3.75 mmol, 0.75 equiv), and $(t\text{Bu})_2\text{ClP}$ (14.2 μL, 1.5 mol%), and after the solution was stirred for 10 min, bromobenzene (523.4 μL, 5 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.5 mol%) were added (65 % yield, 66 % conversion).

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Keywords: aldehydes · aryl bromide · palladium · reductive carbonylation · synthesis gas

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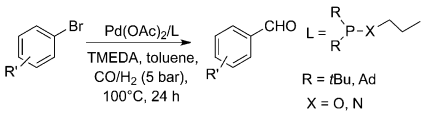
COMMUNICATION

A palladium-catalyzed reductive carbonylation of aryl bromides into the corresponding aryl aldehydes has been described using synthesis gas in the presence of phosphinite ligands. Several products have been synthesized in moderate to good yields (35–97%) under mild reaction conditions.



Reductive Carbonylations

Helfried Neumann, Renat Kadyrov, Xiao-Feng Wu, Matthias Beller** _____ ▮▮▮▮–▮▮▮▮

Palladium-Catalyzed Reductive Carbonylation of Aryl Bromides with Phosphinite Ligands

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